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PAPER

Copper(I) acetate-catalyzed azide–alkyne cycloaddition for highly efficient preparation of 1-(pyridin-2-yl)-1,2,3-triazoles†

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A highly efficient copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) of 6-substituted tetrazolo-[1,5-*a*]pyridines was developed for the preparation of 1-(pyridin-2-yl)-1,2,3-triazoles by simply using copper(I) acetate as a catalyst. The *in situ* formed HOAc played important dual roles and an activation of 2-azidopyridine–copper(I) complex was observed.

Introduction

Many derivatives of 1-(pyridin-2-yl)-1,2,3-triazole (**1**) (Fig. 1) have been used as intermediates[1] in organic synthesis or as ligands[2] in coordination compounds and have shown biologically important properties.[3] In the literature, they were usually prepared by base-promoted substitution between 1,2,3-triazole and 2-halopyridine[4] or by thermal 1,3-dipolar cycloaddition[5] and other multi-step procedures.[6] Although copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has proven to be the most efficient method for the preparation of 1,2,3-triazoles[7] and many 1,2,3-triazoles substituted by *N*-containing heterocyclics have been prepared,[8] the low efficiency was observed for CuAAC of 2-azidopyridines (**2**) even by using the most popular catalytic system $CuSO_4{\cdot}5H_2O$/NaAsc.[9] Only recently, the first article[9a] dealing with the CuAAC methodology of 2-azidopyridines (**2**) was published. This phenomenon may be caused by three factors: (a) the substrate 2-azidopyridine (**2**) naturally occurs as its ring-tautomer tetrazolo[1,5-*a*]pyridines (**3**) in the solid state[10] and as a chain–ring tautomeric equilibrium between **2** and **3** in solution; (b) the pyridine in the key intermediate 5-cupuric 1,2,3-triazole may coordinate with Cu(I) to form the complex **4**, which will lead to difficult protonation of the C–Cu bond; (c) the product **1** may also coordinate with Cu(I) to form the complex **5**,[2] by which the catalytic cycle of Cu(I) will be retarded.

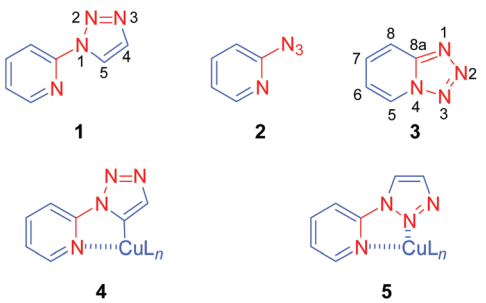
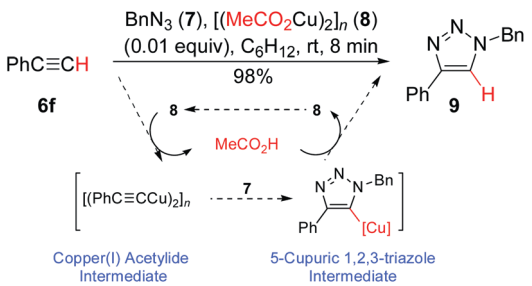


Fig. 1 2-Azidopyridine and its tautomer as well as its CuAAC product and proposed intermediates.

Investigation showed that the chain–ring tautomeric equilibrium between **2** and **3** mostly depended upon the substituent and its position on the pyridine ring. The early studies proved that the chain tautomer **2** benefited from 6-substituted electron-withdrawing groups on tetrazolo[1,5-*a*]pyridine (**3**).[9a,10] Recently, we developed a novel CuAAC strategy, in which the protonation of the key intermediate 5-cupuric 1,2,3-triazole was remarkably promoted by carboxylic acid.[11] As shown in Scheme 1, when the mixture of **6f** and **7** was treated with copper(I) acetate (**8**, as a polymeric dinuclear complex) for 8 min, 1,2,3-triazole **9** was obtained in 98% yield, in which HOAc was produced *in situ*.[11d,e]

Therefore, we hypothesized that a highly efficient CuAAC of tetrazolo[1,5-*a*]-pyridines (**3**) bearing 6-substituted electron-withdrawing groups may be achieved by using copper(I) acetate (**8**) as a catalyst because the *in situ* formed HOAc may play dual roles to promote the protonation of complex **4** and prevent the formation of complex **5**.



Scheme 1

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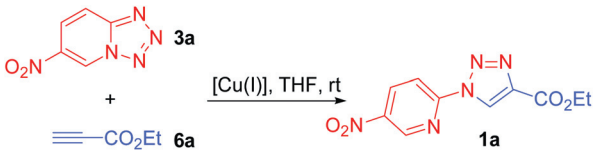
Table 1 Effects of copper(I) sources on CuAAC[a]



Entry	[Cu] (0.025 equiv)	Time (min)	Yield of **1a**[b] (%)
1	—	60	0
2	CuCl	60	37
3	CuBr	60	50
4	CuI	60	21
5[c]	$CuSO_4·5H_2O$/NaAsc	20	71
6	$[(CuOAc)_2]_n$	10	84

[a] The mixture of **3a** (1.1 mmol), **6a** (1.0 mmol) and catalyst (0.025 mmol) in THF (1 mL) was stirred at room temperature. [b] The isolated yields were obtained. [c] The mixture of THF–H_2O (1 : 1) was used as a solvent.

Results and discussion

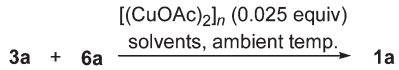
Among the well-studied 6-substituted tetrazolo[1,5-*a*]pyridines (**3**), 6-NO_2 (**3a**) and 6-CO_2R (**3b**) derivatives are two desired candidates due to their relatively high proportions of chain tautomers in aprotic solvents[10c,d] and their preparations are also relatively easier than others. To quickly scan the reaction conditions, the CuAAC of 6-nitro-tetrazolo[1,5-*a*]pyridine (**3a**) and the high active dipolarophile ethyl propynoate (**6a**) was employed as a model reaction.

As shown in Table 1, no expected ethyl 1-(5-nitropyridin-2-yl)-1*H*-[1,2,3]-triazole-4-carboxylate (**1a**) was produced in the absence of Cu(I) species (entry 1). By using different copper(I) halides as the catalyst (entries 2–4), CuBr showed the highest catalytic activity to give **1a** in 50% yield. As was expected, the cycloaddition catalyzed by $CuSO_4·5H_2O$/NaAsc finished within 20 min to give **1a** in 71% yield (entry 5), because the *in situ* formed HAsc is, in fact, a vinylogous carboxylic acid with pK_a values of 4.10 and 11.79, respectively (pK_a value of acetic acid is 4.76). To our delight, the same reaction finished within 10 min to give **1a** in 84% yield by using copper(I) acetate (**8**) as a catalyst (entry 6).

