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Three-component synthesis of new *o*-hydroxyphenyl-substituted pyrazolo[3,4-*b*] pyridines promoted by $FeCl_3$

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Abstract: An efficient three-component synthesis of *o*-hydroxyphenyl-substituted pyrazolo[3,4-*b*]pyridines from substituted salicylic aldehydes, β-keto esters and 5-aminopyrazoles in the presence of $FeCl_3$ is presented. Newly synthesized compounds were fully characterized by means of ^{1}H NMR, ^{13}C NMR, IR, HRMS and elemental analysis.

Keywords: iron(III) chloride; pyrazolo[3,4-*b*]pyridines; three-component reaction.

Introduction

A large number of natural products and biologically active organic compounds contain the hydroxyl group [1]. Hydroxyl-substituted pyrazolo[3,4-*b*]pyridine derivatives have received much attention in drug discovery because of their wide biological activities [2]. In recent years, a variety of strategies have been reported for the synthesis of pyrazolo[3,4-*b*]pyridine derivatives [3–5] in the presence of various catalysts, such as iodine [6], *L*-proline [7], $InCl_3$ [8], acetic acid [9, 10] or under microwave/ultrasound irradiation [11, 12], among other approaches [13]. Iron(III) chloride has been widely used as the catalyst in organic synthesis [14]. Herein, we would like to report an efficient one-pot three-component reaction for the synthesis of novel *o*-hydroxyphenyl-substituted pyrazolo[3,4-*b*] pyridines from 5-aminopyrazoles, β-keto esters and salicylic aldehydes using $FeCl_3$ as the catalyst.

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Results and discussion

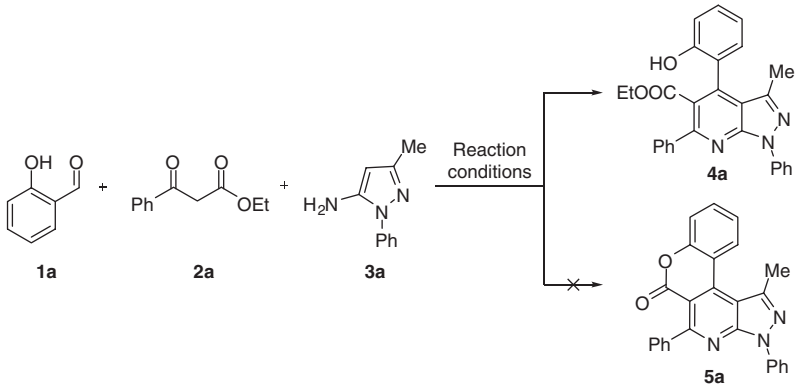
In order to optimize conditions for the synthesis of *o*-hydroxyphenyl-substituted pyrazolo[3,4-*b*]pyridine **4a**, various reaction conditions have been investigated (Table 1). No expected product **4a** was observed when commonly used catalysts iodine, acetic acid and *L*-proline were examined (Table 1, entries 1–3). After screening other catalysts such as $InCl_3$, $ZrCl_4$ and $FeCl_3$, it was found that the best yield of 89% of **4a** was obtained by conducting the reaction in ethanol in the presence of 0.2 equiv of $FeCl_3$ (Table 1, entries 4–6). According to the literature reports, a fused coumarin **5a** could be formed through transesterification reaction between the hydroxyl and ester group at high temperature [13, 15, 16]. In our hands, transesterification product **5a** was not observed probably because of mild reaction conditions. The presence of a small amount of catalyst or lowering the reaction temperature leads to a relatively poor yield (Table 1, entries 7–11). The use of other solvents such as MeOH, MeCN, DMF and toluene also result in a low yield of **4a** (Table 1, entries 12–15).

