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Facile, novel and efficient synthesis of new pyrazolo[3,4-b]pyridine products from condensation of pyrazole-5-amine derivatives and activated carbonyl groups

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An efficient synthesis of novel ethyl-1,3,4-triphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate products has been achieved via condensation of pyrazole-5-amine derivatives and activated carbonyl groups, in refluxing acetic acid. This process has been found to be useful in the preparation of new N-fused heterocycle products in good to excellent yields.

Introduction

N-Fused heterocycles are one of the most important class of organic compounds with multitude of applications and therefore there is intense interest in synthesis of this type of compounds in recent decades.[1-3] They are widely present in naturally occurring alkaloids with a broad range of biological activities.[4] Indeed, recent studies have shown that greater than 90% of molecules currently under analysis by pharmaceutical companies include nitrogen heterocycles, where pyrazol, pyridine and pyrimidine derivatives constitute the most important family of these compounds.[5] In particular, fused pyridine systems such as pyrazolopyridines and their related derivatives have shown wide spectrums of biological activities for accessing the pharmaceutical and medicinal products.[6-7] For example, these heterocycles act as potent cyclin dependent kinase1 (CDK1) inhibitors,[8] HIV reverse transcriptase inhibitors,[9] CCR1 antagonists,[10] protein kinase inhibitors,[11] inhibitors of cGMP degradation, dopamine D3 receptor antagonists, besides possessing antiherpetic and antiallergic,[12] herbicidal and fungicidal activities.[13] Several drugs such as cartazolate, tracazolate and etazolate comprise pyrazolopyridine scaffold (Fig. 1).[14]

There are several synthetic methods for preparation of these compounds under different conditions which has opened new horizons in the synthesis of pyrazolopyridines.[15] For instance, the synthesis of pyrazolopyridines can be achieved via multi-component reaction of 1,3-diphenyl-1H-pyrazol-5-amine, barbituric acid and isatin,[16] intermolecoular cyclization of 3-methyl-1-phenyl-1H-pyrazol-5-amine and bis(arylidene) thiophenones under microwave (MW) conditions,[17] one-pot three-component condensation of kojic acid, 1-H-pyrazol-5-amine and aldehydes,[18] and four-component bicyclization of 2,2-dihydroxy-1-phenylethanone, 3-methyl-1-phenyl-1H-pyrazol-5-amine, aniline and 4-hydroxy-6-methyl-2H-pyran-2-one under microwave heating.[19]

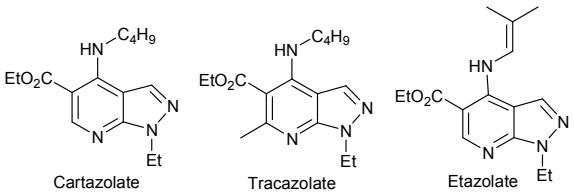

Fig. 1 Some drugs with pyrazolopyridine core.

These methods have one or more disadvantages such as adverse environmentally catalysts, toxic substances, low yields and wearing work up. Furthermore, these methods just provide a limited range of desired pyrazolo[3,4-b]pyridine structures. The biological and medicinal importance of these heterocyclics encourage us to search for a new and efficient method for their synthesis. In addition, we intend to introduce new pyrazolo[3,4-b]pyridine structures which are not available by previously presented strategies. Considering the above, herein we design a new, convenient, easy to handel, rapid and highly efficient protocol for the synthesis of novel analogues of pyrazolopyridines **3** via condensation reaction of pyrazol-5-amine compounds **1** and ethyl 2,4-dioxo-4-phenylbutanoate derivatives **2** under acidic conditions (Scheme 1). The target molecules were obtained in good to excellent isolated yields.

Results and discussion

Initially, the desired starting materials, including 1,3-diphenyl-1H-pyrazol-5-amine **1** (R_1=Ph; prepared from 1-phenyl hydrazine **6** and 3-oxo-3-phenylpropanenitrile **7**), and ethyl-2,4-dioxo-4-arylbutanoates **2** (prepared from acetophenones **5** and diethyl oxalate **4**) were synthesized by conventional methods according to the literature (Scheme 2).[20-22]