Then, the solvents were screened by using $[(CuOAc)_2]_n$ (**8**) as a catalyst. As shown in Table 2, the protonic solvent EtOH showed negative effects on the reaction (entry 1), which may be caused by the fact that the proportion of chain-tautomer was decreased.[10c,d] However, all other aprotic solvents gave satisfying results (entries 2–5). THF gave the highest yield (entry 3) and CH_2Cl_2 gave the shortest reaction time (entry 5). Finally, THF was chosen for our purpose because it was a good solvent for substrates and product.

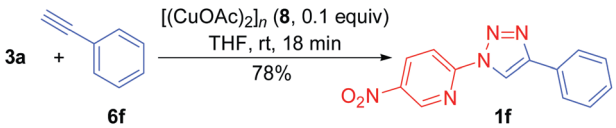
Unfortunately, when the low activity dipolarophile phenylethyne (**6f**) was used as a substrate, its cycloaddition with **3a** could not finish within 24 h when using 0.025 equivalents of $[(CuOAc)_2]_n$ (**8**). But this problem was easily resolved by using 0.1 equivalents of $[(CuOAc)_2]_n$ (**8**) and the desired product 5-nitro-2-(4-phenyl-[1,2,3]triazol-1-yl)-pyridine (**1f**) was obtained in 78% yield after 18 min (Scheme 2).

Table 2 Effects of solvents on CuAAC[a]

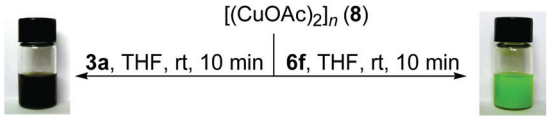


Entry	Solvent	Time (min)	Yield of **1a**[b] (%)
1	EtOH	60	37
2	$CHCl_3$	15	80
3	THF	10	84
4	PhMe	6	80
5	CH_2Cl_2	5	81

[a] The mixture of **3a** (1.1 mmol), **6a** (1.0 mmol) and catalyst $[(CuOAc)_2]_n$ (**8**, 0.025 mmol) in solvent (1 mL) was stirred at ambient temperature. [b] The isolated yields were obtained.



Scheme 2

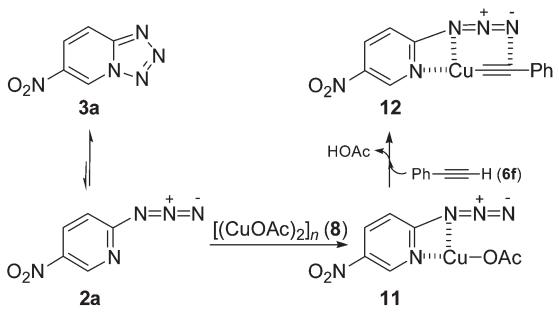


Scheme 3

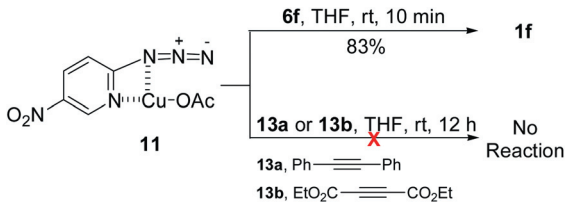
Interestingly, we found that the efficiency of the procedure in Scheme 2 completely depended upon the addition sequence of the substrates. For example, by addition of **6f** to the mixture of **3a** and $[(CuOAc)_2]_n$ (**8**) in THF, the desired **1f** was obtained in 78–83% yield after around 10–18 min. However, the same reaction took for 2 h (72%) by addition of **3a** to the mixture of **6f** and $[(CuOAc)_2]_n$ (**8**) in THF. As shown in Scheme 3, the mixture of **3a**/**8** gave a deep-brown suspension, while the mixture of **6f**/**8** gave a light-yellow suspension when they stood at room temperature for more than 3 min.

The light-yellow suspension was easily assigned to be $[(PhC{\equiv}CCu)_2]_n$, however the deep-brown suspension could not be assigned because it could not afford a stable coordination compound after the solvent was evaporated off. As shown in Scheme 4, we proposed that this suspension may contain a coordination compound **11** produced from **3a** and $[(CuOAc)_2]_n$ (**8**) based on its IR spectrum and elemental analysis results. Then, **11** reacted with **6f** to form a bis-functional complex **12** including the required copper(I) acetylide and azide, by which an intramolecular CuAAC occurs easily. This may be the reason that the deep-brown suspension facilitated to the cycloaddition. In contrast, once the light-yellow intermediate $[(PhC{\equiv}CCu)_2]_n$ was formed, it will take a regular intermolecular CuAAC. Thus, this CuAAC actually was activated by 2-azidopyridine–Cu(I) complex (**11**).

We observed that the most reactive deep-brown suspension could be prepared by mixing **3a** and $[(CuOAc)_2]_n$ (**8**) in THF for 10 min. Further tests proved that it could be also prepared easily



Scheme 4



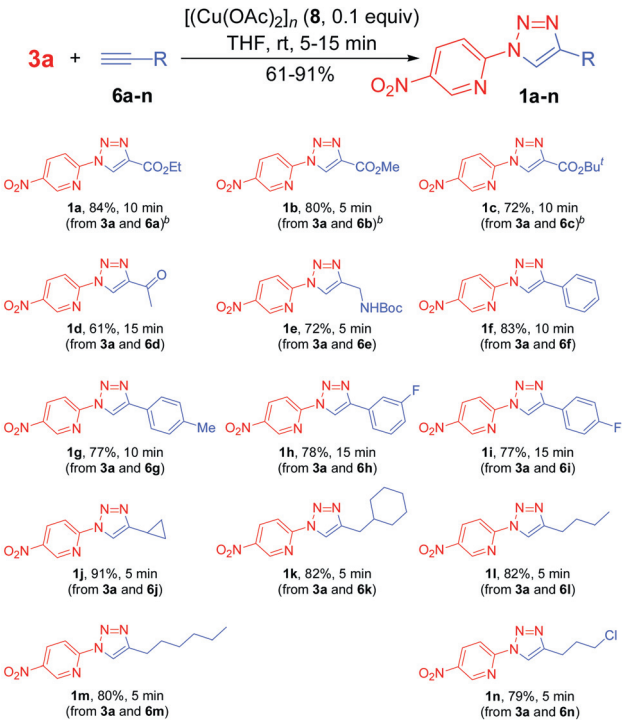
Scheme 5

by treatment of the solution of **3a** and $[(CuOAc)_2]_n$ (**8**) with ultrasonication for 1 min. As shown in Scheme 5, the product **1f** was obtained in 83% yield by using this procedure within 10 min. Unfortunately, no CuAAC occurred when the internal alkynes diphenylacetylene (**13a**) and diethyl acetylenedicarboxylate (**13b**) were used as dipolarophiles, even at the boiling temperature of THF for 2 h. This result strongly indicated that the terminal acetylene is an essential substrate and the hypothesis of intermediate **12** was supported.