With these results in hand, the synthesis of additional products was investigated under the conditions optimized for the model compound **4a** (Scheme 1). The reactions of substituted substrates **2a** and **3a** bearing electron-donating and electron-withdrawing groups afford the corresponding products **4b–g** in good to excellent yields (65–90%). In case when R^2 is an alkyl group, products **4h–j** are obtained in 70–78% yields. The use of ethyl 4,4,4-trifluoroacetoacetate (**2**, R = CF_3) also gives good results, delivering **4k–n** in 70–78% yields. When 1,3-diphenyl-1*H*-pyrazol-5-amine (**3b**) was employed, **4o** and **4p** were isolated in 64% and 57% yields, respectively.

Conclusions

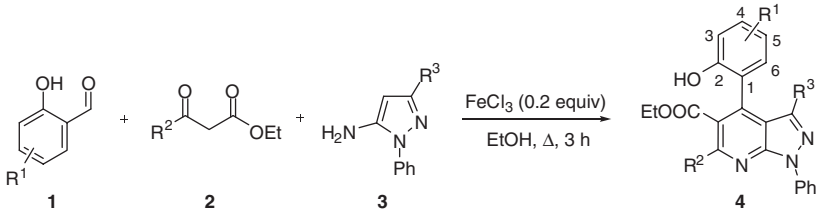
An efficient $FeCl_3$-catalyzed three-component reaction for the synthesis of *o*-hydroxyphenyl-substituted pyrazolo-[3,4-*b*]pyridines from substituted salicylic aldehydes, β-keto esters and 5-aminopyrazoles in refluxing ethanol

Table 1 Optimization of conditions for the synthesis of **4a**.[a,b]



Entry	Catalyst	Solvent	Temp (°C)	Yield[c] (%)
1	AcOH	EtOH	Reflux	0
2	*L*-proline	EtOH	Reflux	0
3	I_2	EtOH	Reflux	0
4	$InCl_3$	EtOH	Reflux	Trace
5	$ZrCl_4$	EtOH	Reflux	42
6	$FeCl_3$	EtOH	Reflux	89
7	$FeCl_3$	EtOH	Reflux	45[d]
8	$FeCl_3$	EtOH	Reflux	30[e]
9	$FeCl_3$	EtOH	60	67
10	$FeCl_3$	EtOH	40	52
11	$FeCl_3$	EtOH	25	30
12	$FeCl_3$	MeOH	65	51
13	$FeCl_3$	MeCN	80	44
14	$FeCl_3$	DMF	80	Trace
15	$FeCl_3$	Toluene	80	32

[a]All reactions were performed with salicylic aldehyde (**1a**, 1.0 mmol), ethyl benzoylacetate (**2a**, 1.0 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3a**, 1.0 mmol) in an appropriate solvent (6 mL) for 3 h.
[b]0.2 Equiv of catalyst was employed in these reactions unless indicated otherwise.
[c]Isolated yield.
[d]0.1 Equiv of catalyst was employed.
[e]0.05 Equiv of catalyst was employed.



4a: R^1 = H; R^2 = Ph; R^3 = Me; 89%
4b: R^1 = 4-OMe; R^2 = Ph; R^3 = Me; 90%
4c: R^1 = 5-Br; R^2 = Ph; R^3 = Me; 75%
4d: R^1 = 3,5-diBr; R^2 = Ph; R^3 = Me; 71%
4e: R^1 = 5-Cl; R^2 = Ph; R^3 = Me; 70%
4f: R^1 = 3,5-diCl; R^2 = Ph; R^3 = Me; 67%
4g: R^1 = 5-NO_2; R^2 = Ph; R^3 = Me; 65%
4h: R^1 = H; R^2 = Me; R^3 = Me; 78%
4i: R^1 = H; R^2 = Et; R^3 = Me; 72%
4j: R^1 = H; R^2 = *n*-Pr; R^3 = Me; 70%
4k: R^1 = H; R^2 = CF_3; R^3 = Me; 73%
4l: R^1 = 4-OMe; R^2 = CF_3; R^3 = Me; 75%
4m: R^1 = 5-Br; R^2 = CF_3; R^3 = Me; 70%
4n: R^1 = 5-Cl; R^2 = CF_3; R^3 = Me; 78%
4o: R^1 = H; R^2 = Ph; R^3 = Ph; 64%
4p: R^1 = H; R^2 = Me; R^3 = Ph; 57%

Scheme 1

was developed. This reaction has the advantages of wide substrate scope, mild reaction conditions and good yields.

