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A NOVEL AND EFFICIENT APPROACH TO PYRAZOLO[1,5-*a*]-PYRIDINE DERIVATIVES VIA ONE-POT TANDEM REACTION

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Abstract – An unusual intramolecular condensation of α,β-unsaturated esters with aldehydes was discovered and the pyrazolo[1,5-*a*]pyridine derivatives were conveniently synthesized by this novel tandem reaction under very mild conditions. The reaction mechanism was also proposed.

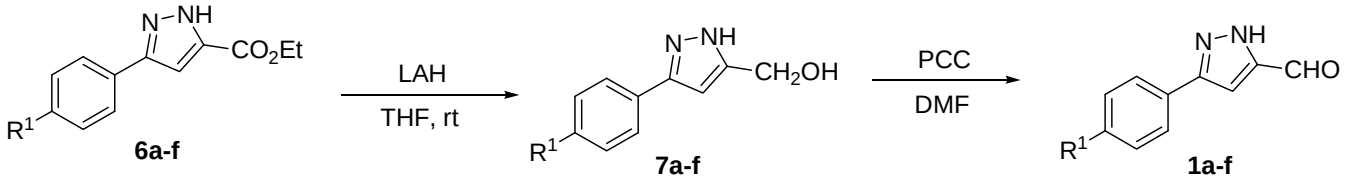
The pyrazolo[1,5-*a*]pyridine derivatives have been of interest for their pharmacological and biological activities. They are used as dopamine D2, D3, D4 receptor antagonist, CRF1 receptor antagonist and nonxanthine adenosine A1 antagonist.[1,2] They are also useful for the treatment of allergic diseases, herpes viral infection and the diseases mediated by MAPKAP-K2 such as inflammatory injury, autoimmune diseases, asteropathia destruens, cancer and growth of tumor.[3,4]

Synthetic approaches to pyrazolo[1,5-*a*]pyridine nucleus are under-represented in the literature.[5] The general method for synthesis of pyrazolo[1,5-*a*]pyridine involves a [3+2] cyclic addition of *N*-aminopyridines with alkynoic esters.[6] This strategy is limited in a number of ways. The low yield in the 1, 3-dipolar cycloaddition is problematic and not compatible with inexpensive synthesis. Besides, aminated pyridines have scarce substitutional availability from commercial sources.

Our previous work[7] prompted us to find a novel method to synthesize the pyrazolo[1,5-*a*]pyridine derivatives. Herein an unusual intramolecular condensation of α,β-unsaturated esters with aldehydes was discovered, and the pyrazolo[1,5-*a*]pyridine derivatives were conveniently synthesized by a novel tandem reaction in mild conditions. The reaction mechanism was also proposed.

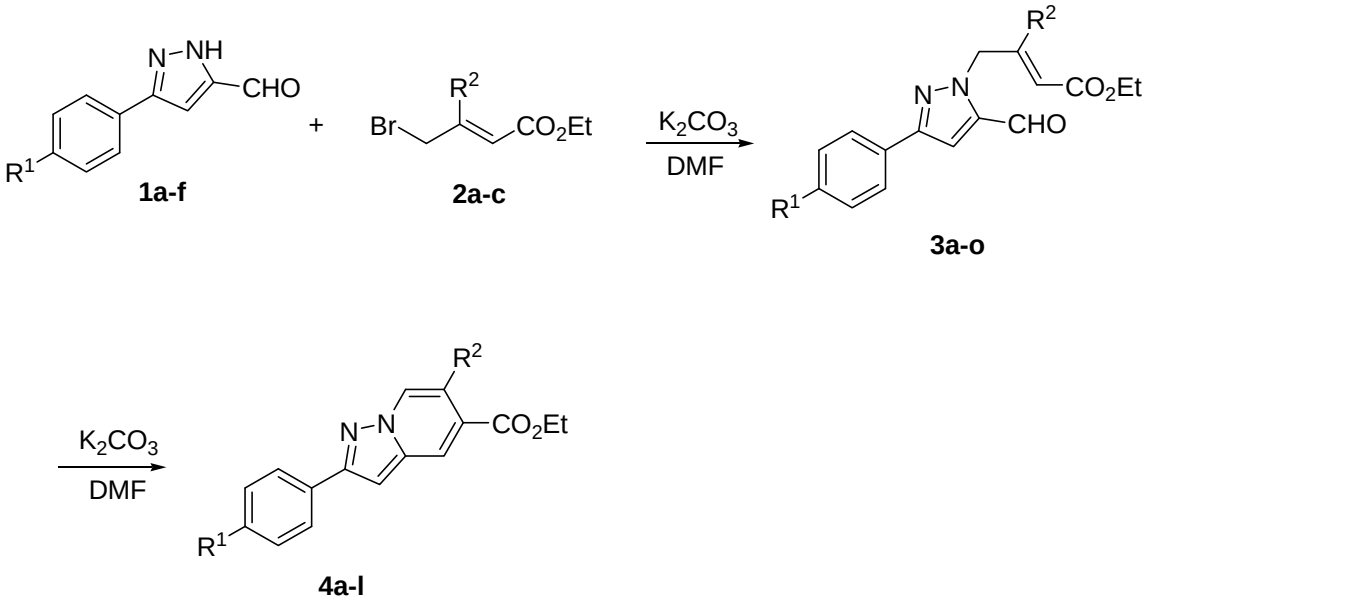
Pyrazoles **6a-f** were prepared according to a literature method.[8] The esters **6a-f** were reduced to alcohols **7a-f** with lithium aluminum hydride followed by oxidation with PCC to yield **1a-f** (Scheme 1). It is well known that the β-carbon of α,β-unsaturated ester is an electrophilic center and can react with a variety of