To generalize this method, the cycloadditions of **3a** with different acetylenes (**6a–6n**) were tested. As shown in Scheme 6, the highly active dipolarophiles propynoates **6a–6c** gave satisfying results with low-loading of $[(CuOAc)_2]_n$ (**8**, 0.025–0.05 equiv.) even without the help of ultrasonication. However, it was better to use 0.1 equivalent of $[(CuOAc)_2]_n$ for all other acetylenes (**6d–6n**) for short reaction time and high quality of products. Under these standard conditions, the cycloadditions usually finished within minutes to give desired products (**1a–1n**) in moderate to excellent yields.

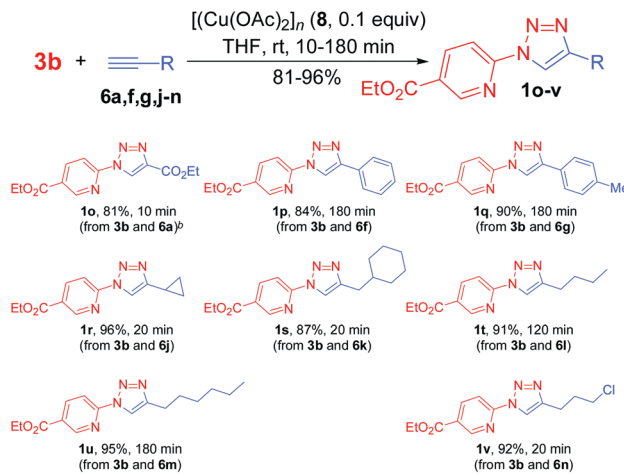
We found that this procedure also worked well for the substrate ethyl tetrazolo[1,5-*a*]pyridine-6-carboxylate (**3b**). Although the preparation and purification of **3b** was less convenient than **3a**, however, its CuAAC usually gave clean products **1o–1v** in moderate to excellent yields (Scheme 7).

We also tried to extend the method for other tetrazoles, such as **3c–3i**. As shown in Fig. 2, although 6-nitro-7-methyl-tetrazolo[1,5-*a*]pyridine (**3c**) could afford a good yield of product **1w** with the help of ultrasonication, it also worked well under heating conditions. Similarly, 6-cyano-tetrazolo[1,5-*a*]pyridine (**3d**), 6,8-dichloro-tetrazolo[1,5-*a*]pyridine (**3e**), even tetrazolo [1,5-*a*]pyrazine (**3f**) were smoothly converted into the corresponding products **1x**, **1y** and **1z** in moderate to excellent yields in boiling THF. Unfortunately, tetrazolo[1,5-*a*]pyrimidine (**3g**) seemed to decompose easily in the presence of $[Cu(OAc)_2]_n$ (**8**) and could not afford the desired product from 0 °C to the boiling temperature of THF. As was expected, both tetrazolo[1,5-*a*]



[a]Isolated yields were obtained. [b]0.025 equiv of $[(CuOAc)_2]_n$ (**8**) were used.

Scheme 6



[a]Isolated yields were obtained. [b]0.025 equiv of $[(CuOAc)_2]_n$ (**8**) were used.

Scheme 7

pyridine (**3h**) and 5-methyl-tetrazolo[1,5-*a*]pyridine (**3i**) did not react, even in boiling THF, because they have very stable ring structures. Although their cycloadditions could finish within 5 h in boiling toluene, the desired products were obtained in low yields as the mixtures included regioisomers, which may be caused by the fact that the cycloadditions may go through both a CuAAC pathway and a thermal pathway.

Finally, the transformations of nitropyridine into aminopyridine and ethyl nicotinate into hydroxymethylpyridine were explored. As shown in Scheme 8, when **1j** was hydrogenated (balloon) in the presence of Pd/C catalyst at room temperature for 2 h, the desired product **14** was obtained in 92% yield. As

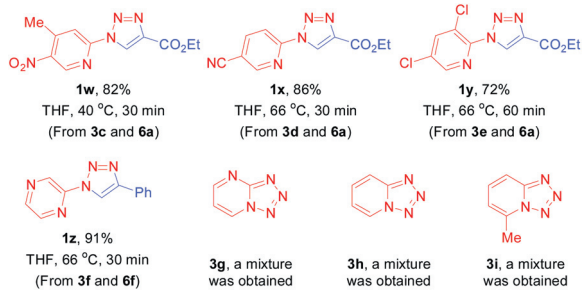
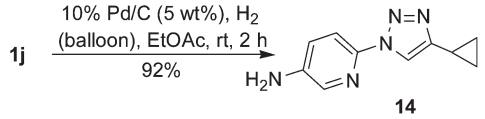
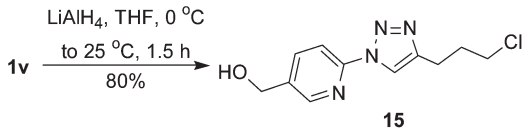


Fig. 2 The substrates **3c–3i** and their products.



Scheme 8



Scheme 9

shown in Scheme 9, by treatment of **1v** with $LiAlH_4$ at 0 °C to 25 °C for 1.5 h, its carboxylate group was reduced into hydroxymethyl group smoothly.

Conclusions

In conclusion, based on the analysis of the structural characters of tetrazolo[1,5-*a*]pyridine, highly efficient CuAAC of its 6-substituted derivatives was achieved by using copper(I) acetate as a catalyst. The *in situ* formed HOAc may play dual roles for efficient protonation of the key intermediate 5-cupuric 1,2,3-triazole (**4**) and prevention of the formation of coordination compound **5**. We observed that the addition sequence of the substrates could significantly influence on the reaction rate. Thus, a 2-azidopyridine-copper(I) complex activated intramolecular CuAAC pathway was proposed. Since the groups of $–NO_2$ and $–CO_2Et$ in the products can be easily converted into the corresponding amino and hydroxymethyl groups, it is expected that this reaction and its products will be found wide uses in organic synthesis and drug discovery.

Experimental section

General remarks

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer. TMS was used as an internal reference and the *J* values are given in Hz. MS were recorded on a VG-ZABMS spectrometer with 70 eV. Elemental analysis data were obtained on a Perkin-Elmer-241C apparatus. PE is petroleum ether (60–90 °C).

A typical procedure for the preparation of ethyl 1-(5-nitropyridin-2-yl)-1*H*-[1,2,3]-triazole-4-carboxylate (1a)

Ethyl propynoate (**6a**, 108 mg, 1.1 mmol) was added to a solution of 6-nitro-tetrazolo[1,5-*a*]-pyridine (**3a**, 165 mg, 1 mmol) and $[(CuOAc)_2]_n$ (**8**, 3 mg, 0.025 mmol, calculated by CuOAc) in chemically pure THF (1 mL) under N_2. After the resultant mixture was stirred at ambient temperature for 10 min (monitored by TLC), the solvent was removed under vacuum. The residue was purified by chromatography (silica gel, EtOAc/PE) to give 221 mg (84%) of **1a** as a white solid.