Experimental

All reagents were commercially available and used without further purification. Solvents were dried and freshly distilled before use. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker AV 300 MHz spectrometers at 300 MHz and 75 MHz, respectively. IR spectra were obtained in KBr pellets using a Nicolet 5700 FT-IR spectrometer. High resolution mass spectra were recorded on a Bruker UltrafleXtreme MALDI TOF/TOF spectrometer. The CHN microanalyses were carried out with a Perkin-Elmer 2400 elemental analyzer. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were determined using X-4 apparatus and are not corrected.

General procedure for the synthesis of products 4

A mixture of substituted salicylic aldehyde (**1**, 1.0 mmol), β-keto ester (**2**, 1.0 mmol), 5-aminopyrazole (**3**, 1.0 mmol) and $FeCl_3$ (0.2 mmol) was heated in anhydrous ethanol (6 mL) under reflux. After the reaction was completed (3 h, monitored by TLC), the mixture was cooled to room temperature, concentrated and the residue was purified by column chromatography using petroleum ether-ethyl acetate as the eluent.

Ethyl 4-(2-hydroxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4a) Yellow solid; mp 177–178°C; ^{1}H NMR: δ 8.30 (d, *J* = 7.9 Hz, 2H), 7.74 (m, 2H), 7.47 (m, 5H), 7.29 (m, 2H), 7.15 (d, *J* = 6.5 Hz, 1H), 6.97 (m, 2H), 6.30 (s, 1H), 3.89 (m, 2H), 2.07 (s, 3H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.3, 156.8, 153.3, 150.1, 143.9, 141.1, 139.9, 139.2, 130.7, 130.1, 129.0, 128.8, 128.3, 125.7, 124.0, 122.6, 121.0, 120.5, 116.9, 114.0, 61.8, 13.4, 13.3; IR: ν 3397, 2923, 2857, 2360, 1693, 1457, 1255, 754 cm^{-1}. HRMS. Calcd for $C_{28}H_{24}N_3O_3$ [M+H]$^+$: *m/z* 450.1812. Found: *m/z* 450.1824. Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 75.06; H, 5.18; N, 9.33.

Ethyl 4-(2-hydroxy-4-methoxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4b) Yellow solid; mp 291–292°C; ^{1}H NMR: δ 8.31 (d, *J* = 8.7 Hz, 2H), 7.75 (m, 2H), 7.48 (m, 5H), 7.27 (m, 1H), 7.07 (m, 1H), 6.60 (m, 2H), 6.06 (s, 1H), 3.93 (m, 2H), 3.83 (s, 3H), 2.13 (s, 3H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.6, 161.8, 156.7, 154.4, 150.1, 144.0, 140.8, 140.0, 139.3, 130.9, 129.0, 128.7, 128.4, 125.7, 124.5, 121.0, 115.0, 114.5, 107.0, 102.7, 61.9, 55.3, 13.7, 13.4; IR: ν 3431, 2359, 1626, 1425, 1162, 1103, 758 cm^{-1}. HRMS. Calcd for $C_{29}H_{26}N_3O_4$ [M+H]$^+$: *m/z* 480.1918. Found: *m/z* 480.1920. Anal. Calcd for $C_{29}H_{25}N_3O_4$: C, 72.64; H, 5.25; N, 8.76. Found: C, 72.83; H, 5.27; N, 8.74.