nucleophiles. The α-carbon of α,β-unsaturated ester is electron-rich relative to the β-carbon, but it is less known that α-carbon is nucleophilic and reacts with electrophiles.



Scheme 1

We investigated the behavior of 1*H*-pyrazole-5-carbaldehyde **1** in a reaction with ethyl (*E*)-4-bromobut-2-enoate **2** in DMF in the presence of potassium carbonate at room temperature. The unexpected product was ethyl *H*-pyrazolo[1,5-*a*]pyridine-5-carboxylate **4a-l** (Scheme 2).



Scheme 2

When R^2 was H or Me, the new annulated compounds **4a-l** were obtained in moderate to good yields (65-82%) as stable solids. However, when R^2 was Cl, we only obtained the products **3m-o** under the same reaction conditions presumably because of the inductive effect. The results of the study are summarized in Table 1. In the light of products **3m-o**, we envisioned that **3** should be the intermediate and could be synthesized through controlling the dosage of potassium carbonate or the reaction time. When 1 equivalent of potassium carbonate was used as a base, we could only get **3j** independent of the reaction time used. While 2 or more equivalents of potassium carbonate were used, we could get **3j** in 2 h, a mixture of **3j** and **4j** in 4 h and **4j** in 6 h. The results are shown in Table 2. The **3j** changed to **4j** (isolated yield 88%) when we subjected it to 1 equivalent of potassium carbonate. Sodium hydroxide was also used

as a base. We obtained a mixture of **3j** and **4j** 10 min later when 1 equivalent of sodium hydroxide was used and also obtained **4j** (isolated yield 48%) in 1 h when 2 equivalents of sodium hydroxide were used. The structures of adducts **3m-o** and **4a-l** were characterized by spectroscopic methods (^{1}H and ^{13}CNMR, IR, and MS). The structure of **4f** was confirmed by X-ray crystallographic analysis as shown in Figure 1.

