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A NEW METHOD FOR THE SYNTHESIS OF [1,2,4]TRIAZOLO[1,5-*a*]-PYRIDINE DERIVATIVES

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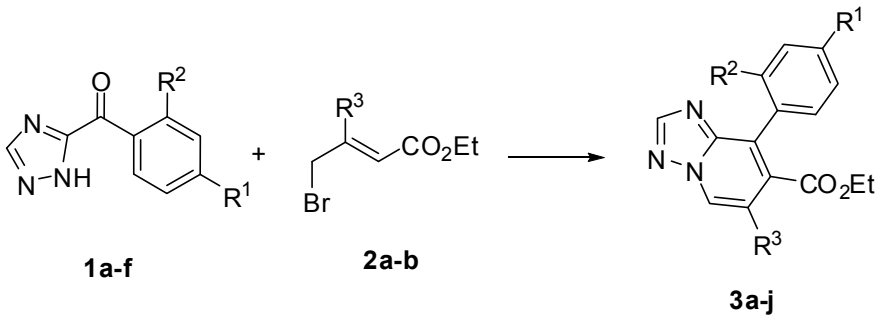
Abstract – [1,2,4]Triazolo[1,5-*a*]pyridine derivatives were conveniently synthesized by tandem reaction under mild conditions. The reaction mechanism was also proposed.

The [1,2,4]triazolo[1,5-*a*]pyridine derivatives are a kind of important heterocyclic compounds which exhibit antifungal, anticancer and anti-inflammatory activity.[1-3] Despite possessing outstanding biological activities, only a few [1,2,4]triazolo[1,5-*a*]pyridines are known. Some commonly used synthetic methods are the annulation of 1,2,4-triazole ring starting with amino substituted pyridines by a multistep procedure.[4] Previously, imidazo[1,5-*a*]pyridines, pyrazolo[1,5-*a*]pyridines, imidazo[1,2-*a*]pyridines and indolizines had been synthesized by a novel tandem reaction in our group.[5-8] Herein we are interested to extend the reaction to synthesize the [1,2,4]triazolo[1,5-*a*]pyridine heterocycles.

1,2,4-triazoles **1a-f** were prepared according to a literature method (Scheme 1)[9] only that we used different reactant. The expected [1,2,4]triazolo[1,5-*a*]pyridine **3a-l** were obtained by the reactions of 1,2,4-triazoles **1a-f** and α,β-unsaturated esters **2a-b** in the presence of K_2CO_3 in dry DMF at room temperature for 6-10 h. The experimental results are collected in Table 1. As observed in Table 1, a variety of substituted 5-benzoyl-1,2,4-triazoles **1** afforded good yields of these products including a variety of electron-donating and electron-withdrawing substituents.