Ethyl 4-(5-bromo-2-hydroxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4c) Yellow solid; mp 231–232°C; ^{1}H NMR: δ 8.30 (d, *J* = 8.7 Hz, 2H), 7.72 (m, 2H), 7.48 (m, 6H), 7.30 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.25 (s, 1H), 3.89 (m, 2H), 2.12 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.4, 156.9, 152.6, 150.1, 143.6, 139.8, 139.2, 139.1, 133.5, 132.7, 129.2, 129.1, 128.7, 128.4, 125.9, 124.8, 123.7, 121.1, 119.2, 113.7, 112.6, 62.2, 13.7, 13.3; IR: ν 3398, 1692, 1498, 1409, 1285, 1164, 764 cm^{-1}. HRMS. Calcd for $C_{28}H_{23}BrN_3O_3$ [M+H]$^+$: *m/z* 528.0917. Found: *m/z* 528.0932. Anal. Calcd for $C_{28}H_{22}BrN_3O_3$: C, 63.65; H, 4.20; N, 7.95. Found: C, 63.86; H, 4.21; N, 7.93.

Ethyl 4-(3,5-dibromo-2-hydroxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carboxylate (4d) Yellow solid; mp 215–216°C; ^{1}H NMR: δ 8.31 (d, *J* = 8.0 Hz, 2H), 7.75 (m, 3H), 7.49 (m, 5H), 7.32 (m, 2H), 5.99 (s, 1H), 3.94 (m, 2H), 2.16 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 168.3, 157.2, 150.0, 149.3, 143.2, 139.9, 139.2, 138.8, 135.1, 132.4, 129.10, 129.05, 128.8, 128.4, 125.9, 125.1, 123.3, 121.0, 113.4, 112.5, 111.8, 61.7, 13.8, 13.4; IR: ν 3375, 2967, 1710, 1563, 1461, 1276, 1238, 1146, 1017, 752, 702 cm^{-1}. HRMS. Calcd for $C_{28}H_{22}Br_2N_3O_3$ [M+H]$^+$: *m/z* 608.0004. Found: *m/z* 608.0018. Anal. Calcd for $C_{28}H_{22}Br_2N_3O_3$: C, 55.38; H, 3.49; N, 6.92. Found: C, 55.52; H, 3.50; N, 6.90.

Ethyl 4-(5-chloro-2-hydroxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4e) Yellow solid; mp 207–209°C; ^{1}H NMR: δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.73 (m, 2H), 7.49 (m, 5H), 7.33 (m, 2H), 7.19 (m, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.04 (s, 1H), 3.95 (m, 2H), 2.12 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.3, 156.9, 152.1, 150.1, 143.5, 139.8, 139.2, 130.7, 129.9, 129.2, 129.1, 128.7, 128.4, 125.9, 125.7, 124.4, 123.8, 121.1, 118.9, 113.7, 62.1, 13.7, 13.3; IR: ν 3432, 2925, 1642, 1499, 1284, 1163, 1106, 763 cm^{-1}. HRMS. Calcd for $C_{28}H_{23}ClN_3O_3$ [M+H]$^+$: *m/z* 484.1422. Found: *m/z* 484.1427. Anal. Calcd for $C_{28}H_{22}ClN_3O_3$: C, 69.49; H, 4.58; N, 8.68. Found: C, 69.62; H, 4.59; N, 8.65.

Ethyl 4-(3,5-dichloro-2-hydroxyphenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4f) Yellow solid; mp 211–213°C; ^{1}H NMR: δ 8.32 (d, *J* = 8.8 Hz, 2H), 7.75 (m, 2H), 7.49 (m, 6H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.20 (m, 1H), 5.93 (s, 1H), 3.95 (m, 2H), 2.17 (s, 3H), 0.87 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 168.3, 157.2, 150.0, 147.9, 143.2, 139.9, 139.2, 138.7, 129.6, 129.09, 129.05, 128.9, 128.8, 128.4, 125.9, 125.5, 124.8, 123.4, 121.6, 121.0, 113.4, 61.7, 13.7, 13.4; IR: ν: 3424, 2923, 1706, 1640, 1462, 1239, 1150, 1101, 749 cm^{-1}. HRMS. Calcd for $C_{28}H_{22}Cl_2N_3O_3$ [M+H]$^+$: *m/z* 518.1033. Found: *m/z* 518.1047. Anal. Calcd for $C_{28}H_{21}Cl_2N_3O_3$: C, 64.87; H, 4.08; N, 8.11. Found: C, 65.03; H, 4.10; N, 8.08.