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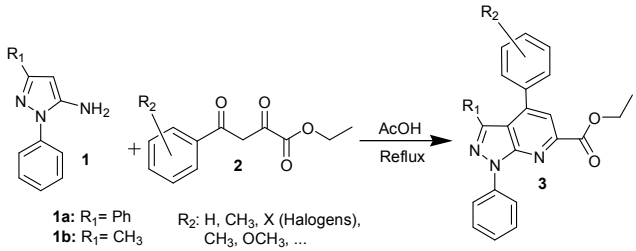
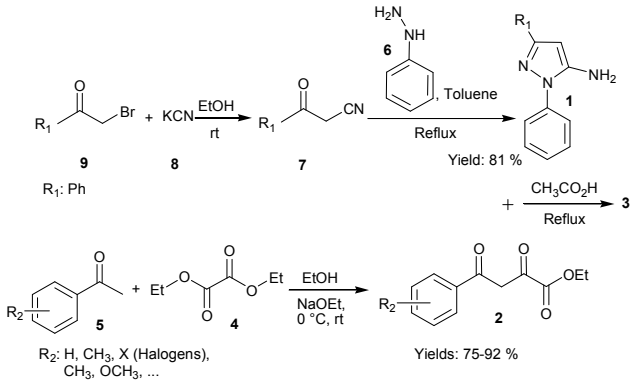


Scheme 1 General route for the synthesis of novel pyrazolo[3,4-b]pyridines.



Scheme 2 Synthesis of starting materials **1a** (R_1=Ph) and **2**, needed for synthesis of pyrazolo[3,4-b]pyridine derivatives **3**.

Next, the reaction of compound **1a** (R_1=Ph) and ethyl 2,4-dioxo-4-arylbutanoate **2a** was studied comprehensively as a representative example. To access product **3a** in a rapid and efficient manner, different solvents were examined (Table 1). As shown in Table 1, the expected product was obtained in good yield in refluxing AcOH (Table 1, entry 8). With these results in hand, different ethyl-1,3,4-triphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate derivatives **3a-q** were prepared using various ethyl-2,4-dioxo-4-arylbutanoates **2** (Table 2, entries 1-17).

Table 1 Solvent screening for the synthesis of compound **3a**.

Entry	Solvent	Temperature	Time (h)	Yield (%)[b]
1	THF	68˚C	10	35
2	MeOH	65˚C	15	40
3	H_2O	100˚C	12	42
4	H_2O, HCl[a]	100	8	38
5	H_2O, $CH_3C_6H_4SO_3H$[a]	100	9	40
6	H_2O, AcOH[a]	100	7	60
7	DMF	130˚C	13	38
8	AcOH	120˚C	5	90
9	HCl	100˚C	10	30

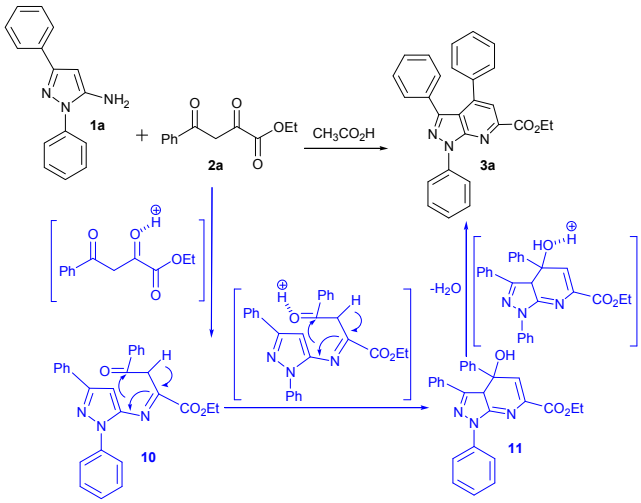
[a]Ctalytic amount (1 ×10^{-4}mol%), [b]Isolated yield.

It was observed that the desired products were obtained in good to excellent yields in almost all cases and their structures were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopies as well as mass spectrometry.

A plausible mechanism for the formation of ethyl-1, 3, 4-triphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate **3a** is proposed in Scheme 3. The acid catalyzed condensation of primary amine group of 1,3-diphenyl-1H-pyrazol-5-amine **1a** with the more active carbonyl group of ethyl 2,4-dioxo-4-phenylbutanoates **2a** in the presence of acetic acid as solvent gave the intermediate **10**. Finally, the products **3a** can be achieved after tautomerization, cyclization and water elimination sequences. It should be noted that acetic acid can act as an efficient catalyst and suitable solvent for the synthesis of entitled fused pyrazolo[3,4-b]pyridine system.

