Synthesis A. Bhatt et al. Paper

A Convenient Synthesis of 1,5-Fused 1,2,4-Triazoles from *N*-Arylamidines via Chloramine-T Mediated Intramolecular Oxidative N–N Bond Formation

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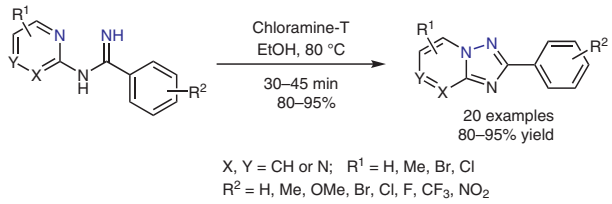

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Abstract A convenient synthesis of 1,5-fused 1,2,4-triazoles from readily available *N*-arylamidines is reported. The reaction is efficiently promoted by chloramine-T to afford the desired products mostly in high yields and in relatively short time, through direct metal-free oxidative N–N bond formation. The mild nature of the synthesis and short reaction time are notable advantages of the developed protocol. This protocol is effective toward various substrates having different functionalities.

Key words *N*-arylamidine, [1,2,4]triazolo[1,5-*a*]pyridine, [1,2,4]triazolo[1,5-*a*]pyrazine, [1,2,4]triazolo[1,5-*a*]pyrimidine, chloramine-T, ethanol

The 1,2,4-triazole nucleus is an important structural motif present in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry, agricultural chemistry, materials science, and organocatalysis.[1] 1,2,4-Triazole scaffolds are found in many biologically active molecules[2] and valuable pharmaceuticals, including maraviroc, triazolam, sitagliptin, and penipanoid (Figure 1).[3] In particular, compounds containing *N*-fused 1,2,4-triazoles, such as triazolopyridine and triazolopyrazine substructures exhibit a wide spectrum of biological activity including antifungal, antimicrobial, antiviral, anti-inflammatory, antiasthmatic, antiproliferative, and hypotonic.[4] In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules.[5] On the other hand, they also play important roles as ligands in transition metal complexes and metal-organic frameworks, exhibiting tremendous application prospects.[6]

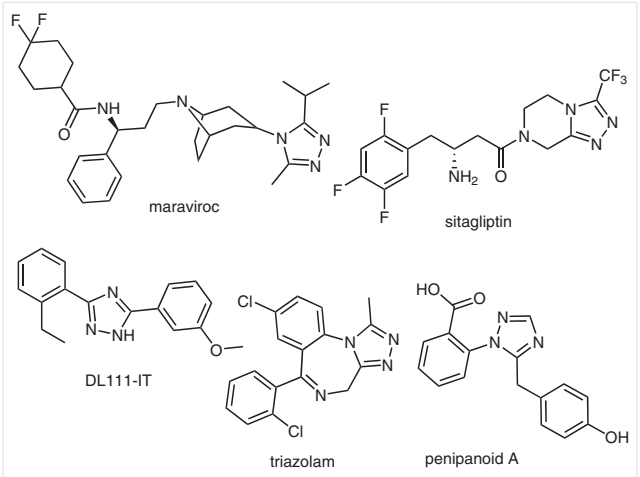

Figure 1 Representative bioactive molecules and natural compounds possessing a 1,2,4-triazole core

Due to their importance, many efficient methods have been developed to access *N*-fused 1,2,4-triazoles.[7] Oxidative cyclization of *N*-(2-pyridyl)amidines is one of the most straightforward strategies for the construction of the 1,2,4-triazolo[1,5-*a*]pyridine framework, which previously has been achieved by utilizing oxidants, such as NaClO/base,[8] $Pb(OAc)_4$,[9] and MnO_2.[10] Nevertheless, these methods are associated with some disadvantages, including low yields, multistep synthetic procedures, limited scopes, and inferior regioselectivity.