A typical procedure for the preparation of 5-nitro-2-(4-phenyl-[1,2,3]triazol-1-yl)-pyridine (1f)

A solution of 6-nitro-tetrazolo[1,5-*a*]-pyridine (**3a**, 165 mg, 1 mmol) and $[(CuOAc)_2]_n$ (**8**, 12 mg, 0.1 mmol, calculated by CuOAc) in chemically pure THF (1 mL) was ultrasonicated for 1 min to give a deep-red color suspension. Then phenylethyne (**6f**, 113 mg, 1.1 mmol) was added and the resultant mixture was stirred at ambient temperature for 10 min (motored by TLC) under N_2, the solvent was removed under vacuum. The residue was purified by chromatography (silica gel, EtOAc/PE) to give 222 mg (83%) of **1f** as a white solid.

By the similar procedure of the preparation of **1a** or **1f**, products **1b–1e** and **1g–1z** were prepared, respectively.

Ethyl 1-(5-nitropyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1a)

It is a white solid, mp 162 °C. IR *v* 3137, 3011, 2976, 2954, 1721, 1609, 1578, 1527 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.42 (d, J = 3.5, 2H), 8.91 (dd, J_1 = 6.2, J_2 = 2.8, 1H), 8.42 (d, J = 8.9, 1H), 4.38 (q, J = 7.2, 2H), 1.36 (t, J = 7.2, 3H); ^{13}C NMR (DMSO-d_6) δ 160.1, 151.2, 145.6, 144.8, 140.6, 136.4, 127.1, 115.3, 61.6, 14.6. MS *m*/*z* (%) 263 (M^+, 1.4%), 163 (100%); Anal. Calcd for $C_{10}H_9N_5O_4$: C, 45.63; H, 3.45; N, 26.61. Found: C, 45.89; H, 3.49; N, 26.86.

Methyl 1-(5-nitropyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1b)

It is a white solid, mp 216–217 °C. IR *v* 3122, 3081, 2955, 1719, 1610, 1539 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.40 (d, J = 2.7, 1H), 9.15 (s, 1H), 8.78 (dd, J_1 = 6.5, J_2 = 2.4, 1H), 8.49 (d, J = 8.9, 1H), 4.03 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 160.4, 151.4, 145.2, 144.0, 140.9, 135.0, 125.5, 114.3, 52.6; MS *m*/*z* (%) 249 (M^+, 1.08%), 190 (100%). Anal. Calcd for $C_9H_7N_5O_4$: C, 43.38; H, 2.83; N, 28.11. Found: C, 43.11; H, 2.79; N, 28.30.

tert-Butyl 1-(5-nitropyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1c)

It is a white solid, mp 160–162 °C. IR *v* 3157, 3104, 2985, 2935, 1728, 1614, 1534 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.35 (d, J =

2.4, 1H), 9.0 (s, 1H), 8.75 (dd, J_1 = 6.2, J_2 = 2.7, 1H), 8.45 (d, J = 8.9, 1H), 1.65 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.1, 151.5, 145.1, 143.8, 142.3, 135.0, 125.0, 114.2, 83.0, 28.1 (3C); MS m/z (%) 291 (M^+, 0.6%), 207 (100%). Anal. Calcd for $C_{12}H_{13}N_5O_4$: C, 49.48; H, 4.50; N, 24.04. Found: C, 49.57; H, 4.63; N, 24.18.

1-[1-(5-Nitropyridin-2-yl)-1*H*-1,2,3-triazol-4-yl]ethanone (1d)

It is a white solid, mp 178 °C. IR ν 3130, 3059, 1992, 1893, 1689, 1615, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.41 (d, J = 2.4, 1H), 9.12 (s, 1H), 8.79 (dd, J_1 = 6.2, J_2 = 2.7, 1H), 8.49 (d, J = 8.5, 1H), 2.78 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 192.0, 151.4, 148.4, 145.3, 144.0, 135.0, 123.4, 114.3, 27.5; MS m/z (%) 233 (M^+, 1.29%), 190 (100%). Anal. Calcd for $C_9H_7N_5O_3$: C, 46.36; H, 3.03; N, 30.03. Found: C, 46.48; H, 3.08; N, 29.87.

***tert*-Butyl [1-(5-nitropyridin-2-yl)-1*H*-1,2,3-triazol-4-yl]-methylcarbamate (1e)**

It is a white solid, mp 179–180 °C. IR ν 3143, 3103, 2984, 2940, 2878, 1668, 1610, 1577, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.41 (d, J = 2.8, 1H), 8.87 (dd, J_1 = 6.2, J_2 = 2.8, 1H), 8.68 (s, 1H), 8.36 (d, J = 9.3, 1H), 7.47 (t, J = 5.5, 1H), 4.31 (d, J = 5.9, 2H), 1.40 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 155.6, 151.2, 147.4, 145.2, 143.7, 135.8, 120.3, 113.9, 78.1, 35.4, 28.2 (3C); MS m/z (%) 320 (M^+, 0.19%), 59 (100%). Anal. Calcd for $C_{13}H_{16}N_6O_4$: C, 48.75; H, 5.03; N, 26.24. Found: C, 48.67; H, 5.11; N, 26.27.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-5-nitropyridine (1f)

It is a white solid, mp 224–226 °C. IR ν 3157, 3054, 1612, 1580, 1527 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.5 (s, 1H), 9.44 (d, J = 2.8, 1H), 8.90 (dd, J_1 = 6.5, J_2 = 2.8, 1H), 8.43 (d, J = 8.91, 1H), 8.08 (d, J = 6.0, 2H), 7.54–7.4 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 152.0, 148.4, 145.5, 144.5, 136.1, 130.1, 129.5 (2C), 129.2, 126.4 (2C), 119.3, 114.8; MS m/z (%) 267 (M^+, 2.47%), 239 (100%). Anal. Calcd for $C_{13}H_9N_5O_2$: C, 58.43; H, 3.39; N, 26.21. Found: C, 58.28; H, 3.38; N, 26.64.

2-(4-*p*-Tolyl-1*H*-1,2,3-triazol-1-yl)-5-nitropyridine (1g)

It is a slight yellow solid, mp 250 °C. IR ν 3156, 3081, 2918, 1615, 1576, 1525 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.42 (s, 1H), 9.41 (s, 1H), 8.88 (dd, J_1 = 6.5, J_2 = 2.4, 1H), 8.40 (d, J = 8.9, 1H), 7.95 (d, J = 7.9, 2H), 7.31 (d, J = 2.9, 2H), 2.36 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 152.0, 148.5, 145.5, 144.4, 138.7, 136.1, 130.0 (2C), 127.4, 126.3 (2C), 118.8, 114.8, 21.3; MS m/z (%) 281 (M^+, 3.11%), 253 (100%). Anal. Calcd for $C_{14}H_{11}N_5O_2$: C, 59.78; H, 3.94; N, 24.90. Found: C, 59.67; H, 3.97; N, 24.98.

