Synthesis M. Nakka et al. Paper

A Simple and Efficient Synthesis of 3,4,5-Trisubstituted/N-Fused 1,2,4-Triazoles via Ceric Ammonium Nitrate Catalyzed Oxidative Cyclization of Amidrazones with Aldehydes Using Polyethylene Glycol as a Recyclable Reaction Medium

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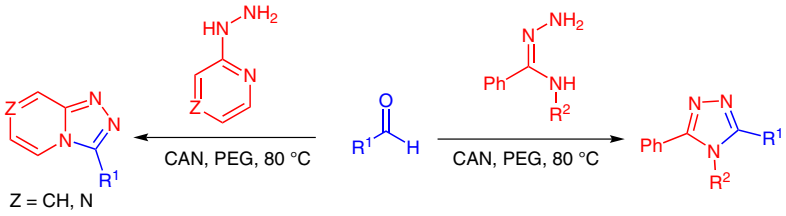

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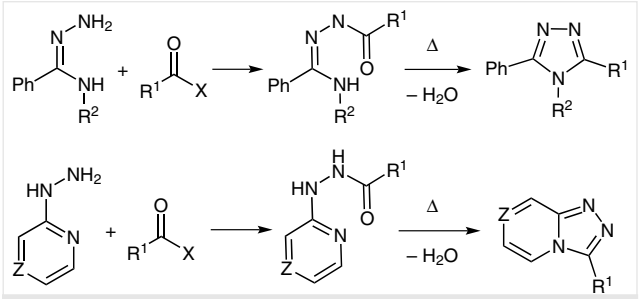
Abstract An environmentally benign protocol is described for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and N-fused 1,2,4-triazoles via ceric ammonium nitrate catalyzed oxidative cyclization of amidrazones and aldehydes using polyethylene glycol as recyclable reaction medium. This protocol is effective toward various substrates having different functionalities. The easy recyclability of the reaction medium makes the process economic and potentially viable for commercial applications.

Key words polyethylene glycol, ceric ammonium nitrate, 1,2,4-triazoles, [1,2,4]triazolo[4,3-*a*]pyridines, [1,2,4]triazolo[4,3-*a*]pyrazines

1,2,4-Triazoles have elicited considerable interest among medicinal chemists because they are considered to be privileged structural constituents of many pharmaceutical agents as well as natural products (Figure 1).[1] In particular, compounds containing 3,4,5-trisubstituted 1,2,4-triazoles and N-fused 1,2,4-triazoles, such as triazolopyridine and triazolopyrazine substructures exhibit a wide spectrum of biological activity including antifungal,[2] antimicrobial,[3] antiviral,[4] anti-inflammatory,[5] antiasthmatic,[6] antiproliferative[7] and hypotonic.[8] In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules.[9] On the other hand, they also play important roles as ligands in organometallic compounds, as precursors for N-heterocyclic carbenes, as ionic liquids and as corrosion inhibitors.[10]

Due to their importance, many efficient methods have been developed to access 3,4,5-trisubstituted/N-fused 1,2,4-triazoles.[11] Among them, coupling of carboxylic acids or their derivatives with amidrazones, followed by cyclodehydration is the most common explored strategy (Scheme 1).[12] However, some of these protocols suffer from the limitations of harsh conditions, tedious synthetic procedures and unsatisfactory yields. Hence, the development of milder and more general procedures to access 3,4,5-trisubstituted 1,2,4-triazoles and N-fused 1,2,4-triazoles remains desirable.



Scheme 1 General synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and N-fused 1,2,4-triazoles

Ceric ammonium nitrate (CAN) has received considerable attention as an easily available and inexpensive catalyst for various synthetically useful reactions such as oxidation, oxidative addition, photooxidation, nitration, graft polymerization, deprotection, etc.[13] In addition, its many advantages such as excellent solubility in water, ecofriendly nature, high reactivity, ease of handling, fast conversions