In 2009, Ueda and Nagasawa[11] reported a copper-catalyzed tandem addition-oxidative cyclization of 2-aminopyridines and aryl nitriles to 2-aryl-1,2,4-triazolo[1,5-*a*]pyridines. Alternatively, Zhao and co-workers[12] developed a recyclable Cu–Zn/Al–Ti catalyst for the same transformation (Scheme 1). Recently, Xia, Huang, and co-workers[13] described a Cu-catalyzed oxidative cyclization of nitriles with

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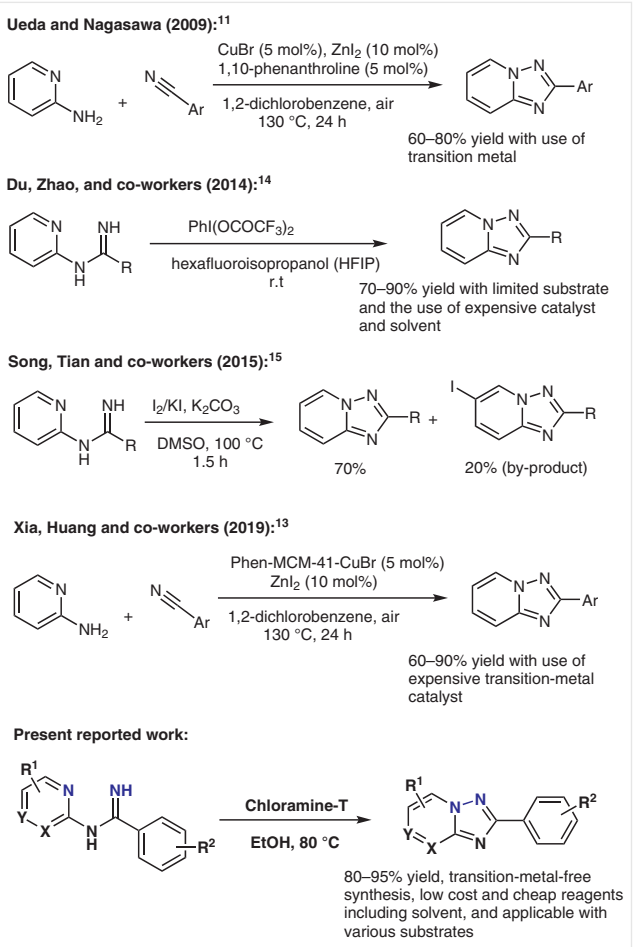
2-aminopyridines or amidines (Scheme 1). However, in almost all cases, copper and other transition metal catalysts with higher loadings (typically 5–20 mol%) were used to achieve high yields, and they are difficult to separate from the reaction mixture and are not recyclable. These problems are of particular environmental and economic concerns in large-scale syntheses and in industry. Moreover, these transition-metal catalysis might cause metal contamination of the desired product because 1,2,4-triazoles are strong ligands for transition metals and could coordinate with metal to form stable complexes.[6c–e] Therefore, it is still of importance to develop transition-metal-free synthetic methods to access this kind of compound class.



Scheme 1 Previously reported synthesis of 1,5-fused 1,2,4-triazoles through the formation of N–N bond

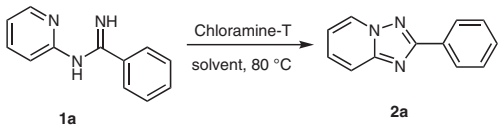
However, some transition-metal-free synthetic methods have also been reported to access *N*-fused 1,2,4-triazoles. For example, Du, Zhao, and co-workers[14] reported a PIFA-mediated cyclization of *N*-(pyridin-2-yl)amidines to 2-aryl/2-alkyltriazolopyridines. Further, in 2015, Song, Tian and co-workers[15] reported a new and efficient I_2/KI-mediated methodology for the synthesis of both 2-aryl- and 2-alkyl-substituted 1,2,4-triazolo[1,5-*a*]pyridines. But these existing methods suffer from some drawbacks in one or another respect, such as use of expensive catalyst, formation of by-product like 20% iodinated product along with desired product in I_2/KI-mediated methodology, inferior regioselectivity, and a limited substrate scope.

Despite these elegant achievements made, it is still of importance to develop novel and general approaches to access this compound class.

Chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt) is a versatile reagent and is becoming increasingly popular because of its commercial availability at low cost. Chloramine-T has been extensively used as an oxidant toward a wide variety of functional groups.[16] This reagent also acts as a chlorinating reagent,[17] as an oxidant for aromatization,[18] and as a nitrogen source that has been used for the aziridination of alkenes.[19] In particular, this oxidizing reagent has been successfully employed to construct C–N, C–O, and C–S bonds.[20] However, to the best of our knowledge, there is no report of chloramine-T mediated N–N bond formation reactions. Encouraged by our previous work, in this paper, we disclose a new and efficient chloramine-T mediated methodology for the synthesis of 2-aryl-substituted 1,2,4-triazolo[1,5-*a*]pyridines, as well as their pyrazido- and pyrimidotriazole derivatives, from *N*-arylamidines through the construction of N–N bonds (Scheme 1).

The required substrates *N*-arylamidines **1** were prepared via the addition reaction of corresponding arylamines to substituted nitriles as per the reported literature procedure.[21] Our preliminary investigation began with the reaction of *N*-(2-pyridyl)amidine **1a** with chloramine-T (1 equiv) in methanol at 80 °C. We were delighted to observe the formation of the desired product **2a**, albeit in a low yield of 65% (Table 1, entry 1). Next, the reaction conditions were optimized in order to increase the yield. Thus, different solvents were screened and the results are summarized in Table 1. It was found that ethanol was the most superior solvent in terms of the reaction time and yield of the product (entry 2). Once, we had established a suitable solvent for the synthesis of 1,2,4-triazolo[1,5-*a*]pyridine, we then focused on the quantity of chloramine-T. An increase in the amount of chloramine-T (from 1 equiv to 2 equiv) not only decreased the reaction time from 1.5 hours to 30 minutes, but also increased the product yield from 75% to 95% (entry 7). Further increasing the quantity of chloramine-T (from 2 equiv to 3 equiv) led to a decrease in the yield to 80% (entry 8). Therefore, we decided to perform the subsequent reactions of the various *N*-arylamidines with chloramine-T (2 equiv) in ethanol at 80 °C. The effect of temperature on the reaction rate as well as on the yields of the products were also investigated. Faster reactions occurred on increasing the temperature but the product yields were not satisfactory. The progress of the reactions was monitored by TLC analysis (using EtOAc–hexane as the eluent).

Table 1 Optimization of the Reaction Conditions

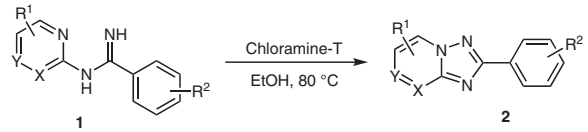


1a 2a

Entry	Solvent	Chloramine-T (equiv)	Time	Yield (%)
1	MeOH	1.0	1.5 h	65
2	EtOH	1.0	1 h	75
3	*i*-PrOH	1.0	2.5 h	55
4	toluene	1.0	3 h	45
5	AcOH	1.0	2 h	50
6	EtOH	1.5	45 min	85
7	EtOH	2	30 min	95
8	EtOH	3	15 min	80

With the optimized reaction conditions established (Table 1, entry 7), the scope of the newly discovered oxidative N–N bond formation reaction was investigated (Table 2). Because **2a** was afforded in an excellent yield from its corresponding substrate **1a**, the effect of substituents on the pyridine ring (R^1) was first examined. This heterocyclic ring was found to be tolerant of both electron-rich groups such as methyl **2b–e** and electron-deficient groups such as halogens **2f–h**. Reactions of halogen-containing substrates provided yields slightly lower than that of the methyl-containing substrates, which was probably due to the relatively low nucleophilicity of the pyridines affected by the halogens (Table 2, entries 1–8). The substitution effect of the R^2 group was then examined. It was found that when R^2 is an aryl group, this methodology is compatible with both electron-donating and electron-withdrawing groups at *para*-, *meta*-, and *ortho*-positions of the benzene ring **2i–r**. Even the nitro group bearing substrate **1m** was smoothly transformed into the desired 1,2,4-triazolo[1,5-*a*]pyridine **2m** under the optimal reaction conditions. *ortho*-Substitution on the 2-phenyl moiety did not affect either the reaction rate or the yields of the products **2p–r**.