2-[4-(3-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-5-nitropyridine (1h)

It is a yellowish solid, mp 143–144 °C. IR ν 3165, 1618, 1572, 1524 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 9.61 (s, 1H), 9.43 (d, J = 2.43, 1H), 8.90 (dd, J_1 = 6.2, J_2 = 2.7, 1H), 8.41 (d, J = 8.9, 1H), 7.91 (t, 9.1, 2H), 7.56 (q, J = 9.0, 1H), 7.25 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 163.1 (J = 241.7), 151.7, 147.1, 145.6, 144.4, 136.3, 132.3 (J = 8.6), 131.7 (J = 8.6), 122.2, 120.2, 115.9 (J = 20.8), 114.7, 112.9 (J = 23.0); MS m/z (%) 258 (15.82%), 176 (100%). Anal. Calcd for $C_{13}H_8FN_5O_2$: C, 54.74; H, 2.83; N, 24.55. Found: C, 54.56; H, 2.88; N, 24.70.

2-[4-(2-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-5-nitropyridine (1i)

It is a white solid, mp 206 °C. IR ν 3169, 3099, 1611, 1576, 1526 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.44 (s, 1H), 9.05 (s, 1H), 8.90 (d, J = 8.9, 1H), 8.43 (d, J = 8.9, 1H), 8.21 (t, J = 7.6, 1H), 7.52–7.37 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 159.5 (J = 122.8), 151.8, 145.6, 144.6, 142.1, 136.2, 131.1 (J = 4.3), 128.6, 125.6, 121.2 (J = 5.0), 117.9 (J = 6.5), 116.7 (J = 10.8), 114.9; MS m/z (%) 285 (M^+, 3.28%), 257 (100%). Anal. Calcd for $C_{13}H_8FN_5O_2$: C, 54.74; H, 2.83; N, 24.55. Found: C, 54.63; H, 2.78; N, 24.67.

2-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-5-nitropyridine (1j)

It is a white solid, mp 194–195 °C. IR ν 3151, 3093, 3031, 1610, 1574, 1530 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.37 (d, J = 2.73, 1H), 8.80 (dd, J_1 = 6.2, J_2 = 2.7, 1H), 8.72 (s, 1H), 8.32 (d, J = 8.9, 1H), 2.10–2.07 (m, 1H), 1.04–0.83 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 151.8, 151.6, 45.6, 144.0, 136.2, 118.8, 114.3, 8.5 (2C), 7.0; MS m/z (%) 231 (M^+, 0.29%), 176 (100%). Anal. Calcd for $C_{10}H_9N_5O_2$: C, 51.95; H, 3.92; N, 30.29. Found: C, 51.71; H, 3.98; N, 30.54.

2-[4-(Cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl]-5-nitropyridine (1k)

It is a white solid, mp 148–149 °C. IR ν 3154, 3116, 3081, 2919, 2846, 1612, 1580, 1528 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.34 (d, J = 2.7, 1H), 8.70 (dd, J_1 = 6.6, J_2 = 2.7, 1H), 8.38 (dd, J_1 = 8.2, J_2 = 0.8, 1H), 8.36 (s, 1H), 2.71 (d, J = 6.9, 2H), 1.79–1.65 (m, 6H), 1.31–0.97 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 152.2, 148.3, 145.0, 143.2, 119.1, 134.5, 113.6, 37.8, 33.2, 32.9 (2C), 26.3, 26.1 (2C); MS m/z (%) 258 (16%), 176 (100%). Anal. Calcd for $C_{14}H_{17}N_5O_2$: C, 58.52; H, 5.96; N, 24.37. Found: C, 58.68; H, 6.00; N, 24.55.

2-(4-Butyl-1*H*-1,2,3-triazol-1-yl)-5-nitropyridine (1l)

It is a white solid, mp 131–132 °C. IR ν 3155, 3094, 3031, 2930, 2866, 1610, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.34 (d, J = 2.4, 1H), 8.70 (dd, J_1 = 6.5, J_2 = 2.4, 1H), 8.41 (d, J = 8.9, 1H), 8.37 (s, 1H), 2.84 (t, J = 7.6, 2H), 1.8–1.7 (m, 2H), 1.5–1.39 (m, 2H), 1.0–0.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.2, 149.8, 145.0, 143.2, 134.6, 118.6, 113.6, 31.1, 25.2, 22.2, 13.8; MS m/z (%) 247 (M^+, 0.33%), 176 (100%). Anal. Calcd for $C_{11}H_{13}N_5O_2$: C, 53.43; H, 5.30; N, 28.32. Found: C, 53.65; H, 5.41; N, 24.55.

2-(4-Hexyl-1*H*-1,2,3-triazol-1-yl)-5-nitropyridine (1m)

It is a white solid, mp 123–125 °C. IR ν 3157, 3108, 3070, 2925, 2859, 1612, 1530 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.34 (d, J =

2.1, 1H), 8.70 (dd, J_1 = 6.5, J_2 = 2.4, 1H), 8.41 (d, J = 8.9, 1H), 8.37 (s, 1H), 2.82 (t, J = 7.6, 2H), 1.81–1.71 (m, 2H), 1.44–1.32 (m, 6H), 0.92–0.87 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 152.2, 150.0, 145.0, 143.2, 134.5, 118.6, 113.6, 31.5, 29.0, 28.8, 25.5, 22.5, 14.0; MS *m/z* (%) 275 (M^+, 0.5%), 176 (100%). Anal. Calcd for $C_{13}H_{17}N_5O_2$: C, 56.71; H, 6.22; N, 25.44. Found: C, 56.68; H, 6.26; N, 25.69.

2-[4-(3-Chloropropyl)-1*H*-1,2,3-triazol-1-yl]-5-nitropyridine (1n)

It is a white solid, mp 132–134 °C. IR ν 3155, 3095, 3034, 2957, 2863, 1611, 1583, 1530, 1486, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.35 (d, J = 2.8, 1H), 8.72 (dd, J_1 = 6.5, J_2 = 2.4, 1H), 8.44 (d, J = 6.2, 1H), 8.40 (s, 1H), 3.64 (t, J = 6.5, 2H), 3.02 (t, J = 7.2, 2H), 2.31–2.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 152.1, 147.8, 145.0, 143.3, 134.6, 119.2, 113.6, 43.9, 31.5, 22.6. MS *m/z* (%) 267 (M^+, 0.32%), 176 (100%). Anal. Calcd for $C_{10}H_{10}ClN_5O_2$: C, 44.87; H, 3.77; N, 26.16. Found: C, 45.03; H, 3.93; N, 26.08.