Scheme 1

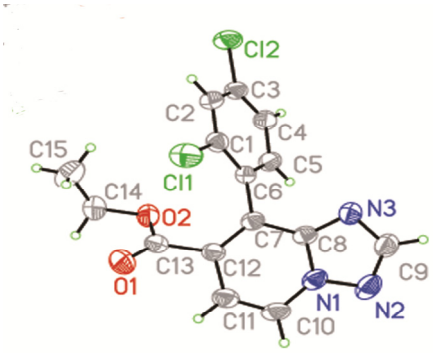


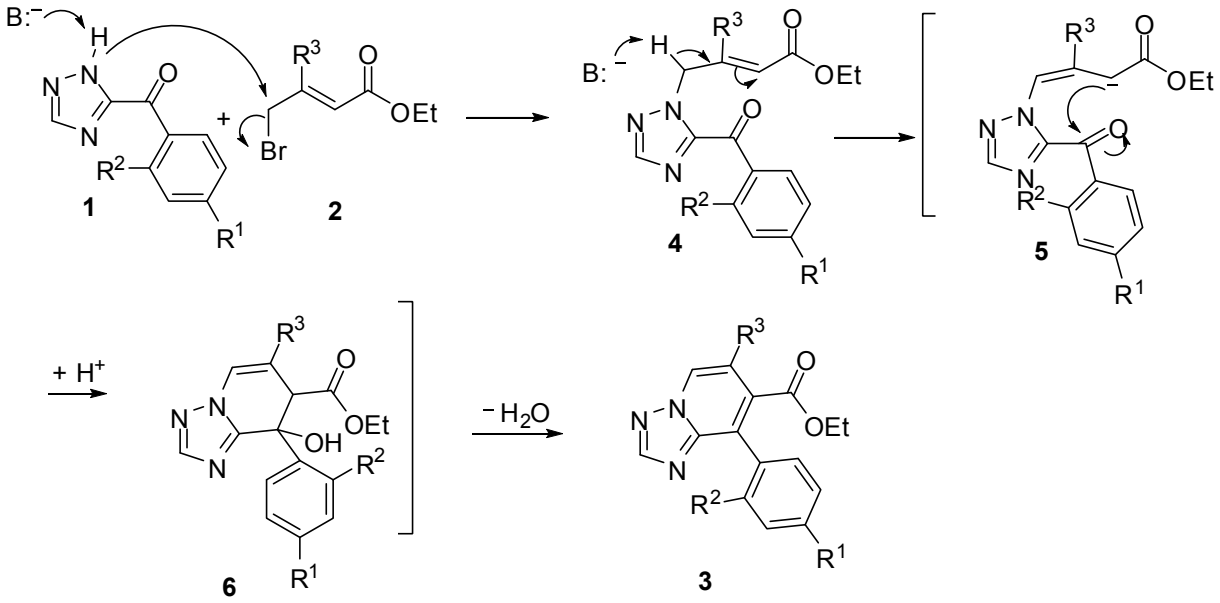
Figure 1. Crystal structure of **3k**

Table 1. Synthesis of [1,2,4]triazolo[1,5-*a*]pyridine derivatives

Entry	R^1	R^2	R^3	Intermediate	Product	Isolated Yield(%)
1	H	H	H	**1a**	**3a**	75
2	H	H	Me	**1a**	**3b**	71
3	Me	H	H	**1b**	**3c**	72
4	Me	H	Me	**1b**	**3d**	69
5	MeO	H	H	**1c**	**3e**	75
6	MeO	H	Me	**1c**	**3f**	70
7	F	H	H	**1d**	**3g**	68
8	F	H	Me	**1d**	**3h**	65
9	H	F	H	**1e**	**3i**	72
10	H	F	Me	**1e**	**3j**	68
11	Cl	Cl	H	**1f**	**3k**	70
12	Cl	Cl	Me	**1f**	**3l**	67

The structures of products **3** were characterized by spectroscopic methods (^{1}H and ^{13}C NMR, IR, and MS). The structure of **3k** was further confirmed by X-ray crystallographic analysis as shown in Figure 1.

In consideration of the result, we proposed the reaction mechanism as follows: Firstly, there would be an intermolecular S_N2 reaction between **1** and α,β-unsaturated esters **2**, through which intermediate **3** was formed. Afterwards, in the presence of K_2CO_3, intermediate **4** was deprotonated to form a γ-carbanion of the ester. In order to be more stable, it would transform to α-carbanion of the ester **5**. Then by intramolecular nucleophilic addition, the α-carbanion reacted with the aldehyde group to obtain intermediate **6**. Afterwards our target product would be gained from **6** by eliminating water. The entire process is shown in Scheme 2.



Scheme 2

In summary, we described a novel tandem reaction to synthesize [1,2,4]triazolo[1,5-*a*]pyridine derivatives under mild conditions in good yields. The reaction mechanism was also proposed. The compounds are particularly interesting molecules due to their 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.[9] 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). MS spectra were recorded on a Trace DSQ mass spectrometer. Elemental analyses were performed on a Vario EL III (Elementar Analysensysteme GmbH) spectroanalyzer.