Table 2 Synthesis of Various 1,5-Fused 1,2,4-Triazoles with the Scope of Substituents R^1 and R^2 on *N*-Arylamidines



1 2

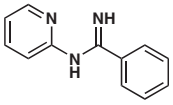
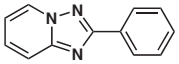
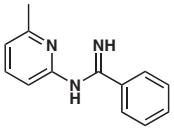
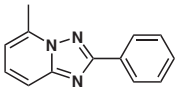
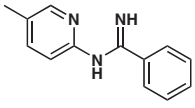
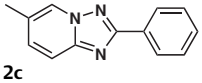
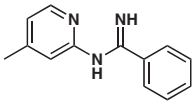
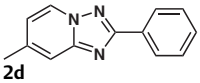
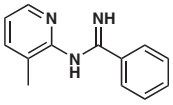
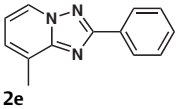
Entry	Substrate	Product **21**	Time (min)	Yield (%)
1		 **2a**	30	95
2		 **2b**	35	93
3		 **2c**	30	94
4		 **2d**	30	95
5		 **2e**	40	91

Table 2 (continued)

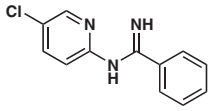
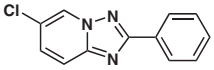
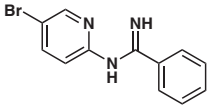
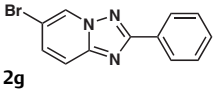
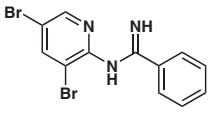
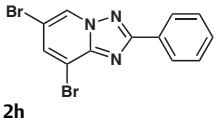
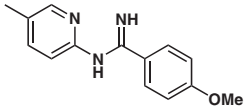
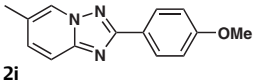
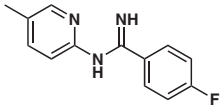
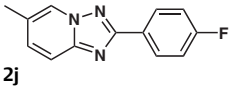
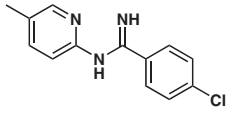
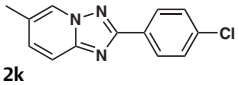
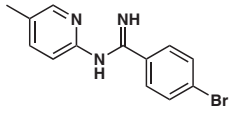
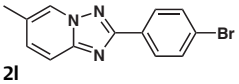
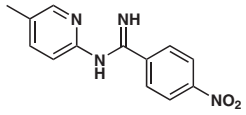
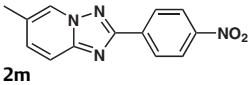
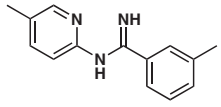
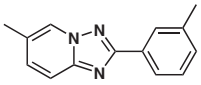
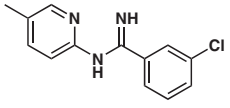
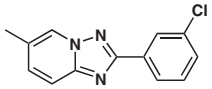
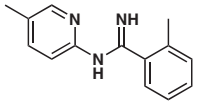
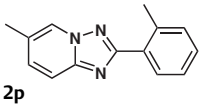
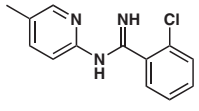
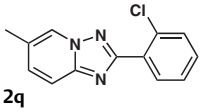
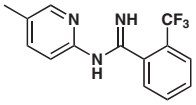
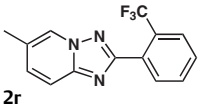
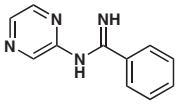
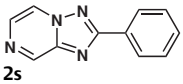
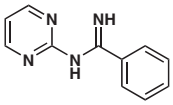
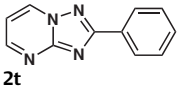
Entry	Substrate	Product **21**	Time (min)	Yield (%)
6		 **2f**	30	87
7		 **2g**	35	89
8		 **2h**	35	85
9		 **2i**	30	90
10		 **2j**	30	87
11		 **2k**	30	86
12		 **2l**	35	84
13		 **2m**	45	80
14		 **2n**	30	90
15		 **2o**	30	85
16		 **2p**	35	90
17		 **2q**	35	85

Table 2 (continued)