Ethyl 6-[4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]nicotinate (1o)[9a]

It is a white solid, mp 114 °C. ^{1}H NMR ($CDCl_3$) δ 9.14 (d, J = 2.1, 1H), 9.13 (s, 1H), 8.56 (dd, J_1 = 6.5, J_2 = 2.1, 1H), 8.34 (d, J = 8.6, 1H), 4.52–4.43 (m, 4H), 1.45 (t, J = 6.9, 6H); ^{13}C NMR ($CDCl_3$) δ 164.0, 160.3, 150.7, 150.6, 140.7, 140.6, 126.8, 125.1, 113.5, 61.9, 61.6, 14.3, 14.2.

Ethyl 6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1p)[9a]

It is a white solid, mp 194–196 °C. ^{1}H NMR ($CDCl_3$) δ 9.48 (s, 1H), 9.11 (s, 1H), 8.61 (d, J = 8.6, 1H), 8.33 (d, J = 8.6, 1H), 8.07 (d, J = 7.8, 2H), 7.53–7.38 (m, 3H), 4.41 (q, J = 7.2, 2H), 1.38 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 151.4, 150.5, 148.4, 140.3, 129.9, 128.9 (2C), 128.6, 126.1 (2C), 126.0, 117.0, 113.1, 61.8, 14.3.

Ethyl 6-(4-p-tolyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1q)[9a]

It is a white solid, mp 193–194 °C; ^{1}H NMR ($CDCl_3$): δ 9.12 (d, J = 1.7, 1H), 8.79 (s, 1H), 8.50 (dd, J_1 = 6.5, J_2 = 2.1, 1H), 8.30 (d, J = 8.3, 1H), 7.82 (d, J = 7.9, 2H), 7.26 (d, J = 7.9, 2H), 4.45 (q, J = 7.2, 2H), 2.40 (s, 3H), 1.44 (t, J = 6.8, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 151.4, 150.4, 148.4, 140.2, 138.5, 129.6 (2C), 127.0, 125.9, 125.8 (2C), 116.6, 113.1, 61.7, 21.3, 14.2.

Ethyl 6-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1r)

It is a white solid, mp 122 °C. IR ν 3148, 3113, 2983, 1712, 1594, 1485 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.07 (d, J = 6.2, 1H), 8.46 (t, J = 8.6, 1H), 8.29 (d, J = 6.5, 1H), 8.22 (d, J = 8.2, 1H), 4.48–4.38 (m, 2H), 2.1–2.0 (m, 1H), 1.40 (q, J = 6.9, 3H), 1.03–0.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 164.4, 151.6, 151.2, 150.4, 140.2, 125.8, 117.3, 113.0, 61.7, 14.3, 8.0 (2C), 6.8; MS *m/z* (%): 258 (M^+, 0.43%), 201 (100%). Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.63; H, 5.56; N, 21.44.

Ethyl 6-(4-cyclohexyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1s)

It is a white solid, mp 126 °C. IR ν 3145, 3070, 2924, 2850, 1712, 1598, 1487 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.09 (d, J = 2.1, 1H), 8.49 (dd, J_1 = 6.5, J_2 = 2.1, 1H), 8.34 (s, 1H), 8.26 (d, J = 8.6, 1H), 4.45 (q, J = 7.2, 2H), 2.70 (d, J = 6.9, 2H), 1.75–1.64 (m, 6H), 1.44 (q, J = 6.9, 3H), 1.34–0.92 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 164.3, 151.6, 150.3, 147.7, 140.1, 125.7, 118.9, 112.9, 61.6, 37.9, 33.3, 32.9 (2C), 26.3, 26.1 (2C), 14.2; MS *m/z* (%) 314 (M^+, 0.45%), 203 (100%). Anal. Calcd for $C_{17}H_{22}N_4O_2$: C, 64.95; H, 7.05; N, 17.82. Found: C, 65.23; H, 7.17; N, 17.64.

Ethyl 6-(4-butyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1t)

It is a white solid, mp 102 °C. IR ν 3140, 2947, 2864, 1712, 1605, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.09 (s, 1H), 8.49 (d, J = 7.9, 1H), 8.36 (s, 1H), 8.26 (d, J = 8.2, 1H), 4.45 (q, J = 6.9, 2H), 2.82 (t, J = 6.7, 2H), 1.79–1.69 (m, 2H), 1.50–1.38 (m, 5H), 0.99–0.94 (t, J = 7.6, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 151.5, 150.3, 149.2, 140.1, 125.7, 118.3, 112.9, 61.6, 31.2, 25.2, 22.2, 14.2, 13.7; MS *m/z* (%) 274 (M^+, 0.53%), 203 (100%). Anal. Calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.43; H, 6.74; N, 20.51.

Ethyl 6-(4-hexyl-1*H*-1,2,3-triazol-1-yl)nicotinate (1u)

It is a white solid, mp 100 °C. IR ν 3138, 3082, 2924, 2858, 1712, 1602, 1486 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.09 (d, J = 1.4, 1H), 8.45 (d, J = 6.5, 1H), 8.31 (s, 1H), 8.22 (d, J = 8.6, 1H), 4.45 (q, J = 7.2, 2H), 2.81 (t, J = 7.2, 2H), 1.80–1.70 (m, 2H), 1.46–1.30 (m, 9H), 0.89 (t, J = 6.9, 3H); ^{13}C NMR ($CDCl_3$) δ 164.3, 151.6, 150.3, 149.2, 140.1, 125.7, 118.3, 112.9, 61.6, 31.5, 29.1, 28.8, 25.6, 22.5, 14.2, 14.0; MS *m/z* (%) 302 (M^+, 0.53%), 217 (100%). Anal. Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.36; H, 7.28; N, 18.65.

Ethyl 6-[4-(3-chloropropyl)-1*H*-1,2,3-triazol-1-yl]nicotinate (1v)[9a]

It is a white solid, mp 128–130 °C. ^{1}H NMR ($CDCl_3$) δ 9.10 (d, J = 0.7, 1H), 8.50 (dd, J_1 = 6.5, J_2 = 0.7, 1H), 8.43 (s, 1H), 8.26 (dd, J_1 = 7.9, J_2 = 0.7, 1H), 4.45 (q, J = 6.9, 2H), 3.64 (t, J = 6.5, 2H), 3.01 (t, J = 7.2, 2H), 2.3–2.2 (m, 2H), 1.44 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 164.2, 151.4, 150.3, 147.2, 140.2, 125.9, 118.9, 112.9, 61.6, 43.9, 31.6, 22.6, 14.2.