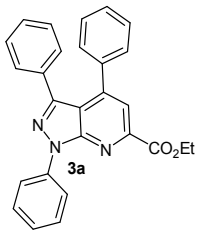
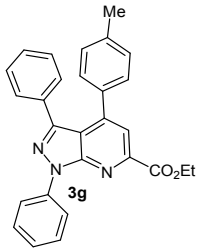
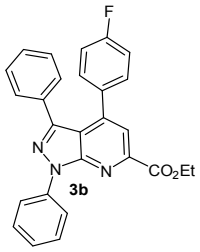
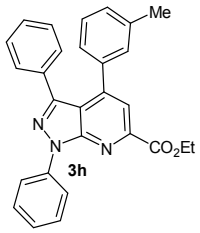
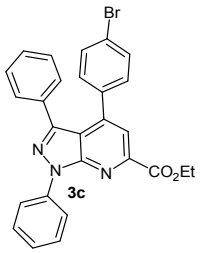
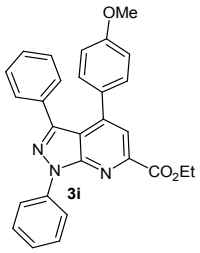
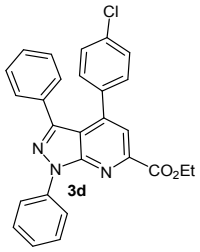
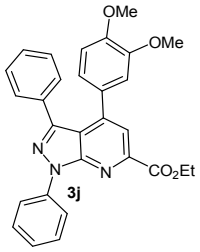
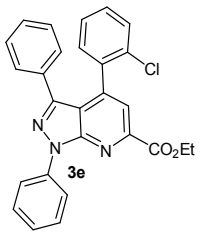
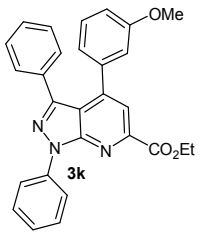
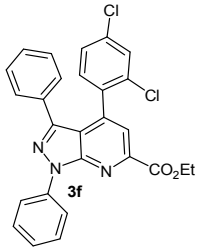
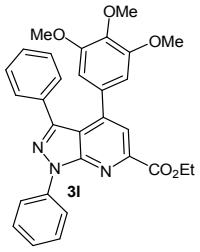
Electron withdrawing groups on Ar of compound **2**, draw electrons away from the neighboring carbonyl reaction center in intermediate **10**, activate the carbonyl group and accelerate the cyclization step, which finally lead to higher yields of target products (Table 2, entries 2-6).

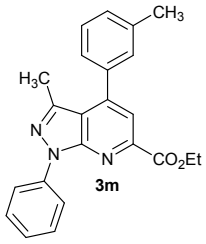
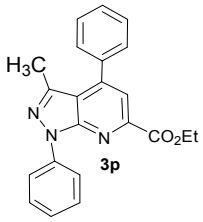
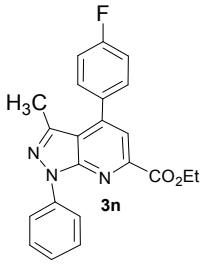
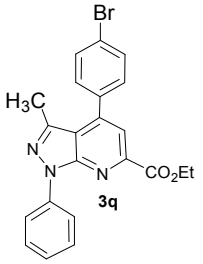
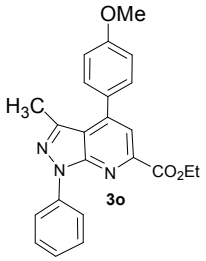
Meanwhile, the electron donating groups on Ar moiety of compound **2**, decrease the nucleophilic attack to carbonyl group in intermediate **10**, which lead to lower yields of desired products. In addition, the substitution effect on C-3 of compound **1**, does not affect significantly the yield of the reaction (Table 2).



Scheme 3 Plausible mechanism for the formation of ethyl-1,3,4-triphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate **3a**.

Table 2 Synthesis of pyrazolo[3,4-b]pyridine-6-carboxylate derivatives **3**.