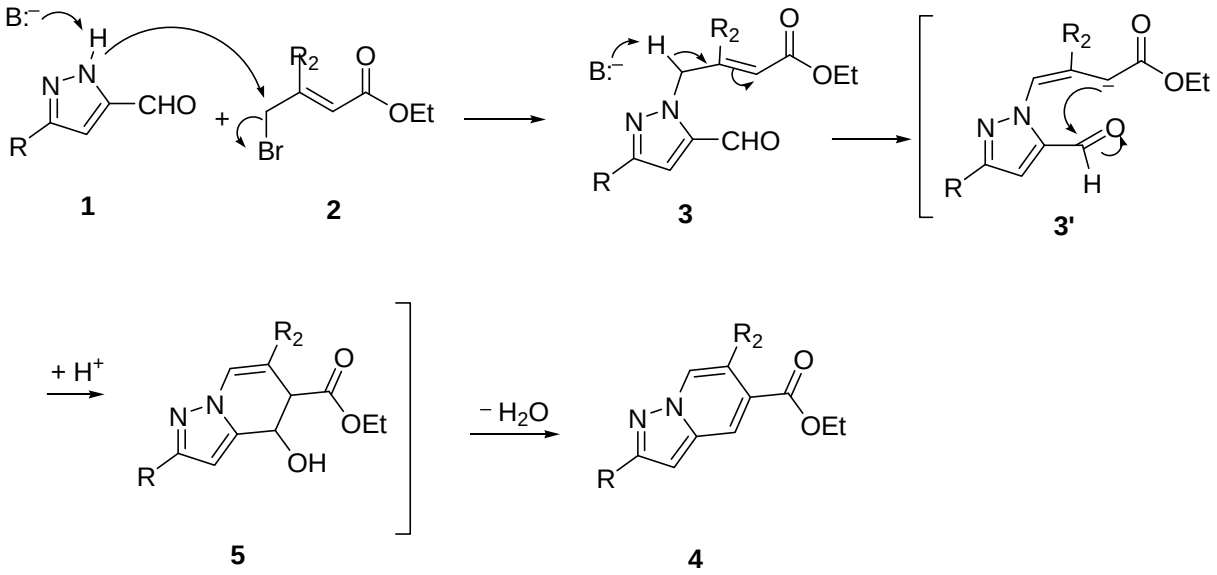
Table 1. Synthesis of pyrazolo[1,5-*a*]pyridine derivatives from pyrazoles

Entry	Pyrazole 1	Crotonate 2	R^1	R^2	Product 3	Product 4	Time (h)	Isolated Yield (%)
1	1a	2a	H	H	-	4a	6	78
2	1a	2b	H	Me	-	4b	6	76
3	1b	2a	F	H	-	4c	6	75
4	1b	2b	F	Me	-	4d	6	76
5	1c	2a	Cl	H	-	4e	6	82
6	1c	2b	Cl	Me	-	4f	6	78
7	1d	2a	Br	H	-	4g	6	70
8	1d	2b	Br	Me	-	4h	6	72
9	1e	2a	Me	H	-	4i	6	75
10	1e	2b	Me	Me	3j	4j	6	69
11	1f	2a	OMe	H	-	4k	6	66
12	1f	2b	OMe	Me	-	4l	6	65
13	1a	2c	H	Cl	3m	-	12	86
14	1c	2c	Cl	Cl	3n	-	12	85
15	1e	2c	Me	Cl	3o	-	12	88

Table 2. Conditions for the synthesis of **3j** and **4j**

Entry	K_2CO_3	Time/h	Product	Isolated Yield
1	1eq	2	3j	70%
2	1eq	36	3j	70%
3	2eq	2	3j	71%
4	2eq	4	3j, 4j	45% (3j), 25% (4j)
5	2eq	6	4j	69%
6	3eq	2	3j	70%
7	3eq	6	4j	68%

On the basis of the above results, we proposed the reaction mechanism as follows: Firstly, an intermolecular S_N2 reaction between 1*H*-pyrazole-5-carbaldehyde **1** and ethyl (*E*)-4-bromobut-2-enoate **2** occurs, and the intermediate **3** is formed. Subsequently, intermediate **3** is deprotonated by the existing base to form a γ-carbanion of the ester, and in turn the electron pair transfers from the γ position to α position. Then the formed β,γ-unsaturated α-carbanion of ester (**3'**) cyclizes with the aldehyde group by intramolecular nucleophilic addition to afford intermediate **5**. The final products **4** can be obtained *in situ* from **5** by eliminating water. The whole process is shown in Scheme 3.



Scheme 3. The Mechanism of the tandem reaction

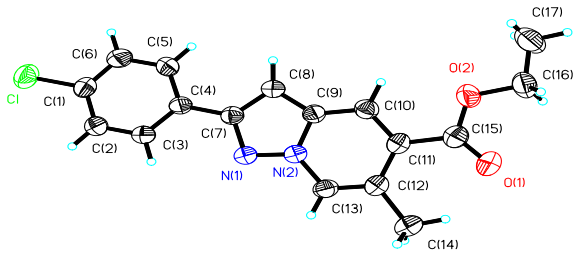


Figure 1. Crystal structure of **4f**

In conclusion, we have described in this paper a novel tandem reaction to prepare pyrazolo[1,5-*a*]pyridine derivatives under mild conditions in good yields. The method can be useful to get access to this class of compounds. A reaction mechanism was also proposed. The compounds 4d, 4f, 4h are particularly interesting molecules due to their fluorescence (in both solution and solid state) and potential biological activity, which will be presented in due course.