Ethyl 4-(2-hydroxy-5-nitrophenyl)-3-methyl-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4g) Yellow solid; mp 216–217°C; ^{1}H NMR: δ 8.17 (m, 4H), 7.67 (m, 2H), 7.45 (m, 5H), 7.25 (m, 1H), 6.82 (m, 1H), 3.89 (m, 2H), 2.08 (s, 3H), 0.82 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.7, 159.7, 157.2, 149.9, 143.3, 140.6, 139.6, 138.9, 138.7, 129.2, 129.0, 128.6, 128.4, 126.5, 126.2, 126.1, 123.5, 122.8, 121.2, 116.2, 113.5, 62.3, 13.5, 13.2; IR: ν 3424, 1690, 1587, 1341, 1284, 1161, 1097, 697 cm^{-1}. HRMS. Calcd for $C_{28}H_{23}N_4O_5$ [M+H]$^+$: *m/z* 495.1663. Found: *m/z* 495.1668. Anal. Calcd for $C_{28}H_{22}N_4O_5$: C, 68.01; H, 4.48; N, 11.33. Found: C, 68.19; H, 4.50; N, 11.30.

Ethyl 4-(2-hydroxyphenyl)-3,6-dimethyl-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4h) Yellow solid; mp 143–145°C; ^{1}H NMR: δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.49 (m, 2H), 7.31 (m, 2H), 7.13–7.10 (m, 1H), 6.98 (m, 2H), 5.82 (s, 1H), 4.09 (m, 2H), 2.75 (s, 3H), 2.02 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 168.8, 156.4, 153.1, 150.0, 143.8, 140.0, 139.1, 130.5, 129.8, 129.0, 125.8, 124.2, 122.6, 121.2, 120.4, 116.4, 113.5, 61.6, 23.9, 13.5, 13.3; IR ν 3434, 2360, 1715, 1642, 1444, 1376, 1234, 1103, 752 cm^{-1}. HRMS. Calcd for $C_{23}H_{22}N_3O_3$ [M+H]$^+$: *m/z* 388.1656. Found: *m/z* 388.1664. Anal. Calcd for $C_{23}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85. Found: C, 71.47; H, 5.47; N, 10.83.

Ethyl 6-ethyl-4-(2-hydroxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4i) Yellow solid; mp 152–153°C; ^{1}H NMR: δ 8.32 (d, *J* = 8.2 Hz, 2H), 7.49 (m, 2H), 7.31 (m, 2H), 7.12 (m, 1H), 6.99 (m, 2H), 5.79 (s, 1H), 4.09 (m, 2H), 3.04 (m, 2H), 2.04 (s, 3H), 1.43 (t, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 168.9, 160.8, 153.1, 150.2, 143.8, 139.7, 139.3, 130.5, 129.9, 128.9, 125.6, 124.0, 122.6, 120.8, 120.4, 116.4, 113.4, 61.6, 29.8, 13.5, 13.3, 13.2; IR: ν 3421, 2972, 1693, 1601, 1443, 1214, 1097, 752 cm^{-1}. HRMS. Calcd for $C_{24}H_{24}N_3O_3$ [M+H]$^+$: *m/z* 402.1812. Found: *m/z* 402.1812. Anal. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.92; H, 5.79; N, 10.44.

Ethyl 4-(2-hydroxyphenyl)-3-methyl-1-phenyl-6-propyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4j) Yellow solid; mp 121–125°C; ^{1}H NMR: δ 8.28 (d, *J* = 7.8 Hz, 2H), 7.47 (m, 2H), 7.25 (m, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.92 (m, 2H), 6.67 (s, 1H), 4.05 (q, *J* = 7.4 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.03 (s, 3H), 1.92 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.1, 159.8, 153.5, 150.0, 143.9, 140.5, 139.2, 130.3, 129.9, 128.9, 125.5, 124.2, 122.6, 120.9, 120.0, 116.0, 113.4, 61.5, 38.5, 22.4, 14.1, 13.5, 13.3; IR: ν 3442, 2366, 1644, 1447, 1248, 1101, 752 cm^{-1}. HRMS. Calcd for $C_{25}H_{26}N_3O_3$ [M+H]$^+$: *m/z* 416.1969. Found: *m/z* 416.1978. Anal. Calcd for $C_{25}H_{25}N_3O_3$: C, 72.27; H, 6.06; N, 10.11. Found: C, 72.41; H, 6.08; N, 10.09.