Entry	Ar-R_2 on **2**	Product **3**	Yield (%)[a]	Entry	Ar-R_2 on **2**	Product **3**	Yield (%)[a]
1[b]	Ph	 **3a**	90	7[b]	4-Me-C_6H_4	 **3g**	70
2[b]	4-F-C_6H_4	 **3b**	85	8[b]	3-Me-C_6H_4	 **3h**	65
3[b]	4-Br-C_6H_4	 **3c**	80	9[b]	4-MeO-C_6H_4	 **3i**	60
4[b]	4-Cl-C_6H_4	 **3d**	82	10[b]	3,4-$(MeO)_2$-C_6H_3	 **3j**	65
5[b]	2-Cl-C_6H_4	 **3e**	80	11[b]	3-MeO-C_6H_4	 **3k**	60
6[b]	2,4-Cl_2-C_6H_3	 **3f**	85	12[b]	3,4,5-$(MeO)_3$-C_6H_2	 **3l**	trace

Entry	Ar-R_2 on **2**	Product **3**	Yield (%)[a]	Entry	Ar-R_2 on **2**	Product **3**	Yield (%)[a]
13[c]	3-Me-C_6H_4	 **3m**	78	16[c]	Ph	 **3p**	82
14[c]	4-F-C_6H_4	 **3n**	87	17[c]	4-Br-C_6H_4	 **3q**	84
15[c]	4-MeO-C_6H_4	 **3o**	74				

[a]The reaction time was prolonged to 5 h, [b]The **1a** was used as starting material, [c]The **1b** was used as starting material.

Experimental

Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Bruker FT-500, using TMS as an internal standard. IR spectra were obtained with a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). MS were recorded with an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was done by Elemental Analysensystem GmbH VarioEL CHNS mode.

General procedure for the synthesis of pyrazolo[3,4-b]pyridine-6-carboxylate 3

At the outset, a mixture of 1,3-diphenyl-1H-pyrazol-5-amine **1** (1 mmol) and ethyl 2,4-dioxo-4-arylbutanoates **2** (1 mmol) in refluxing CH_3CO_2H (10 mL) was stirred for 5 h. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane: 1/2). After completion of the reaction, it was cooled to room temperature, and the precipitated product was filtered, washed with ethanol (20 mL) and purified by crystallization or column chromatography to afford the pure product **3a-K** as a pure powder.

Ethyl-1,3,4-triphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3a)

Yield: 90%; yellow crystals; mp 114-116 °C; IR (KBr): 3063, 2983, 1722, 1596 cm^{-1}. 1H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.1 Hz, 3H, CH_3), 3.96 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.37 (t, *J* = 7.3 Hz, 1H, Ar), 7.47-7.61 (m, 8H, Ar), 7.68 (d, *J* = 7 Hz, 2H, Ar), 8.06 (s, 1H, Pyridine), 8.23 (d, *J* = 7.4 Hz, 2H, Ar), 8.44 (d, *J* = 8.1 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 62.0, 110.2, 115.1, 121.6, 126.2, 127.5, 128.2, 128.4, 128.6, 128.9, 129.0, 130.0, 134.0, 135.5, 138.1, 139.3, 145.4, 151.8, 157.0, 166.6. MS: m/z (%) = 419 $[M]^+$(100), 346 (50), 265 (30), 117 (25), 77 (15). Anal. Calcd for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02; Found: C, 76.91; H, 4.65; N, 9.62.

Ethyl-4-(4-fluorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3b)

Yield: 85%; yellow crystals; mp 151 °C; IR (KBr): 3062, 2979, 1724, 1499 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.80 (t, *J* = 7.5 Hz, 3H, CH_3), 3.94 (q, *J* = 7.5 Hz, 2H, OCH_2), 7.20-7.25 (m, 2H, Ar), 7.35-7.38 (m, 1H, Ar), 7.46-7.52 (m, 3H, Ar), 7.55-7.59 (m, 2H, Ar), 7.64-7.66 (m, 2H, Ar), 7.98 (s, 1H, Pyridine), 8.19-8.22 (m, 2H,Ar), 8.38-8.40 (m, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 62.1, 110.2, 114.8, 115.9 (d, J_{C-F} = 21.2 Hz), 121.7, 126.3, 128.3, 128.5, 128.6, 129.0, 129.5 (d, J_{C-F} = 8.7 Hz), 133.9, 134.3, 135.7, 139.2, 145.4, 151.7, 156.0 (d, J_{C-F} = 250 Hz), 164.1, 166.5. MS: m/z (%) = 424 $[M]^+$ (100), 418 (45), 346 (30), 77 (25). Anal. Calcd for $C_{27}H_{20}FN_3O_2$: C, 74.13; H, 4.61; N, 9.61; Found: C, 73.73; H, 4.21; N, 9.21.