General procedure for the synthesis and analytical data of 1a-1f

To a 250 mL three-necked, round-bottomed flask, 3.45 g (0.05 mol)1,2,4-triazole and triethylamine (7 mL) were dissolved in pyridine (30 mL) at 0 °C under nitrogen. Then benzoyl chloride (0.1 mol) was added dropwise to the flask. The mixture was stirred for 6 h at rt. After that, sodium hydroxide (0.15 mol) dissolved in 20 mL water was added in the mixture, refluxing for 1.5 h. Then this system was cooled to room temperature and added in water (150 mL), adjusted PH value to 5-6 by using diluted hydrochloric acid. It would precipitate solid compounds. After that, it was filtered and washed with water and ice-cold EtOAc. The crude intermediates were depurated by column chromatography.

Phenyl(1*H*-1,2,4-triazol-5-yl)methanone (1a)[10]

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.83 (s, 1H), 8.83 (s, 1H), 7.57-7.84 (m, 5H). ESI-MS *m/z* Calcd: 173.1. Found: 174.1 [M^++1].

***p*-Tolyl(1*H*-1,2,4-triazol-5-yl)methanone (1b)**

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.82 (s, 1H), 8.81 (s, 1H), 7.82-7.85 (m, 2H), 7.29-7.32 (m, 2H), 2.37 (s, 3H). ESI-MS *m/z* Calcd: 187.1. Found: 188.1 [M^++1]. *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.22; H, 4.91; N, 22.49.

(4-Methoxyphenyl)(1*H*-1,2,4-triazol-5-yl)methanone (1c)[10]

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.80 (s, 1H), 8.80 (s, 1H), 7.87-7.92 (m, 2H), 7.00-7.03 (m, 2H), 3.82 (s, H). ESI-MS *m/z* Calcd: 203.1. Found: 204.1 [M^++1].

(4-Fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methanone (1d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.93 (s, 1H), 8.71 (s, 1H), 8.39-8.43 (m, 2H), 7.38-7.45 (m, 2H). ESI-MS *m/z* Calcd: 191.1. Found: 192.1 [M^++1]. *Anal.* Calcd for $C_9H_6FN_3O$: C, 56.55; H, 3.16; N, 21.98. Found: C, 56.59; H, 3.20; N, 21.98.

(2-Fluorophenyl)(1*H*-1,2,4-triazol-5-yl)methanone (1e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.86 (s, 1H), 8.74 (s, 1H), 7.70-7.81 (m, 1H), 7.67-7.69 (m, 1H), 7.33-7.39 (m, 2H). ESI-MS *m/z* Calcd: 191.1. Found: 192.1 [M^++1]. *Anal.* Calcd for $C_9H_6FN_3O$: C, 56.55; H, 3.16; N, 21.98. Found: C, 56.57; H, 3.22; N, 22.04.

(2,4-Dichlorophenyl)(1*H*-1,2,4-triazol-5-yl)methanone (1f) [10]

^{1}H NMR (300 MHz, $CDCl_3$): δ 14.89 (s, 1H), 8.76 (s, 1H), 7.78-7.79 (m, 1H), 7.69-7.71 (m, 1H), 7.57-7.60 (m, 1H). ESI-MS *m/z* Calcd: 241.0. Found: 242.0 [M^++1].

General procedure for the synthesis and analytical data of 3a-3l

Intermediate **1** (6 mmol), α,β-unsaturated esters (12 mmol), potassium carbonate (1.8 g, 13.2 mmol) and DMF (30 mL) were added to a 100 mL round-bottomed flask. The reaction system was stirred for 6-10 h. Then the mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (3 x 50 mL). Organic layers were combined and dried over anhydrous Na_2SO_4, then filtered. By rotary evaporation, the mixture was concentrated. After that, these crude products were depurated by using column chromatography.

Ethyl 8-phenyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3a)

Yellow solid: mp 77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, 1H, *J* = 6.9 Hz), 8.41 (s, 1H), 7.48-7.50 (m, 6H), 4.10-4.17 (q, 2H, *J* = 7.2 Hz), 0.98-1.02 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.9, 155.6, 150.9, 134.6, 131.4, 129.7, 129.4, 128.8, 127.6, 114.8, 77.9, 77.5, 77.1, 62.3, 14.0. IR (KBr) ν = 3112, 3068, 2925, 1712, 1536, 1486, 1366, 1324, 1257, 1183, 1124, 767, 657 cm^{-1}. ESI-MS *m/z* Calcd: 267.1. Found: 268.1 [M^++1]. *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.38; H, 4.94; N, 15.74.