EXPERIMENTAL

All reagents and solvents were purchased from Sinopharm Chemical Reagent Co. Ltd and used without further purification unless otherwise noted. Starting materials were prepared according to literatures. Thin-layer chromatography (TLC) was conducted on silica gel 60 F254 plates (Merck KGaA). ^{1}H NMR spectra were recorded on a Bruker Avance 300 (300 MHz) spectrometer, using $CDCl_3$ or DMSO-d_6 as solvents and tetramethylsilane (TMS) as an internal standard. Melting points were determined on an XD-4 digital micro-melting point apparatus and are uncorrected. IR spectra were recorded with an IR spectrophotometer Avtar 370 FT-IR (Termo Nicolet). Elemental analyses were performed on a Vario EL III (Elementar Analysensysteme GmbH) spectroanalyzer. MS spectra were recorded on a Trace DSQ mass spectrometer.

General procedure for the synthesis and analytical data of 7a-f, 3j, 3m-o and 4a-l.

6a-e (1 mmol) was dissolved in THF and LAH (1 mmol) was added at 0 °C portionwise. The resulting mixture was stirred at the same temperature for 2 h and then allowed to warm to rt. The reaction was quenched by adding water before the mixture was partitioned between chloroform and water. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated to afford **7a-f** (yield: 81%-88%). To a 50-mL round-bottomed flask were added **7a-e** (6.0 mmol), powdered pyridinium chlorochromate (2.59 g, 12 mmol) and DMF (10 mL). The mixture was stirred at rt for 3 h. After the staring material was consumed (monitored by TLC), the reaction mixture was poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude products **1a-e** were used in the following step without further purification. To a 50-mL round-bottomed flask were added **1a-e** (6.0 mmol), enoate **2a-c** (7.2 mmol), potassium carbonate (1.60 g, 12.5 mmol) and DMF (10 mL). The mixture was stirred at rt for 2-8 h and then filtered. The filtrate was poured into water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with water (2 x 50 mL), dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed by rotary evaporation. The crude products were purified by column chromatography.

Ethyl (*Z*)-3-chloro-4-(5-formyl-3-phenyl-1*H*-pyrazol-1-yl)but-2-enoate (3m)

Column chromatography (1:10 EtOAc: hexane) yielded a yellow oil. Yield: 86% ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.36-7.84 (m, 5H), 7.26 (s, 1H), 6.29 (s, 1H), 6.09 (s, 2H), 4.28 (q, 2H, J = 7.2 Hz), 1.46 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.7, 164.0, 151.8, 148.6, 141.0, 131.8, 128.8, 128.6, 125.8, 121.7, 111.9, 61.1, 52.7, 14.2. IR (KBr) ν =3126, 3014, 2900, 2885, 1715, 1698, 1556, 1255, 1108, 758cm^{-1}. *Anal.* Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.33; H, 4.75; N, 8.75.

Ethyl (*Z*)-3-chloro-4-(3-(4-chlorophenyl)-5-formyl-1*H*-pyrazol-1-yl)but-2-enoate (3n)

Column chromatography (1:10 EtOAc: hexane) yielded a yellow oil. Yield: 85% ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.77 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.4 Hz) 7.20 (s, 1H), 6.29 (s, 1H), 6.08 (s, 2H), 4.28 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.5, 163.9, 150.8, 148.3, 141.1, 134.4, 130.4, 129.0, 127.1, 121.8, 111.7, 61.1, 52.7, 14.2. IR (KBr) ν =3118, 3009, 2915, 2883, 1722, 1701, 1555, 1246, 1100, 762cm^{-1}. *Anal.* Calcd for $C_{16}H_{14}Cl_2N_2O_3$: C, 54.41; H, 4.00; N, 7.93. Found: C, 54.45; H, 4.01; N, 7.90.

Ethyl (*Z*)-3-chloro-4-(5-formyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)but-2-enoate (3o)

Column chromatography (1:10 EtOAc: hexane) yielded a yellow oil. Yield: 88% ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.72 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.1 Hz) 7.19 (s, 1H), 6.28 (s, 1H), 6.07 (s, 2H), 4.27 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 179.0, 178.9, 163.3, 163.2, 151.2, 148.0, 147.9, 140.2, 140.1, 137.7, 128.7, 128.3, 128.2, 125.0, 120.9, 111.1, 111.0, 60.4, 52.0, 20.6, 13.5. IR (KBr) ν =3202, 3043, 2926, 2855, 1715, 1689, 1567, 1238, 1121, 785cm^{-1}. *Anal.* Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; N, 10.65. Found: C, 61.33; H, 5.13; N, 10.67.