Ethyl 4-(2-hydroxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*] pyridine-5-carboxylate (4k) Yellow solid; mp 189–190°C; ^{1}H NMR: δ 8.27 (d, *J* = 8.8 Hz, 2H), 7.53 (m, 2H), 7.36 (m, 2H), 7.14 (m, 1H), 6.99 (m, 2H), 5.98 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.10 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 166.8, 153.3, 148.4, 144.2, 143.3 ($^2J_{C\text{-}F}$ = 35.0 Hz), 143.1, 142.7, 138.7, 131.2, 129.9, 129.2, 126.3, 122.3, 121.3 ($^1J_{C\text{-}F}$ = 274.1 Hz), 120.8, 120.5, 117.0, 116.7, 62.5, 29.7, 13.5, 13.3; IR: ν 3429, 2924, 2360, 1711, 1607, 1452, 1189, 751 cm^{-1}. HRMS. Calcd for $C_{23}H_{19}F_3N_3O_3$ [M+H]$^+$: *m/z* 442.1373. Found: *m/z* 442.1384. Anal. Calcd for $C_{23}H_{18}F_3N_3O_3$: C, 62.58; H, 4.11; N, 9.52. Found: C, 62.74; H, 4.12; N, 9.50.

Ethyl (2-hydroxy-4-methoxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo [3,4-*b*]pyridine-5-carboxylate (4l) Yellow solid; mp 211–212°C; ^{1}H NMR: δ 8.26 (d, *J* = 7.8 Hz, 2H), 7.53 (m, 2H), 7.31 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.52 (m, 2H), 6.37 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 2.16 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 167.1, 162.0, 154.5, 148.4, 144.3, 143.3 ($^2J_{C\text{-}F}$ = 34.9 Hz), 142.7, 138.7, 130.6, 129.2, 126.3, 122.7, 121.3 ($^1J_{C\text{-}F}$ = 274.2 Hz), 120.8, 117.5, 113.5, 106.7, 102.3, 62.6, 55.3, 13.6, 13.5; IR: ν 3436, 2994, 2360, 1711, 1622, 1437, 1192, 846, 751 cm^{-1}. HRMS. Calcd for $C_{24}H_{21}F_3N_3O_4$ [M+H]$^+$: *m/z* 472.1479. Found: *m/z* 472.1480. Anal. Calcd for $C_{24}H_{20}F_3N_3O_3$: C, 63.29; H, 4.43; N, 9.23. Found: C, 63.47; H, 4.44; N, 9.20.

Ethyl 4-(5-bromo-2-hydroxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo [3,4-*b*]pyridine-5-carboxylate (4m) Yellow solid; mp 188–190°C; ^{1}H NMR: δ 8.24 (d, *J* = 7.8 Hz, 2H), 7.53 (m, 2H), 7.42 (m, 1H), 7.32 (m, 2H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.64 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.16 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 167.1, 152.8, 148.3, 143.9, 143.3 ($^2J_{C\text{-}F}$ = 34.9 Hz), 141.0, 138.5, 133.9, 132.3, 129.2, 126.5, 123.0, 121.9, 121.2 ($^1J_{C\text{-}F}$ = 274.1 Hz), 120.9, 118.5, 116.7, 112.3, 63.0, 13.6, 13.5; IR: ν 3437, 2360, 1709, 1643, 1396, 1265, 1192, 749 cm^{-1}. HRMS. Calcd for $C_{23}H_{18}BrF_3N_3O_3$ [M+H]$^+$: *m/z* 520.0478. Found: *m/z* 520.0475. Anal. Calcd for $C_{23}H_{17}BrF_3N_3O_3$: C, 53.09; H, 3.29; N, 8.08. Found: C, 53.17; H, 3.30; N, 8.06.