Ethyl-4-(4-bromophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3c):

Yield: 80%; yellow crystals; mp 186 °C; IR (KBr): 3062, 2986, 1724, 1574 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.85 (t, *J = 7.1* Hz, 3H, CH_3), 3.99 (q, *J = 7.1* Hz, 2H, OCH_2), 7.04 (t, *J = 7,1* HZ, 1H, Ar), 7.50-7.54 (m, 3H, Ar), 7.59.7.62 (m, 2H, Ar), 7.68-7.72 (m, 4H, Ar), 8.03 (s, 1H, Pyridine), 8.12(d, *J* = 8.5 Hz, 2H, Ar), 8.43 (d, *J = 7.7* Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.6, 62.5, 110.2, 115.2, 121.5, 126.2, 127.5, 128.2, 128.4, 128.6, 128.9, 129, 130.0, 134.0, 135.5, 138.1, 139.3, 145.5, 151.8, 157.0, 166.6. MS: m/z (%) = 497 $[M^+]$ (100), 470 (30), 242 (25), 77 (35). Anal. Calcd for $C_{27}H_{20}BrN_3O_2$: C, 65.07; H, 4.04; N, 8.43. Found: C, 64.67; H, 3.64; N, 8.04

Ethyl-4-(4-chlorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3d)

Yield: 80%; yellow crystals; mp 186 °C; IR (KBr): 3060, 2987, 1723, 1565 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.85 (t, *J* = 7.1 Hz, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.40 (t, *J* = 7Hz, 1H, Ar), 7.50-7.56 (m, 5H, Ar), 7.59-7.62 (m, 2H, Ar), 7.68-7.70 (m, 2H, Ar), 8.03 (s, 1H, Pyridine), 8.19 (dd, *J* = 6.7, 1.8 Hz, 2H, Ar), 8.4 (dd, *J* = 8, 0.90 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.6, 62.5, 110.2, 115.2, 122.1, 128.7, 128.9, 129.1, 129.2, 129.3, 129.5, 129.6, 130.0, 134.0, 135.1, 138.7, 139.6, 145.4, 151.5, 157.4, 166.6. MS: m/z (%) = 453 $[M^+]$ (100), 418 (40), 346(35), 77(30). Anal. Calcd for $C_{27}H_{20}ClN_3O_2$: C, 71.44; H, 4.44; N, 9.26. Found: C, 71.04; H, 4.04; N, 8.86.

Ethyl-4-(2-chlorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3e)

Yield: 80%; yellow crystals; mp 190°C; IR (KBr): 3062, 2975, 1731, 1595 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.83 (t, *J* = 7.2 Hz, 3H, CH_3), 3.97 (q, *J* = 7.2 Hz, 2H, OCH_2), 7.34 (t, *J* = 7.2 Hz, 1H, Ar), 7.42-7.45 (m, 2H, Ar), 7.51-7.56 (m, 6H, Ar), 7.68-7.75 (m, 3H, Ar), 7.92 (s, 1H, Pyridine), 8.4 (d, J = *7.8* Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 62.1, 118.7, 119.1, 119.6, 121.5, 121.9, 126.3, 127.2, 128.6, 128.9, 129.2, 129.5, 130.3, 130.6, 132.1, 132.6, 133.9, 134.8, 138.3, 139.1, 156.7, 166.3. MS: m/z (%) = 435 $[M^+]$ (100), 418 (40), 346 (30), 77(15). Anal. Calcd for $C_{27}H_{20}ClN_3O_2$: C, 70.40; H, 5.46; N, 7.68. Found: C, 70.0; H, 5.02; N, 7.28.

Ethyl-4-(2,4-dichlorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3f)

Yield: 85%; yellow crystals; mp 135°C; IR (KBr): 2982, 2929, 1719, 1592 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.82 (t, *J* = 7.1 Hz, 3H, CH_3), 3.96 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.49-7.50 (m, 1H, Ar), 7.51-7.53 (m, 1H, Ar), 7.56-7.58 (m, 6H, Ar), 7.66-7.69 (m, 3H, Ar), 7.89 (s, 1H, Pyridine), 8.35-8.38 (m, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 62.1, 110.4, 118.8, 121.6, 126.4, 127.5, 128.3, 128.6, 128.7, 129.0, 130.2, 132.8, 133.3, 133.8, 134.9, 135.6, 136.7, 139.0, 145.4, 151.3, 155.5, 166.1. Anal. Calcd for $C_{27}H_{20}Cl_2N_3O_2$: C, 66.40; H, 3.92; N, 8.60. Found: C, 66.0; H, 3.52; N, 8.20.