Ethyl 4-(5-formyl-3-(*p*-tolyl)-1*H*-pyrazol-1-yl)-3-methylbut-2-enoate (3j)

Column chromatography (1:10 EtOAc: hexane) yielded a yellow oil. Yield: 70% ^{1}H NMR (300 MHz, $CDCl_3$) (*Z* or *E*): δ 9.90 (s, 1H), 7.72 (d, 2H, *J* = 3.0 Hz), 7.25 (d, 2H, *J* = 3.0 Hz), 7.20 (s, 1H), 5.89 (s, 2H), 5.85 (s, 1H), 4.24 (q, 2H, *J* = 7.2 Hz), 1.35 (t, 3H, *J* = 7.2 Hz). (Z or *E)* δ 9.86 (s, 1H), 7.70 (d, 2H, *J* = 3.0 Hz), 7.22 (d, 2H, *J* =3.0 Hz) 7.20 (s, 1H), 5.20 (s, 2H), 5.25 (s, 1H), 4.10 (q, 2H, *J* =7.2 Hz), 1.23 (t, 3H, *J* =7.2 Hz). IR (KBr) ν =3134, 3013, 2936, 2832, 1725, 1704, 1604, 1559, 1248, 1115, 762cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.22; H, 6.44; N, 8.99.

Ethyl 2-phenylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4a)

White solid: mp 156-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, 1H, *J* =7.2Hz), 7.28 (dd, 1H, *J* = 7.2, 1.8 Hz), 8.36 (d, 1H, *J* = 1.8 Hz), 7.37 (s, 1H), 8.00-8.02 (d, 2H), 7.42-7.53 (m, 3H), 4.36 (q, 2H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 164.4, 153.9, 139.8, 131.9, 128.1, 127.5, 125.8, 124.9, 120.1, 110.2, 96.1, 60.9, 13.6. IR (KBr) ν =3120, 3054, 2973, 2898, 1712, 1529, 1506, 1473, 1455, 1296, 1268, 1254, 1192, 1100, 1083, 762, 753, 690cm^{-1}. ESI-MS *m/z* Calcd: 266.3. Found: 267.3 [M^++1]. *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.26; H, 5.32; N, 10.55.

Ethyl 6-methyl-2-phenylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4b)

White solid: mp 118-119 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.22 (s, 1H), 6.92 (s, 1H), 7.96 (d, 2H, *J* = 7.2 Hz), 7.38-7.48 (m, 3H), 4.40 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz), 2.55 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.3, 153.2, 138.6, 132.2, 128.1, 127.9, 126.9, 125.9, 125.7, 120.7, 120.5, 95.2, 60.6, 18.0, 13.6. IR (KBr) ν = 3121, 2984, 2973, 2928, 1716, 1520, 1471, 1445, 1313, 1262, 1253, 1220, 1183, 1150, 1087, 1051, 776, 767, 701 cm^{-1}. ESI-MS *m/z* Calcd: 280.3. Found: 281.3 [M^++1].

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.96; H, 5.76; N, 9.93.

Ethyl 2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4c)

White solid: mp 117-118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (d, 1H, *J* = 7.5 Hz), 7.34 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz), 8.29 (d, 1H, *J* = 1.8 Hz), 6.95 (s, 1H), 7.95(m, 2H), 7.16 (m, 2H), 4.42 (q, 2H, *J* = 7.2 Hz), 1.44 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.1, 164.9, 153.7, 140.6, 128.9, 128.8, 128.3, 128.2, 128.1, 125.8, 120.8, 116.0, 115.7, 111.0, 96.5, 61.6, 14.3. IR (KBr) ν = 3123, 3051, 2990, 1710, 1600, 1516, 1475, 1270, 1231, 1192, 1101, 1026, 840, 783, 754, 519 cm^{-1}. ESI-MS *m/z* Calcd: 284.3. Found: 285.3 [M^++1]. *Anal.* Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.71; H, 4.60; N, 9.89.