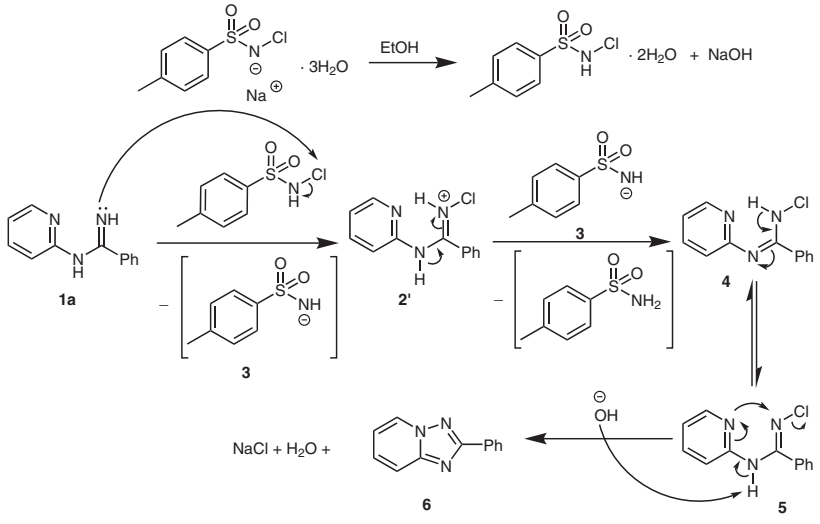
Entry	Substrate	Product **21**	Time (min)	Yield (%)
18		 **2r**	40	81
19		 **2s**	30	90
20		 **2t**	35	85

Additionally, pyrazido- **2s** and pyrimidotriazoles **2t** were prepared via the oxidative cyclization of *N*-pyrazyl- **1s** and *N*-pyrimidyl-substituted benzimidamides **1t**, respectively, in good yields.

Based on our experimental data and previous report,[8,15,22] a plausible reaction mechanism for the formation of 1,5-fused 1,2,4-triazole **6** (≡ **2a**) is proposed (Scheme 2). According to this route, chloramine-T transfers the Cl^+ ion to the *N*-arylamidine **1a** and generates *N*-chloroamidinium cation **2′** and *p*-toluenesulfonamide anion **3** as a proton acceptor. *N*-Chloroamidinium cation, further by the cleavage of N–Cl bond, deprotonation, and after rearomatization provides the desired 1,5-fused 1,2,4-triazole framework **6** (≡ **2a**).

In conclusion, we have developed a short and efficient synthesis of 1,5-fused 1,2,4-triazoles using a mild oxidative cyclization method with chloramine-T through the construction of N–N bond. This facile and transition-metal-free synthetic process works well with a wide range of *N*-aryl-substituted amidines. A variety of substituents are tolerated allowing the synthesis of diverse products in good to excellent yields. The main advantage of this procedure is to access 1,5-fused 1,2,4-triazoles with high yields and short reaction time. The newly developed synthetic route is believed to be valuable for the construction of building blocks but also for medicinal chemistry studies comprising 1,5-fused 1,2,4-triazole moiety.

All solvents and reagents were purchased from commercial sources and used without further purification. Melting points were determined on a Stuart SMP3 melting point apparatus without correction. IR spectra were obtained using a PerkinElmer FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance using the solvents indicated with 400 and 100 MHz respectively.



Scheme 2 Plausible mechanism for the synthesis of 1,5-fused 1,2,4-triazoles from *N*-arylamidines

High-resolution mass spectra (HRMS) were performed on a Thermo Finnigan MAT95XP mass spectrometer. TLC was performed on silica gel 60 F254 (Merck) TLC plates using hexane/EtOAc (7:3 v/v) as the mobile phase. Column chromatography was carried out using Merck silica gel (200–300 mesh) and hexane/EtOAc (7:3 v/v) as the eluent.