Ethyl-1,3-diphenyl-4-p-tolyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3g)

Yield: 70%; yellow crystals; mp 164 °C; IR (KBr): 2982, 2929, 1729, 1493, 1462 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.84 (t, *J* = 7.1 Hz, 3H, CH_3), 2.48 (S, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H. OCH_2), 7.39 (t, *J* = 8.1 Hz, 3H, Ar), 7.49-7.55 (m, 3H, Ar), 7.60 (t, *J* = 8.2 Hz, 2H, Ar), 7.69-7.70 (m, 2H, Ar), 8-05 (s, 1H, Pyridine), 8.15 (d, *J* = 8.1 Hz, 2H, Ar), 8.47 (d, *J* = 7.7 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 22.0, 62.3, 110.2, 115.2, 122.1, 128.7, 128.9, 129.1, 129.2, 129.3, 129.5, 129.6, 130.0, 134.0, 135.0, 138.7, 139.6, 145.4, 151.8, 157.0, 166.0. Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.18; H, 4.95; N, 9.29.

Ethyl-1,3-diphenyl-4-m-tolyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3h)

Yield: 70%; yellow crystals; mp 141°C; IR (KBr): 3035, 2974, 2919, 1720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.85 (t, *J* = 7.1 Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.29 (s, 1H, Ar), 7.35 (s, 1H, Ar), 7.39 (s, 1H, Ar), 7.47-7.51 (m, 1H, Ar), 7.54-7.55 (m, 2H, Ar), 7.59-7.62 (m, 2H, Ar), 7.69-7.71 (m, 2H, Ar), 8.03 (d, *J* = 7 Hz, 2H, Ar), 8.07 (s, 1H, Pyridine), 8.48 (d, *J* = 7.6 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) : δ_c = 13.17, 24.7, 60.08, 109.2, 115.2, 115.7, 121.5, 121.8, 126.1, 128.5, 128.8, 129.1, 129.8,130.7, 132.7, 134.0, 135.5,
139.3, 139.6, 145.4, 151.9, 156.8, 160.1, 166.6. Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.18; H, 4.95; N, 9.29.

Ethyl-4-(4-methoxyphenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3i)

Yield: 60%; yellow crystals; mp 169°C; IR (KBr): 3061, 2962, 2928, 1732, 1571 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.08 (t, *J* = 7.1 Hz, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.95 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.06 (d, *J* = 8.8 Hz, 2H),7.25 (t, *J* = 7 Hz, 1H, Ar) , 7.48-7.51 (m, 3H, Ar), 7.55-7.60 (m, 2H. Ar), 7.65-7.68 (m, 2H, Ar), 7.99 (s, 1H, Pyridine), 8.19 (d, *J* = 8.8 Hz, 2H, Ar), 8.43 (dd, *J* = 8.5, 1.1Hz, 2H, Ar), ^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 55.4, 61.9, 109.7, 110.2, 114.3, 114.5, 121.6, 126.1, 128.2, 128.4, 128.6, 129.0, 130.7, 134.1, 135.3, 139.3, 145.4, 151.9, 156.7, 161.3, 166.7. MS: m/z (%) = 449.5 $[M^+]$ (100), 419 (40), 342 (30), 77(25). Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.42; H, 4.76; N, 8.95.

Ethyl-4-(3,4-dimethoxyphenyl)-1,3-diphenyl-1pyrazolo[3,4-b]pyridine-6-carboxylate (3j)

Yield: 65%; yellow crystals; mp 109°C; IR (KBr): 2923, 2851, 1722, 1571 cm^{-1}. ^1H NMR(500 MHz, $CDCl_3$): δ_H =0.80 (t, *J* = 7.1 Hz, 3H, CH_3), 3.93 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.98 (s. 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.02 (d, *J* = 8.4 Hz, 1H, Ar), 7.26-7.35 (m, 1H, Ar), 7.49-7.58 (m, 5H, Ar), 7.56-7.68 (m, 2H, Ar), 7.78-7.81 (m, 1H, Ar), 7.87 (d, *J* = 1.8 Hz, 1H, Ar), 8.0 (s, 1H, Pyridine), 8.44 (d, *J* = 7.8 Hz, 2H, Ar). ^{13}C

NMR (125 MHz, $CDCl_3$): 13.1, 55.9, 56.0, 62.0, 109.8, 110.2, 111.1, 114.5, 120.5, 121.6, 126.1, 128.3, 128.4, 128.6, 128.9, 130.9, 134.0, 135.4, 139.3, 145.4, 149.3, 150.9, 156.5, 166.8. MS: m/z (%) = 479 [M+] (100), 418 (60), 342 (35), 77 (25). Anal. Calcd for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.24; H, 4.75; N, 8.36.