Ethyl 4-(5-chloro-2-hydroxyphenyl)-3-methyl-1-phenyl-6-(trifluoromethyl)-1*H*-pyrazolo [3,4-*b*]pyridine-5-carboxylate (4n) Yellow solid; mp 201–202°C; ^{1}H NMR: δ 8.25 (d, *J* = 7.8 Hz, 2H), 7.53 (m, 2H), 7.32 (m, 2H), 7.15 (m, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.52 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.16 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 166.9, 152.2, 148.3, 143.9, 143.3 ($^2J_{C\text{-}F}$ = 35.0 Hz), 141.0, 138.5, 131.0, 129.5, 129.2, 126.5, 125.4, 122.6, 122.0, 121.2 ($^1J_{C\text{-}F}$ = 274.1 Hz), 120.9, 118.2, 116.7, 62.9, 13.6, 13.5; IR: ν 3440, 2359, 1707, 1642, 1398, 1192, 1135, 751 cm^{-1}. HRMS. Calcd for $C_{23}H_{18}ClF_3N_3O_3$ [M+H]$^+$: *m/z* 476.0983. Found: *m/z* 476.0983. Anal. Calcd for $C_{23}H_{17}ClF_3N_3O_3$: C, 58.05; H, 3.60; N, 8.83. Found: C, 58.21; H, 3.61; N, 8.81.

Ethyl 4-(2-hydroxyphenyl)-1,3,6-triphenyl-1*H*-pyrazolo[3,4-*b*] pyridine-5-carboxylate (4o) Yellow solid; mp 309–310°C; ^{1}H NMR: δ 8.42 (d, *J* = 8.0 Hz, 2H), 7.80 (m, 2H), 7.52 (m, 5H), 7.32 (m, 1H), 7.12 (m, 6H), 6.89 (d, *J* = 6.7 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.64 (m, 1H), 5.96 (s, 1H), 3.89 (q, *J* = 7.1 Hz, 2H), 0.76 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.7, 156.9, 153.1, 150.4, 147.2, 141.1, 140.0, 139.3, 132.0, 130.6, 129.15, 129.06, 128.8, 128.7, 128.4, 127.7, 127.5, 126.2, 124.8, 123.3, 121.5, 120.7, 117.5, 112.9, 62.0, 13.2; IR: ν 3406, 2359, 1701, 1644, 1555, 1257, 755 cm^{-1}. HRMS. Calcd for $C_{33}H_{26}N_3O_3$ [M+H]$^+$: *m/z* 512.1969. Found: *m/z* 512.1970. Anal. Calcd for $C_{33}H_{25}N_3O_3$: C, 77.48; H, 4.93; N, 8.21. Found: C, 77.60; H, 4.94; N, 8.20.

Ethyl 4-(2-hydroxyphenyl)-6-methyl-1,3-diphenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (4p) Yellow solid; mp 311–312°C; ^{1}H NMR: δ 8.36 (d, *J* = 8.2 Hz, 2H), 7.54 (m, 2H), 7.34 (m, 1H), 7.09 (m, 6H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.72 (m, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 5.26 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.80 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ 169.1, 156.2, 152.8, 150.3, 147.0, 139.8, 139.2, 132.0, 130.4, 130.1, 129.0, 128.8, 127.7, 127.4, 126.2, 125.1, 123.0, 121.7, 120.5, 116.4, 112.3, 61.7, 23.9, 13.5; IR: ν 3372, 2359, 1698, 1563, 1500, 1450, 1259, 1142, 755 cm^{-1}. HRMS. Calcd for $C_{28}H_{24}N_3O_3$ [M+H]$^+$: *m/z* 450.1812. Found: *m/z* 450.1812. Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.98; H, 5.17; N, 9.32.

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