1,5-Fused 1,2,4-Triazoles 2a–t; General Procedure

A stirred solution of *N*-arylamidine **1** (0.1 mmol, 1.0 equiv) in EtOH (10 mL) was treated with chloramine-T trihydrate (56.3 mg, 0.2 mmol, 2.0 equiv). The reaction mixture was refluxed at 80 °C until the starting material was completely consumed (monitored by TLC, 30 min). The mixture was quenched with sat. aq $NaHCO_3$ (30 mL) and extracted with EtOAc (50 mL). The organic layer was washed with H_2O (40 mL), dried (Na_2SO_4), and evaporated. The resulting crude compound was purified by silica gel column chromatography (EtOAc/hexane, 3:7 v/v) to afford the desired pure 1,5-fused 1,2,4-triazole derivative **2**.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2a)[11]

White solid; yield: 47.1 mg (95%); mp 134–136 °C.

IR (KBr): 3037, 1611, 1497, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (dt, *J* = 6.8, 1.2 Hz, 1 H), 8.31–8.28 (m, 2 H), 7.75 (dt, *J* = 8.8, 0.8 Hz, 1 H), 7.52–7.46 (m, 4 H), 6.99 (dt, *J* = 1.2, 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 151.7, 130.7, 130.1, 129.5, 128.7, 128.3, 127.3, 116.4, 113.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_9N_3$: 196.0869; found: 196.0867.

5-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2b)[23a]

White solid; yield: 46 mg (93%); mp 84–86 °C.

IR (KBr): 3041, 2912, 1624, 1503, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.32 (m, 2 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.52–7.40 (m, 4 H), 6.81 (dt, *J* = 7.2, 0.8 Hz, 1 H), 2.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 151.8, 138.9, 131.2, 129.9, 129.3, 128.6, 127.3, 113.5, 112.8, 17.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3$: 210.1026; found: 210.1022.

6-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2c)

White solid; yield: 46.5 mg (94%); mp 118–120 °C.

IR (KBr): 3054, 2931, 1641, 1511, 769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.28–8.26 (m, 2 H), 7.64 (d, *J* = 9.2 Hz, 1 H), 7.51–7.45 (m, 3 H), 7.33 (dd, *J* = 9.2, 1.6 Hz, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 150.3, 132.3, 130.9, 129.9, 128.6, 127.1, 126.3, 123.7, 115.5, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3$: 210.1026; found: 210.1024.

7-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2d)[11]

White solid; yield: 47.1 mg (95%); mp 141–143 °C.

IR (KBr): 3049, 2935, 1645, 1507, 781 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.2 Hz, 1 H), 8.28–8.26 (m, 2 H), 7.51–7.45 (m, 4 H), 6.80 (dd, *J* = 7.2, 2.0 Hz, 1 H), 2.47 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 151.9, 141.0, 130.9, 129.9, 128.6, 127.2, 116.0, 115.0, 21.6.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3$: 210.1026; found: 210.1023.

8-Methyl-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2e)[11]

White solid; yield: 45 mg (91%); mp 96–98 °C.

IR (KBr): 3057, 2925, 1636, 1516, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 6.8 Hz, 1 H), 8.31–8.29 (m, 2 H), 7.51–7.45 (m, 3 H), 7.26–7.22 (m, 1 H), 6.87 (t, *J* = 6.8 Hz, 1 H), 2.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 152.2, 131.0, 129.9, 128.6, 128.1, 127.3, 127.0, 125.9, 113.4, 17.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{11}N_3$: 210.1026; found: 210.1027.

6-Chloro-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2f)[14]

White solid; yield: 43.1 mg (87%); mp 165–167 °C.

IR (KBr): 3050, 1651, 1499, 826, 714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1 H), 8.27–8.25 (m, 2 H), 7.69 (d, *J* = 9.6 Hz, 1 H), 7.52–7.46 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 150.3, 130.9, 130.34, 130.31, 128.7, 127.3, 126.6, 121.5, 116.4.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8ClN_3$: 230.0479; found: 230.0477.

6-Bromo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2g)[14]

White solid; yield: 44.1 mg (89%); mp 165–167 °C.

IR (KBr): 3042, 1628, 1502, 818, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 1.6 Hz, 1 H), 8.27–8.25 (m, 2 H), 7.66–7.63 (m, 1 H), 7.58–7.55 (m, 1 H), 7.52–7.47 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 150.4, 133.1, 130.34, 130.29, 128.8, 128.7, 127.3, 116.8, 107.7.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_8BrN_3$: 273.9955; found: 273.9953.