Ethyl-4-(3-methoxyphenyl)-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3k)

Yield: 60%; yellow crystals; mp 139°C; IR (KBr): 2922, 2853, 1721, 1572 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.82 (t, *J* = 7.2 Hz, 3H, CH_3), 3.94 (s, 3H, OCH_3), 4.00 (q, *J* = 7.5 Hz, OCH_2), 7.06 (d, *J* = 7.5 Hz, 1H, Ar), 7.37 (t, *J* = 7.5 Hz, 1H, Ar), 7.39-7.61 (m, 6H, Ar), 7.68 (d, *J* = 6.6 Hz, 2H, Ar), 7.80 (d, *J* = 7.2 Hz, 2H, Ar), 8.04 (s, 1H, Pyridine), 8.45 (d, *J* = 8 Hz, 2H, Ar).^{13}C NMR (125 MHz, $CDCl_3$): 13.1, 55.9, 62.0, 109.2, 115.2, 115.7, 121.5, 121.8, 126.1, 128.5, 128.8, 129.1, 129.8, 130.0, 132.7, 134.0, 135.5, 139.3, 139.6, 151.8, 156.8, 157.1, 160.1, 166.6. Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.42; H, 4.76; N, 8.95.

Ethyl-3-methyl-1-phenyl-4-*m*-tolyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3m)

Yield: 78%; yellow crystals; mp 128-130˚C; IR (KBr): 2912, 2853, 1721, 1562 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 1.5 (t, *J* = 7 Hz, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 4.54 (q, *J = 7 Hz*, OCH_2), 7.27-7.31 (m, 2H, Ar), 7.40 (t, *J = 7.5 Hz,* 1H, Ar), 7.53 (t, *J= 7.5 Hz*, 2H, Ar), 7.97 (d, *J = 8 Hz*, 2H, Ar), 8.09 (s, 1H, Pyridine), 8.35 (d, *J = 8 Hz*, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 14.30, 16.28, 21.59, 62.03, 111. 96, 115.25, 121.32, 124.77, 125.68, 128.18, 128.81, 128.94, 130.62, 134.24, 138.40, 138.50, 139.47, 142.51, 152.16, 156.87, 165.72. Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.44; H, 5.77; N, 11.62.

Ethyl-4-(4-fluorophenyl)-3-methyl-1-phenyl-1H-pyrazolo [3,4-b]pyridine-6-carboxylate (3n)

Yield: 87%; yellow crystals; mp 132 ˚C, IR (KBr): 2942, 2753, 1731, 1562 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 1.50 (t, *J*= 7 Hz, 3H, CH_3), 2.78 (s, 3H, CH_3), 4.53 (q, *J*= 7 Hz, 2H, OCH_2), 7.19 (t, *J*= 8 Hz, 2H, Ar), 7.30 (t, *J*= 7.5 Hz, 1H, Ar), 7.53 (t, *J*= 8 Hz, 2H, Ar), 8.04 (s, 1H, Pyridine), 8.15 (d, *J*= 8 Hz, 2H, Ar), 8.30 (d, *J*= 8 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 14.29, 16.30, 62.01, 111.95, 114.74, 115.87 (d_{C-F}, *J*= 21.25 Hz), 121.32, 125.79, 128.97, 129.4 (d_{C-F}, *J*= 8.75 Hz), 134.41, 134.50, 139.35, 142.57, 152.04, 155.50, 163.07, 165.0 (d_{C-F}, *J*= 240 Hz). Anal. Calcd for $C_{22}H_{18}FN_3O_2$: C, 70.39; H, 4.83; N, 11.19. Found: C, 70.52; H, 4.74; N, 11.27.