Ethyl 1-(4-methyl-5-nitropyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1w)

It is a yellow solid, mp 168–170 °C. IR ν 3146, 2989, 2943, 1727, 1614, 1561, 1480 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1H), 9.11 (s, 1H), 8.30 (s, 1H), 4.49 (q, J = 7.2, 2H), 2.84 (s, 3H), 1.46 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 160.0, 149.9, 147.6, 146.0, 145.3, 140.9, 125.3, 116.8, 61.7, 20.7, 14.2. Anal. Calcd for $C_{11}H_{11}N_5O_4$: C, 47.66; H, 4.00; N, 25.26. Found: C, 47.94; H, 4.13; N, 25.14.

Ethyl 1-(5-cyanopyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1x)

It is a white solid, mp 156–159 °C. IR ν 3137, 2991, 2235, 1722, 1593, 1486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.11 (s, 1H), 8.86 (s, 1H), 8.45 (d, J = 8.6, 1H), 8.29 (d, J = 8.6, 1H), 4.50 (q, J = 7.2, 2H), 1.45 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 160.0, 152.1, 150.1, 142.7, 140.9, 125.1, 115.4, 114.2, 110.1, 61.7, 14.2. Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.79. Found: C, 54.53; H, 3.79; N, 28.85.

Ethyl 1-(3,5-dichloropyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (1y)

It is a white solid, mp 68–69 °C. IR ν 3182, 2993, 2979, 1714, 1557, 1455, 1378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.7 (s, 1H), 8.5 (d, J = 1.4, 1H), 8.1 (d, J = 1.4, 1H), 4.5 (q, J = 7.2, 2H), 1.4 (t, J = 7.2, 3H); ^{13}C NMR ($CDCl_3$) δ 160.0, 146.1, 143.6, 140.0 (2C), 133.5, 128.3, 126.3, 61.6, 14.2. Anal. Calcd for $C_{10}H_8Cl_2N_4O_2$: C, 41.83; H, 2.81; N, 19.51. Found: C, 41.97; H, 2.90; N, 19.39.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-pyrazine (1z)[9a]

It is a white solid, mp 134–138 °C. ^1H NMR ($CDCl_3$) δ 9.59 (d, J = 1.4, 1H), 8.76 (s, 1H), 8.67 (d, J = 2.8, 1H), 8.51 (d, J = 1.0, 1H), 7.96–7.93 (m, 2H), 7.51–7.39 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 148.3, 145.3, 144.0, 142.4, 136.4, 129.6, 128.9 (2C), 128.7, 125.9 (2C), 116.7.

Preparation of 2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)-5-aminopyridine (14)

A stirred suspension of compound **1j** (231 mg, 1 mmol) and 10% Pd/C (23 mg, 10 wt%) in chemically pure EtOAc (20 mL) was hydrogenated (balloon) at room temperature overnight. After the catalyst was filtrated off through a pad of celite, the solvent was evaporated. The residue was purified by column chromatography (silica gel, EtOAc/PE = 1 : 1) to give 185 mg (92%) of the product **14** as a yellowish solid, mp 67–69 °C. IR ν 3428, 3338, 3087, 1589 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.79–7.72 (m, 2H), 7.07–7.03 (dd, J_1 = 2.4, J_2 = 10.9, 1H), 4.12 (s, 2H), 1.97–1.88 (m, 1H), 0.91–0.74 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 150.3, 143.0, 140.8, 134.2, 123.9, 116.4, 114.1, 7.7 (2C), 6.6. Anal. Calcd for $C_{10}H_{11}N_5$: C, 59.69; H, 5.51; N, 34.80. Found: C, 59.97; H, 5.60; N, 34.64.

Preparation of 2-[4-(3-chloropropyl)-1*H*-1,2,3-triazol-1-yl]-5-(hydroxylmethyl)pyridine (15)

A THF solution of $LiAlH_4$ (0.6 M, 2 mL, 1.2 mmol) was added dropwise to a stirred solution of compound **1v** (295 mg, 1 mmol) in chemically pure THF (2 mL) at 0 °C under N_2. After the mixture was stirred at 0 °C for 30 min, it was warmed to room temperature for another 1 h (monitored by TLC). Then, it was quenched by saturated aqueous solution of NH_4Cl (1 mL) at 0 °C. The mixture was filtered through a pad of celite and the solvent was evaporated. The residue was purified by column chromatography (silica gel, EtOAc/PE = 1 : 2) to give 202 mg (80%) of the product **15** as a white solid, mp 62–64 °C. IR ν 3410, 2963, 2934, 1602, 1486, 1446 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (s, 1H), 8.35 (s, 1H), 8.10 (d, J = 8.3, 1H), 7.94 (d, J = 8.3, 1H), 4.82 (d, J = 5.5, 2H), 3.61 (t, J = 6.5, 2H), 3.43 (t, J = 5.5, 1H), 2.97 (t, J = 7.2, 2H), 2.31–2.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.2, 146.9, 146.8, 137.9, 136.6, 118.7, 113.3, 61.8, 44.0, 31.6, 22.6. Anal. Calcd for $C_{11}H_{13}ClN_4O$: C, 52.28; H, 5.19; N, 22.17. Found: C, 52.43; H, 5.12; N, 22.01.

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Notes and references

1 (*a*) I. E. Sayed, P. Van der Veken, K. Steert, L. Dhooghe, S. Hostyn, G. Van Baelen, G. Lemiere, B. U. W. Maes, P. Cos, L. Maes, J. Joossens, A. Haemers, L. Pieters and K. Augustyns, *J. Med. Chem.*, 2009, **52**, 2979–2988; (*b*) V. Zimmermann and S. Brase, *J. Comb. Chem.*, 2007, **9**, 1114–1137; (*c*) P. Vera-Luque, R. Alajarin, J. Alvarez-Builla and J. J. Vaquero, *Org. Lett.*, 2006, **8**, 415–418; (*d*) M. H. V. Huynh, M. A. Hiskey, D. E. Chavez and R. D. Gilardi, *Angew. Chem., Int. Ed.*, 2005, **44**, 7089–7094; (*e*) H. Mastalarz, R. Jasztold-Howorko, F. Rulko, A. Croisyb and D. Carrezb, *Arch. Pharm. Pharm. Med. Chem.*, 2004, **337**, 434–439; (*f*) Y.-L. Chen, H.-M. Hung, C.-M. Lu, K.-C. Li and C.-C. Tzeng, *Bioorg. Med. Chem.*, 2004, **12**, 6539–6546; (*g*) W. K. Janowski, R. H. Prager and J. A. Smith, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3212–3216; (*h*) W. Peczynska-Czoch, F. Pognan, E. Kaczmarek and J. Boratynski, *J. Med. Chem.*, 1994, **37**, 3503–3510.