Ethyl 6-methyl-8-phenyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3b)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.33 (s, 1H), 7.55-7.59 (m, 2H), 7.44-7.51 (m, 3H), 4.10-4.17 (q, 2H, *J* = 7.2 Hz), 2.44 (s, 3H), 0.97-1.02 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.0, 154.4, 148.8, 135.1, 133.3, 129.1, 128.5, 128.3, 126.1, 121.4, 77.4, 77.0, 76.6, 61.8, 16.7, 13.6. IR (KBr) ν = 3101, 3061, 2981, 2928, 1229, 1498, 1323, 1241, 1185, 1141, 788, 699 cm^{-1}. ESI-MS *m/z* Calcd: 281.1. Found: 282.1 [M^++1]. *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.34; H, 5.35; N, 14.99.

Ethyl 8-*p*-tolyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3c)

Yellow oil. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.61 (d, 1H, *J* = 7.2 Hz), 8.39 (s, H), 7.46 (d, 1H, *J* = 7.2 Hz), 7.39-7.41 (m, 2H), 7.27-7.31 (m, 2H), 4.13-4.20 (q, 2H, *J* = 7.2 Hz), 2.43 (s, 3H), 1.03-1.08 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.5, 155.0, 150.5, 138.8, 131.9, 131.1, 130.6, 129.1, 126.9, 114.3, 77.4, 77.0, 76.6, 61.8, 21.4, 13.6. IR (KBr) ν = 3110, 2981, 2922, 1718, 1492, 1324, 1258, 1180, 1134, 820, 758 cm^{-1}. ESI-MS *m/z* Calcd: 281.1. Found: 282.1 [M^++1]. *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.30; H, 5.35; N, 14.98.

Ethyl 6-methyl-8-*p*-tolyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3d)

Yellow solid: mp 115-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.31 (s, 1H), 7.46-7.49 (m, 2H), 7.27-7.30 (m, 2H), 4.13-4.20 (q, 2H, *J* = 7.2 Hz), 2.41-2.43 (m, 6H), 1.03-1.08 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.1, 154.4, 149.0, 139.0, 134.8, 130.6, 129.1, 128.3, 125.9, 121.4, 77.5, 77.0, 76.6, 61.8, 21.4, 16.7, 13.7. IR (KBr) ν = 3103, 2963, 2926, 1727, 1609, 1500, 1434, 1322, 1250, 1181, 1140, 831, 665 cm^{-1}. ESI-MS *m/z* Calcd: 295.1. Found: 296.1 [M^++1]. *Anal.* Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.20; H, 5.85; N, 14.29.

Ethyl 8-(4-methoxyphenyl)[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3e)

Yellow solid: mp 99-101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, H, *J* = 6.9 Hz), 8.41 (s, 1H), 7.44-7.49 (m, 3H), 7.02-7.05 (m, 2H), 4.15-4.22 (q, 2H, *J* = 7.2 Hz), 3.87 (s, 3H), 1.06-1.11 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.2, 160.7, 155.4, 151.0, 131.8, 131.2, 131.1, 127.2, 126.6, 114.6, 77.9, 77.5, 77.1, 62.3, 55.9, 14.2. IR (KBr) ν = 3747, 3674, 2922, 2850, 1716, 1650, 1558, 1509, 1458, 1385, 1325, 1116, 839, 760 cm^{-1}. ESI-MS *m/z* Calcd: 297.1. Found: 298.1 [M^++1]. *Anal.* Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.67; H, 5.12; N, 14.19.