Ethyl 4-(4-methoxyphenyl)-3-methyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3o)

Yield: 74%; yellow crystals; mp 131-132 ˚C, IR (KBr): 2922, 2973, 1721, 1512 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.50 (t, *J= 7 Hz,* 3H, CH_3), 2.78 (s, CH_3), 3.88 (s, OCH_3), 4.53 (q, *J= 7Hz*, 2H, OCH_2), 7.02-7.05 (m, 2H, Ar), 7.28-7.31 (m, 1H, Ar), 7.51-7.54 (m, 2H, Ar), 8.06 (s, 1H, Pyridine), 8.13-8.16 (m, 2H, Ar), 8.33-8.35 (m, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 14.30, 16.30, 55.42, 62.01, 111.5, 114.33, 114.60, 121.31, 125.63, 128.94, 130.98, 134.20, 139.50, 142.54, 144.30, 152.20, 156.36, 161.27, 165.79. Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.45; H, 5.64; N, 10.72.

Ethyl-3-methyl-1,4-diphenyl-1H-pyrazolo[3,4-b]pyridine-6-carboxylate (3p)

Yield: 82%; yellow crystals; mp 128-129 ˚C; IR (KBr): 2902, 2753, 1721, 1562 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H = 1.49 (t, *J*= 7 Hz, 3H, CH_3), 2.78 (s, CH_3), 4.52 (q, *J* = 7 Hz, OCH_2), 7.29 (t, *J*= 7 Hz, 1H, Ar), 7.45-7.53 (m, Ar, 5H), 8.09 (s, Pyridine), 8.16 (d, *J*= 8 Hz, 2H, Ar), 8.34 (d, *J*= 8 Hz, 2H, Ar). ^{13}C NMR (125 MHz, CDC_{l3}): 14.26, 16.29, 62.02, 112.00, 115.10, 121.26, 125.67, 127.50, 128.86, 128.92, 129.80, 134.25, 138.33, 139.40, 142.51, 152.11, 156.58, 165.60. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.15; H, 5.52; N, 11.98.

Ethyl-4-(4-bromophenyl)-3-methyl-1-phenyl-1H-pyrazolo [3,4-b]pyridine-6-carboxylate (3q)

Yield: 84%; yellow crystals; mp 141-142 ˚C, IR (KBr): 2942, 2773, 1701, 1522 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.50 (t, *J= 7 Hz,* 3H, CH_3), 2.80 (s, CH_3), 4.54 (q, *J= 7Hz*, 2H, OCH_2), 7.31 (t, *J=7.5Hz*, 1H, Ar), 7.53 (t, *J= 7.5 Hz*, 2H, Ar), 7.65 (d, *J= 8.5 Hz*, 2H, Ar), 8.05 (d, *J= 8.5 Hz*, 2H, Ar), 8.07 (s, 1H, Pyridine), 8.30 (d, *J= 8.5 Hz*, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): 14.30, 16.28, 62.16, 112.90, 114.77, 119.90, 121.39, 124.50, 124.90, 125.89, 129.01, 129.05, 132.12, 134.1, 137.4, 139.2, 142.6, 155.3. Anal. Calcd for $C_{22}H_{18}BrN_3O_2$: C, 60.56; H, 4.16; N, 9.63. Found: C, 60.78; H, 4.35; N, 9.86.

Conclusions

In conclusion, we have introduced a simple, innovative and efficient route for the synthesis of new pyrazolo[3,4-b]pyridine-6-carboxylates **3** using readily available starting materials. Advantages such as the absence of complex synthetic catalyst, relatively short reaction times, high yields of the products, operational simplicity, easy work-up procedure and no requirement for time-consuming purification steps can make the method useful for chemists interested in developing novel pyrazolopyridine-based drugs. Furthermore, our strategy expands the scope of available pyrazolo[3,4-b]pyridine fused heterocycles which can not be prepared by previously reported methods.

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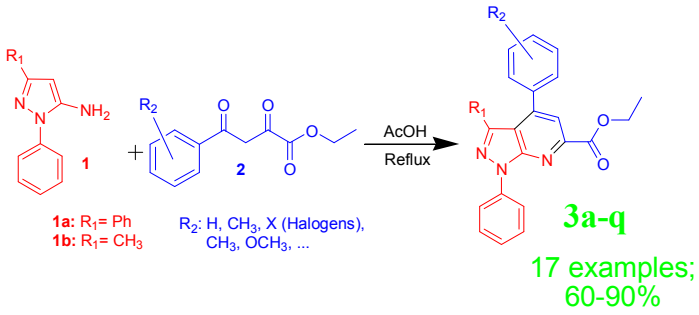

A novel, simple and efficient route for the synthesis of new fused pyrazolo[3,4-b]pyridines is described.