Ethyl 2-(4-fluorophenyl)-6-methylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4d)

Green solid: mp 192-193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.21 (s, 1H), 6.86 (s, 1H), 7.92 (m, 2H), 7.15 (m, 2H), 4.40 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz), 2.55 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.9, 164.7, 161.5, 139.4, 129.2, 129.1, 128.2, 128.1, 127.6, 126.8, 121.3, 115.9, 115.6, 95.6, 61.3, 18.6, 14.3. IR (KBr) ν = 3062, 2980, 2925, 1722, 1606, 1517, 1477, 1448, 1312, 1269, 1232, 1082, 1050, 857, 845, 780, 527 cm^{-1}. ESI-MS *m/z* Calcd: 298.3. Found: 299.3 [M^++1]. *Anal.* Calcd for $C_{17}H_{15}FN_2O_2$: C, 68.45; H, 5.07; N, 9.39. Found: C, 68.52; H, 5.08; N, 9.43.

Ethyl 2-(4-chlorophenyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4e)

White solid: mp 184-185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (d, 1H, *J* = 7.2 Hz), 7.35 (dd, 1H, *J* = 7.2 Hz, 1.2 Hz), 8.30 (d, 1H, *J* = 1.2 Hz), 6.97 (s, 1H), 7.90-7.93 (d, 2H, *J* = 7.2 Hz), 7.43-7.45 (d, 2H, *J* = 7.2 Hz), 4.44 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 164.3, 152.9, 139.9, 133.9, 130.4, 128.3, 128.1, 127.4, 127.0, 125.8, 125.1, 120.1, 110.4, 96.0, 60.9, 13.6. IR (KBr) ν = 3119, 3054, 2987, 2901, 1711, 1602, 1528, 1505, 1475, 1269, 1253, 1192, 1089, 1023, 784, 755 cm^{-1}. ESI-MS *m/z* Calcd: 300.7. Found: 301.7 [M^++1]. *Anal.* Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 63.99; H, 4.37; N, 9.33.

Ethyl 2-(4-chlorophenyl)-6-methylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4f)

White solid: mp 133-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.21 (s, 1H), 6.89 (s, 1H), 7.89 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 4.41 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz), 2.55 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.2, 152.0, 138.7, 133.7, 130.7, 128.3, 127.0, 126.9, 126.2, 120.8, 120.6, 95.2, 60.6, 18.0, 13.6. IR (KBr) ν = 3138, 2981, 2929, 1725, 1520, 1473, 1446, 1407, 1312, 1261, 1222, 1187, 1150, 1083, 1053, 1021, 827, 782, 606 cm^{-1}. ESI-MS *m/z* Calcd: 314.7. Found: 315.7 [M^++1]. *Anal*. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.91; H, 4.93; N, 8.94.

Ethyl 2-(4-bromophenyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4g)

White solid: mp 175-177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (d, 1H, *J* = 7.2 Hz), 7.37 (dd, 1H, *J* = 7.2 Hz, 1.8 Hz), 8.30 (d, 1H, *J* = 1.8 Hz), 6.98 (s, 1H), 7.85 (d, 2H, *J* = 8.7 Hz), 7.60 (d, 2H, *J* = 8.7 Hz),

4.42 (q, 2H, *J* = 7.2 Hz), 1.44 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 164.3, 152.8, 140.0, 131.3, 130.9, 128.1, 127.5, 127.3, 125.8, 125.1, 122.2, 120.1, 110.4, 96.0, 60.9, 13.6. IR (KBr) ν = 3117, 3053, 2984, 2900, 1712, 1596, 1527, 1505, 1474, 1362, 1270, 1253, 1191, 1102, 1023, 783, 754, 507 cm^{-1}. ESI-MS *m/z* Calcd: 345.2. Found: 346.2 [M^++1]. *Anal*. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; N, 8.12. Found: C, 55.74; H, 3.81; N, 8.14.

Ethyl 2-(4-bromophenyl)-6-methylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4h)

Green solid: mp 157-158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.22 (s, 1H,), 6.91 (s, 1H), 7.83 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 4.40 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz), 2.56 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.9, 152.8, 139.4, 131.9, 131.8, 127.9, 127.6, 126.8, 122.6, 121.5, 121.4, 95.9, 61.3, 18.7, 14.3. IR (KBr) ν = 3134, 2978, 2927, 1724, 1612, 1519, 1471, 1457, 1445, 1404, 1311, 1260, 1220, 1186, 1152, 1084, 1020, 1009, 829, 780, 605, 506 cm^{-1}. ESI-MS *m/z* Calcd: 359.2. Found: 359.2 [M^++1]. *Anal.* Calcd for $C_{17}H_{15}BrN_2O_2$: C, 56.84; H, 4.21; N, 7.80. Found: C, 56.89; H, 4.21; N, 7.82.