Ethyl 8-(4-methoxyphenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3f)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.32 (s, 1H), 7.52-7.57 (m, 2H), 6.99-7.04 (m, 2H), 4.16-4.22 (q, 2H, *J* = 7.2 Hz), 3.86 (s, 3H), 2.42 (s, 3H), 1.06-1.11 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.2, 160.2, 154.3, 149.0, 134.7, 130.6, 127.9, 125.8, 121.4, 114.1, 77.4, 77.0, 76.6, 61.8, 55.4, 16.7, 13.8. IR (KBr) ν = 3748, 3673, 2824, 2854, 1717, 1650, 1558, 1506, 1459, 1385, 1324, 1117, 720 cm^{-1}. ESI-MS *m/z* Calcd: 311.1. Found: 312.1 [M^++1]. *Anal.* Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.54; H, 5.52; N, 13.56.

Ethyl 8-(4-fluorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3g)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (d, 1H, *J* = 7.2 Hz), 8.40 (s, 1H), 7.47-7.52 (m, 3H), 7.17-7.23 (m, 3H), 4.14-4.21 (q, 2H, *J* = 7.2 Hz), 1.05-1.10 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.8, 161.5, 155.1, 150.5, 131.5, 131.1, 130.7, 130.4, 127.3, 114.3, 77.4, 77.0, 76.6, 61.9, 13.8. IR (KBr) ν = 3112, 2925, 2853, 1719, 1603, 1493, 1368, 1326, 1233, 1180, 839, 760 cm^{-1}. ESI-MS *m/z* Calcd: 285.1. Found: 286.1 [M^++1]. *Anal.* Calcd for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; N, 14.73. Found: C, 63.14; H, 4.30; N, 14.79.

Ethyl 8-(4-fluorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3h)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.32 (s, 1H), 7.52-7.57 (m, 2H), 6.99-7.04 (m, 2H), 4.15-4.22 (q, 2H, *J* = 7.2 Hz), 3.86 (s, 3H), 1.06-1.11 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.2, 160.2, 154.3, 149.0, 134.7, 130.6, 127.9, 125.8, 121.4, 114.1, 77.4, 77.0, 76.6, 61.8, 16.7, 12.9. IR (KBr) ν = 2924, 2854, 1721, 1602, 1495, 1458, 1321, 1246, 1142, 841 cm^{-1}. ESI-MS *m/z* Calcd: 299.1. Found: 300.1 [M^++1]. *Anal.* Calcd for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.71; N, 14.04. Found: C, 64.24; H, 4.70; N, 14.09.

Ethyl 8-(2-fluorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3i)

Yellow solid: mp 120-122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, 1H, *J* = 7.2 Hz), 8.43 (s, 1H), 7.40 (d, 1H, *J* = 7.2 Hz), 7.45-7.54 (m, 2H), 7.17-7.34 (m, 2H), 4.17-4.24 (q, 2H, *J* = 7.2 Hz), 1.05-1.10 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.7, 161.8, 158.5, 155.7, 150.8, 131.4, 126.5, 124.5, 122.6, 115.8, 77.9, 77.5, 77.1, 62.4, 14.0. IR (KBr) ν = 3446, 2925, 2853, 1702, 1651, 1540, 1457, 1324, 1254, 757 cm^{-1}. ESI-MS *m/z* Calcd: 285.1. Found: 286.1 [M^++1]. *Anal.* Calcd for $C_{15}H_{12}FN_3O_2$: C, 63.15; H, 4.24; N, 14.73. Found: C, 63.17; H, 4.20; N, 14.79.

Ethyl 8-(2-fluorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3j)

Yellow solid: mp 135-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.33 (s, 1H), 7.39-7.50 (m, 2H), 7.18-7.28 (m, 2H), 4.10-4.17 (q, 2H, *J* = 7.2 Hz), 2.47 (s, 3H), 0.97-1.02 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.2, 161.6, 158.3, 154.6, 148.6, 131.1, 127.0, 124.2, 121.6, 115.9, 77.4, 77.0, 76.6, 61.8, 16.9, 13.6. IR (KBr) ν = 3443, 2924, 2854, 1718, 1651, 1540, 1500, 1457, 1328, 1260, 758 cm^{-1}. ESI-MS *m/z* Calcd: 299.1. Found: 300.1 [M^++1]. *Anal.* Calcd for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.71; N, 14.04. Found: C, 64.23; H, 4.74; N, 14.05.