2 (*a*) F. Wang, X.-Y. Wu, R.-M. Yu, Z.-G. Zhao and C.-Z. Lu, *J. Coord. Chem.*, 2009, **62**, 3296–3305; (*b*) C. Richardson and P. J. Steel, *Dalton Trans.*, 2003, 992–1000.

3 (*a*) A. S. Kiselyova, M. Semenova and V. V. Semenov, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1344–1348; (*b*) M. Klein, P. Diner, D. Dorin-Semblat, C. Doerig and M. Grotli, *Org. Biomol. Chem.*, 2009, **7**, 3421–3429; (*c*) S. Ito, A. Satoh, Y. Nagatomi, Y. Hirata, G. Suzuki, T. Kimura, A. Satow, S. Maehara, H. Hikichi, M. Hata, H. Kawamoto and H. Ohta, *Bioorg. Med. Chem.*, 2008, **16**, 9817–9829; (*d*) S. Sviridov, J. Pickens, S. Tandel, E. Brahmachary, Y. Yang, J. Wang, S. Freel, S. Fisher, A. Sullivan, J. Zhou, S. Stanfield-Oakley, M. Greenberg, D. Bolognesi, B. Bray, B. Koszalka, P. Jeffs, A. Khasanov, Y.-A. Ma, C. Jeffries, C. Liu, T. Proskurina, T. Zhu, A. Chucholowski, R. Li and C. Sexton, *J. Med. Chem.*, 2007, **50**, 6535–6544; (*e*) C. B. Madsen-Duggan, J. S. Debenham, T. F. Walsh, R. B. Toupence, S. X. Huang, J. Wang, X. Tong, J. Lao, T. M. Fong, M.-T. Schaeffer, J. C. Xiao, C. R.-R. C. Huang, C.-P. Shen, D. S. Stribling, L. P. Shearman, A. M. Strack, D. E. MacIntyre, L. H. T. Van der Ploegd and M. T. Goulet, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2031–2035; (*f*) Y. W. Jo, W. B. Im, J. K. Rhee, M. J. Shim, W. B. Kimb and E. C. Choi, *Bioorg. Med. Chem.*, 2004, **12**, 5909–5915.

4 (*a*) K. Prabakaran, P. Manivel and F. N. Khan, *Tetrahedron Lett.*, 2010, **51**, 4340–4343; (*b*) P. F. Pagoria, *J. Heterocycl. Chem.*, 2000, **37**, 1597–1602.

5 (*a*) S. V. Chapyshev, *Chem. Heterocycl. Compd.*, 2001, **37**, 861–866; (*b*) R. A. Abramovitch, S. R. Challand and Y. Yamada, *J. Org. Chem.*, 1975, **40**, 1541–1547; (*c*) D. Balachari and M. L. Trudell, *Tetrahedron Lett.*, 1997, **38**, 8607–8610.

6 (*a*) J. M. Keith, *J. Org. Chem.*, 2010, **75**, 2722–2725; (*b*) M.-L. Teyssot, L. Nauton, J.-L. Canet, F. Cisnetti, A. Chevry and A. Gautier, *Eur. J. Org. Chem.*, 2010, 3507–3515; (*c*) N. Kaval, D. Ermolat'ev, P. Appukkuttan, W. Dehaen, C. O. Kappe and E. Van der Eycken, *J. Comb. Chem.*, 2005, **7**, 490–502; (*d*) Z.-Y. Chen and M.-J. Wu, *Org. Lett.*, 2005, **7**, 475–477; (*e*) I. P. Beletskaya, D. V. Davydov and M. Moreno-Mafias, *Tetrahedron Lett.*, 1998, **39**, 5617–5620.

7 For selected reviews, see: (*a*) L. Liang and D. Astruc, *Coord. Chem. Rev.*, 2011, **255**, 2933–2944; (*b*) S. Diez-Gonzalez, *Catal. Sci. Technol.*, 2011, **1**, 166–178; (*c*) J. E. Hein and V. V. Fokin, *Chem. Soc. Rev.*, 2010, **39**, 1302–1315; (*d*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (*e*) V. D. Bock, H. Hiemstra and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51–68.

8 (*a*) G. Colombano, C. Travelli, U. Galli, A. Caldarelli, M. G. Chini, P. L. Canonico, G. Sorba, G. Bifulco, G. C. Tron and A. A. Genazzani, *J. Med. Chem.*, 2010, **53**, 616–623; (*b*) M. K. Lakshman, M. Singh, G. Parrish, R. Balachandran and B. W. Day, *J. Org. Chem.*, 2010, **75**, 2461–2473; (*c*) M. Klein, P. Diner, D. Dorin-Semblat, C. Doerig and M. Grotli, *Org. Biomol. Chem.*, 2009, **7**, 3421–3429; (*d*) B. Saha, S. Sharma, D. Sawant and B. Kundu, *Synlett*, 2007, 1591–1599.

9 (*a*) B. Chattopadhyay, C. I. Rivera Vera, S. Chuprakov and V. Gevorgyan, *Org. Lett.*, 2010, **12**, 2166–2169; (*b*) S. Gu, H. Xu, N. Zhang and W. Chen, *Chem.–Asian J.*, 2010, **5**, 1677–1686.

10 (*a*) C. Boga, E. Del Vecchio, L. Forlani, A. Mazzanti, C. M. Lario, P. E. Todesco and S. Tozzi, *J. Org. Chem.*, 2009, **74**, 5568–5575; (*b*) P. Cmoch, H. Korczak, L. Stefaniak and G. A. Webb, *J. Phys. Org. Chem.*, 1999, **12**, 470–478; (*c*) P. Cmocha, J. W. Wiencha, L. Stefaniaka and G. A. Webbb, *J. Mol. Struct.*, 1999, **510**, 165–178; (*d*) P. Cmoch, L. Stefaniak and G. A. Webb, *Magn. Reson. Chem.*, 1997, **35**, 237–242; (*e*) J. H. Boyer and E. J. Miller Jr., *J. Am. Chem. Soc.*, 1959, **81**, 4671–4673.

11 (*a*) C. Shao, X. Wang, Q. Zhang, S. Luo, J. Zhao and Y. Hu, *J. Org. Chem.*, 2011, **76**, 6832–6836; (*b*) Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao and Y. Hu, *Tetrahedron*, 2011, **67**, 6294–6299; (*c*) C. Shao, R. Zhu, S. Luo, Q. Zhang, X. Wang and Y. Hu, *Tetrahedron Lett.*, 2011, **52**, 3782–3785; (*d*) C. Shao, X. Wang, J. Xu, J. Zhao, Q. Zhang and Y. Hu, *J. Org. Chem.*, 2010, **75**, 7002–7005; (*e*) C. Shao, G. Cheng, D. Su, J. Xu, X. Wang and Y. Hu, *Adv. Synth. Catal.*, 2010, **352**, 1587–1592.