Ethyl 2-(*p*-tolyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4i)

White solid: mp 158-159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, 1H, *J* = 7.2 Hz), 7.26 (dd, 1H, *J* = 7.2 Hz, 1.8 Hz), 8.34 (d, 1H, *J* = 1.8 Hz), 7.29 (s, 1H), 7.88-7.91 (d, 2H, *J* = 7.2 Hz), 7.30-7.32 (d, 2H, *J* = 7.2 Hz), 4.36 (q, 2H, *J* = 7.2 Hz), 1.36 (t, 3H, *J* = 7.2 Hz), 2.36 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 164.5, 153.9, 139.8, 138.0, 129.1, 128.8, 127.4, 125.7, 124.8, 120.0, 110.0, 95.8, 60.8, 20.7, 13.6. IR (KBr) ν = 3120, 3056, 2983, 1709, 1616, 1530, 1511, 1484, 1316, 1293, 1254, 1182, 1097, 1088, 1007, 825, 777, 758, 512 cm^{-1}. ESI-MS *m/z* Calcd: 280.3 Found: 281.3 [M^++1]. *Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.93; H, 5.75; N, 9.95.

Ethyl 6-methyl-2-(*p*-tolyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4j)

White solid: mp 137-138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.20 (s, 1H), 6.89 (s, 1H), 7.85 (d, 2H, *J* = 8.1 Hz), 7.27 (d, 2H, *J* = 8.1 Hz), 4.39 (q, 2H, *J* = 7.2 Hz), 1.43 (t, 3H, *J* = 7.2 Hz), 2.55 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.3, 153.3, 138.6, 137.8, 129.3, 128.8, 126.9, 125.8, 125.6, 120.6, 120.3, 95.0, 60.5, 20.6, 18.0, 13.6. IR (KBr) ν = 3130, 2979, 2928, 2902, 1708, 1615, 1517, 1477, 1447, 1403, 1310, 1263, 1148, 1088, 1023, 804, 510 cm^{-1}. ESI-MS *m/z* Calcd: 294.3. Found: 295.3 [M^++1]. *Anal*. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.52; H, 6.15; N, 9.50.

Ethyl 2-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine-5-carboxylate (4k)

White solid: mp 144.5-145.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (d, 1H, *J* = 7.2 Hz), 8.27 (d, 1H, J = 1.8 Hz), 7.91 (d, 2H, *J* = 8.7Hz), 7.30 (dd, 1H, *J* = 7.2 Hz, 1.8 Hz), 7.00 (d, 2H, *J* = 8.7 Hz), 6.92 (s, 1H), 4.42 (q, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 1.43 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.2, 160.2, 154.5, 140.6, 128.1, 127.8, 125.6, 125.3, 120.6, 114.2, 110.5, 96.1, 61.5, 55.4, 14.3. IR (KBr) ν =

3116, 3053, 2980, 2957, 2837, 1718, 1614, 1514, 1478, 1305, 1270, 1253, 1180, 1101, 1035, 833, 778, 754 cm^{-1}. ESI-MS *m/z* Calcd: 296.3. Found: 297.3 [M^++1]. *Anal.* Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.97; H, 5.42; N, 9.48.

Ethyl 2-(4-methoxyphenyl)-6-methylpyrazolo[1,5-*a*]pyridine-5-carboxylate (4l)

White solid: mp 135-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.20 (s, 1H), 7.90 (d, 2H, *J* = 8.7 Hz), 6.99 (d, 2H, *J* =8.7Hz), 6.84 (s, 1H), 4.40 (q, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 2.55 (s, 3H), 1.43 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.0, 160.1, 153.7, 139.3, 127.7, 127.6, 126.7, 125.4, 121.1, 121.0, 114.2, 95.2, 61.3, 55.4, 18.6, 14.3. IR (KBr) ν = 3121, 2975, 2929, 1718, 1610, 1521, 1477, 1459, 1439, 1312, 1244, 1177, 1082, 1026, 849, 782 cm^{-1}. ESI-MS *m/z* Calcd: 296.3. Found: 297.3 [M^++1]. *Anal*. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03; O, 15.47 Found: C, 69.71; H, 5.83; N, 9.07.

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