Ethyl 8-(2,4-dichlorophenyl)[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3k)

Yellow solid: mp 96-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H, *J* = 7.2 Hz), 8.40 (s, 1H), 7.68-7.71 (d, 1H, *J* = 7.2 Hz), 7.55-7.60 (m, 1H), 7.39-7.42 (m, 1H), 7.26-7.32 (m, 1H), 4.26-4.33 (q, 2H, *J* = 7.2 Hz), 1.08-1.13 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 164.5, 155.3, 150.1, 135.4, 134.0, 132.3, 131.3, 129.5, 127.2, 114.3, 77.4, 77.0, 76.6, 62.1, 13.6. IR (KBr) ν = 3119, 2982, 1724, 1588, 1467, 1322, 1240, 1120, 863, 751 cm^{-1}. ESI-MS *m/z* Calcd: 335.0. Found: 336.0 [M^++1]. *Anal.* Calcd for $C_{15}H_{11}Cl_2N_3O_2$: C, 53.59; H, 3.30; N, 12.50. Found: C, 53.64; H, 3.33; N, 12.54.

Ethyl 8-(2,4-dichlorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine-7-carboxylate (3l)

Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.32 (s, 1H), 7.56-7.57 (m, 1H), 7.34-7.38 (m, 1H), 7.27-7.30 (m,1H), 4.11-4.18 (q, 2H, *J* = 7.2 Hz), 2.48 (s, 3H), 1.01-1.06 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 165.8, 154.7, 148.2, 135.8, 134.8, 131.8, 131.4, 129.7, 127.2, 121.5, 77.5, 77.1, 76.7, 61.9, 17.0, 13.7. IR (KBr) ν = 3093, 2918, 1729, 1589, 1501, 1322, 1241, 1142, 863, 781 cm^{-1}. ESI-MS *m/z* Calcd: 349.0. Found: 350.0 [M^++1]. *Anal.* Calcd for $C_{16}H_{13}Cl_2N_3O_2$: C, 54.87; H, 3.74; N, 12.00. Found: C, 54.84; H, 3.76; N, 12.05.

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REFERENCES (AND NOTES)

1. Y. Luo and Y. Hu, *Arch. Pharm. Chem. Life Sci.*, 2006, **339**, 262.
2. T. Liu and Y. Hu, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2411.
3. S. P. East, C. B. White, O. Barker, S. Barker, J. Bennett, D. Brown, E. A. Boyd, C. Brennan, C. Chowdhury, I. Collins, E. Convers-Reignier, B. W. Dymock, R.Fletcher, D. J. Haydon, M. Gardiner, S. Hatcher, P. Ingram, P. Lancett, P. Mortenson, K. Papadopoulos, C. Smee, H. B. Thomaides-Brears, H. Tye, J. Workman, and L. G. Czaplewski, *Bioorg. Med. Chem. Lett.*, 2009, **19**,

894.

4. G. Jones and D. R. Sliskovic, *Adv. Heterocycl. Chem.*, 1983, **34**, 86.
5. J. W. Wang, J. Jia, D. J. Hou, H. M. Li, and J. Yin, *Chin. J. Org. Chem.*, 2003, **23**, 173.
6. Y. Q. Ge, J. Jia, Y. Li, L. Yin and J. W. Wang, *Heterocycles*, 2009, **78**, 197.
7. Y. Q. Ge, J. Jia, H. Yang, G. L. Zhao, F. X. Zhan, and J. W. Wang, *Heterocycles*, 2009, **78**, 725.
8. J. Jia, Y. Q. Ge, X. T. Tao, and J. W. Wang, *Heterocycles*, 2010, **81**, 185.
9. L. A. M. Bastiaansen and E. F. Godefroi, *Synthesis*, 1978, 675.
10. S. Ohta, I. Kawasaki, A. Fukuno, M. Yamashita, T. Tada, and T. Kawabata, *Chem. Pharm. Bull.*, 1993, **41**, 1226.