6,8-Dibromo-2-phenyl[1,2,4]triazolo[1,5-*a*]pyridine (2h)

White solid; yield: 42.2 mg (85%); mp 149–151 °C.

IR (KBr): 3059, 1662, 1521, 827, 705 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 1.6 Hz, 1 H), 8.30–8.28 (m, 2 H), 7.84 (d, *J* = 1.6 Hz, 1 H), 7.50–7.48 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 149.7, 135.0, 130.6, 129.8, 128.7, 127.9, 127.6, 110.1, 106.9.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_7Br_2N_3$: 351.9059; found: 351.9056.

2-(4-Methoxyphenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2i)

White solid; yield: 44.6 mg (90%); mp 166–168 °C.

IR (KBr): 3041, 2916, 1610, 1498, 1140, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.36–8.35 (m, 1 H), 8.22–8.18 (m, 2 H), 7.61 (d, *J* = 9.2 Hz, 1 H), 7.32 (dd, *J* = 8.8, 1.6 Hz, 1 H), 7.03–6.99 (m, 2 H), 3.87 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 161.0, 150.3, 132.3, 128.6, 126.2, 123.5, 123.4, 115.3, 114.0, 55.3, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_3O$: 240.1131; found: 240.1127.

2-(4-Fluorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2j)

White solid; yield: 43.1 mg (87%); mp 163–165 °C.

IR (KBr): 3068, 2931, 1635, 1511, 1224, 837, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (m, 1 H), 8.27–8.22 (m, 2 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.34 (dd, *J* = 9.2, 1.6 Hz, 1 H), 7.19–7.14 (m, 2 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9 (d, $^1J_{C,F}$ = 247.8 Hz), 163.0, 150.3, 132.4, 129.1 (d, $^3J_{C,F}$ = 8.4 Hz), 127.2, 126.3, 123.8, 115.7 (d, $^2J_{C,F}$ = 21.6 Hz), 115.5, 18.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}FN_3$: 228.0932; found: 228.0934.

2-(4-Chlorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2k)

White solid; yield: 42.6 mg (86%); mp 169–171 °C.

IR (KBr): 3056, 2918, 1623, 1487, 820, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.21–8.18 (m, 2 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 7.46–7.44 (m, 2 H), 7.35 (dd, *J* = 9.2, 1.6 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 150.3, 135.9, 132.5, 129.5, 128.9, 128.4, 126.3, 123.9, 115.5, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}ClN_3$: 244.0636; found: 244.0634.

2-(4-Bromophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2l)

White solid; yield: 41.7 mg (84%); mp 179–181 °C.

IR (KBr): 3047, 2919, 1602, 1514, 834, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 8.14–8.11 (m, 2 H), 7.64–7.59 (m, 3 H), 7.35 (dd, *J* = 9.2, 1.6 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 150.3, 132.5, 131.8, 130.0, 128.7, 126.3, 124.2, 123.9, 115.6, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}BrN_3$: 288.0131; found: 288.0129.

6-Methyl-2-(4-nitrophenyl)[1,2,4]triazolo[1,5-*a*]pyridine (2m)

Light yellow solid; yield: 39.6 mg (80%); mp 275–277 °C.

IR (KBr): 3063, 2941, 1636, 1552, 1503, 1344, 850 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.89 (s, 1 H), 8.45–8.37 (m, 4 H), 7.84 (d, *J* = 8.8 Hz, 1 H), 7.62 (dd, *J* = 9.2, 1.6 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, CF_3CO_2D): δ = 153.3, 150.3, 141.8, 141.4, 132.5, 128.8, 128.7, 128.4, 124.5, 110.8, 16.2.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}N_4O_2$: 255.0876; found: 255.0875.

6-Methyl-2-(*m*-tolyl)[1,2,4]triazolo[1,5-*a*]pyridine (2n)

White solid; yield: 44.6 mg (90%); mp 129–131 °C.

IR (KBr): 3054, 3011, 2917, 1607, 1464, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38–8.37 (m, 1 H), 8.10 (s, 1 H), 8.07 (d, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 9.2 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.33 (dd, *J* = 9.2, 1.6 Hz, 1 H), 7.27 (d, *J* = 7.2 Hz, 1 H), 2.45 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 150.3, 138.4, 132.4, 130.8, 130.7, 128.6, 127.8, 126.3, 124.3, 123.7, 115.5, 21.4, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_3$: 224.1182; found: 224.1179.

2-(3-Chlorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2o)

White solid; yield: 42.1 mg (85%); mp 153–155 °C.

IR (KBr): 3026, 2916, 1629, 1494, 826, 711 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 8.28–8.27 (m, 1 H), 8.17–8.12 (m, 1 H), 7.64 (d, *J* = 8.8 Hz, 1 H), 7.42–7.41 (m, 2 H), 7.36 (dd, *J* = 9.2, 1.6 Hz, 1 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 150.3, 134.7, 132.8, 132.6, 129.9, 129.8, 127.3, 126.3, 125.2, 124.1, 115.6, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}ClN_3$: 244.0636; found: 244.0637.

6-Methyl-2-(*o*-tolyl)[1,2,4]triazolo[1,5-*a*]pyridine (2p)

White solid; yield: 44.6 mg (90%); mp 95–97 °C.

IR (KBr): 3049, 3015, 2911, 1617, 1506, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (m, 1 H), 8.06–8.03 (m, 1 H), 7.66 (d, *J* = 9.2 Hz, 1 H), 7.36–7.30 (m, 4 H), 2.70 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 144.8, 132.9, 127.4, 126.4, 125.6, 125.4, 124.5, 121.5, 121.0, 118.7, 110.8, 17.0, 13.3.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_3$: 224.1182; found: 224.1179.

2-(2-Chlorophenyl)-6-methyl[1,2,4]triazolo[1,5-*a*]pyridine (2q)

White solid; yield: 42.1 mg (85%); mp 109–110 °C.

IR (KBr): 3034, 2925, 1627, 1510, 839, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 8.00–7.98 (m, 1 H), 7.70 (d, *J* = 9.2 Hz, 1 H), 7.55–7.52 (m, 1 H), 7.39–7.37 (m, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 149.6, 133.1, 132.5, 132.0, 130.7, 130.5, 130.2, 126.7, 126.4, 124.0, 115.8, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}ClN_3$: 244.0636; found: 244.0633.

6-Methyl-2-[2-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*a*]pyridine (2r)

White solid; yield: 40.2 mg (81%); mp 80–82 °C.

IR (KBr): 3039, 2928, 1629, 1514, 1105, 1062, 837, 795 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44–8.43 (m, 1 H), 7.88 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 1 H), 7.70 (d, *J* = 9.2 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.40 (dd, *J* = 9.2, 2.0 Hz, 1 H), 2.44 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7, 149.7, 132.6, 132.3, 131.5, 130.5, 129.4, 129.2 (q, $^2J_{C,F}$ = 31.4 Hz), 126.6 (q, $^3J_{C,F}$ = 5.4 Hz), 126.4, 124.1, 123.8 (q, $^1J_{C,F}$ = 272.1 Hz), 115.9, 18.1.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{10}F_3N_3$: 278.0899; found: 278.0897.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyrazine (2s)

White solid; yield: 44.5 mg (90%); mp 179–181 °C.

IR (KBr): 3035, 1616, 1447, 709 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 1.2 Hz, 1 H), 8.56 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.32–8.30 (m, 2 H), 8.18 (d, *J* = 4.4 Hz, 1 H), 7.54–7.51 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 147.3, 142.7, 131.6, 130.8, 129.8, 128.9, 127.6, 121.5.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8N_4$: 197.0822; found: 197.0820.

2-Phenyl[1,2,4]triazolo[1,5-*a*]pyrimidine (2t)[23b]

White solid; yield: 42.1 mg (85%); mp 184–186 °C.

IR (KBr): 3039, 1614, 1479, 1351, 769, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (dd, *J* = 6.4, 2.0 Hz, 1 H), 8.80 (dd, *J* = 4.4, 2.0 Hz, 1 H), 8.36–8.34 (m, 2 H), 7.53–7.50 (m, 3 H), 7.09 (dd, *J* = 6.8, 4.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 156.1, 154.4, 135.5, 130.8, 130.2, 128.8, 127.5, 110.0.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_8N_4$: 197.0822; found: 197.0818.

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Supporting Information

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