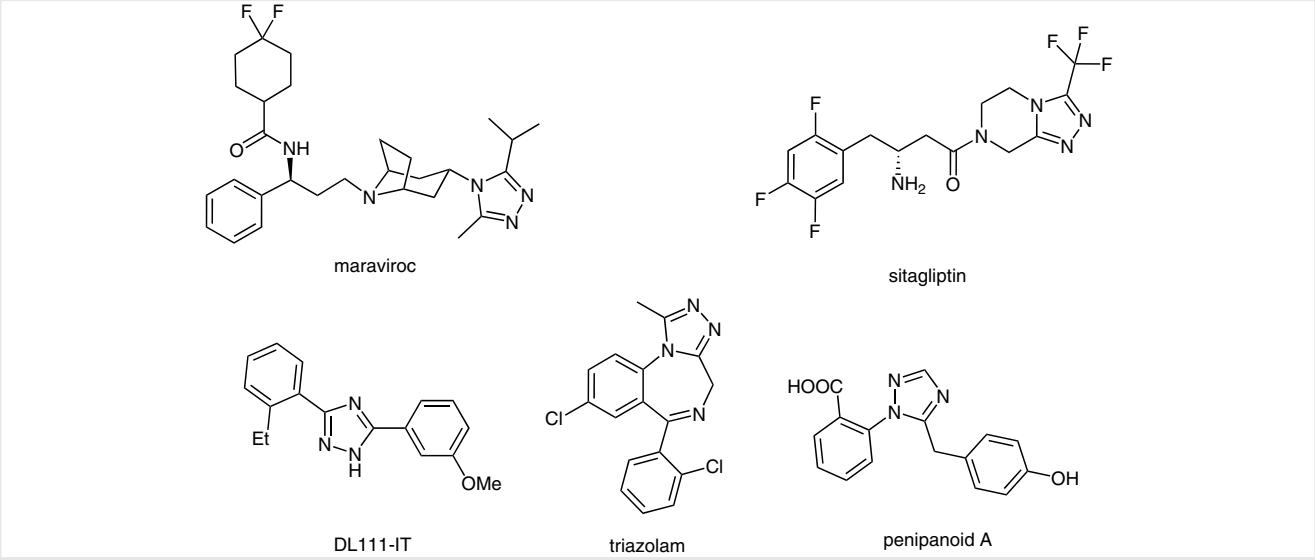
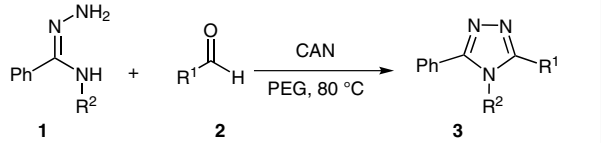


Figure 1 Examples of biologically active and natural compounds possessing a 1,2,4-triazole core

and convenient work-up procedures make ceric ammonium nitrate a potent catalyst in organic synthesis. However, it has not been investigated as a catalyst in the synthesis of 1,2,4-triazoles until now.

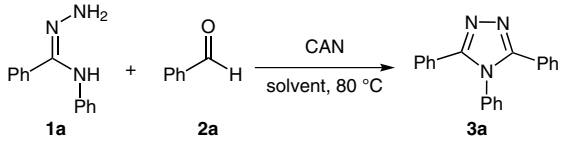
Polyethylene glycol (PEG) has been found to be an interesting, ecofriendly solvent in synthetic organic chemistry.[14] It is non-toxic, inexpensive and can function as a non-ionic liquid solvent of low volatility, all of which represent beneficial properties. Recently, we described the use of polyethylene glycol as a reaction medium for the synthesis of 1,2,4-triazoles,[15] 1,2,4-oxadiazoles,[15] 2-(*N*-acyl)aminobenzimidazoles,[16] 2-(*N*-acyl)aminobenzothiazoles[16] and dihydropyridines.[17] In continuation of our studies on developing inexpensive and environmentally benign methodologies for the synthesis of bioactive molecules,[15–17] herein we report a novel, convenient and efficient ceric ammonium nitrate catalyzed synthesis of 3,4,5-trisubstituted 1,2,4-triazoles via oxidative cyclization of amidrazones with aldehydes in PEG (Scheme 2).



Scheme 2 Synthesis of 3,4,5-trisubstituted 1,2,4-triazoles

Our preliminary investigation began with the reaction of *N*-phenylbenzamidrazone (**1a**) and benzaldehyde (**2a**) in the presence of a catalytic amount of ceric ammonium nitrate (2 mol%) in ethanol at 80 °C. We were delighted to observe the formation of the desired product **3a**, albeit in a low yield of 61% (Table 1, entry 1). Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents were screened and the results are summarized in Table 1. It was found that polyethylene glycol was the most superior solvent in terms of the reaction time and yield of the product (Table 1, entry 4). Once we had established a suitable solvent for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles, we then focused on the quantity of ceric ammonium nitrate. An increase in the amount of ceric ammonium nitrate (from 2 mol% to 5 mol%) not only decreased the reaction time from two hours to one hour, but also increased the product yield from 82% to 96% (Table 1, entry 6). Further increasing the quantity of ceric ammonium nitrate to 10 mol% led to a decrease in the yield to 71% (Table 1, entry 7). Therefore, we decided to perform the subsequent reactions of the amidrazones with different aldehydes in the presence of ceric ammonium nitrate (5 mol%) as the catalyst in polyethylene glycol at 80 °C. The effect of temperature on the reaction rate as well as on the yields of the products was 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



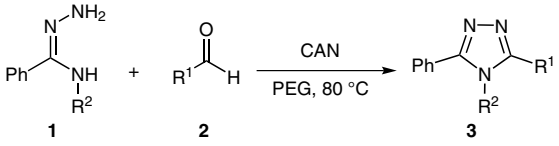
1a **2a** **3a**

Entry	Solvent	CAN (mol%)	Time (h)	Yield (%)[a]
1	EtOH	2%	3	61
2	1,4-dioxane	2%	3	53
3	MeCN	2%	3.5	48
4	PEG-300	2%	2	82
5	toluene	2%	4	28
6	PEG-300	5%	1	96
7	PEG-300	10%	0.5	71

[a] Yield of isolated product after column chromatography.

With optimized conditions in hand, the scope of the reaction was investigated and the results are summarized in Table 2. As expected, all of the aldehydes employed gave the corresponding 3,4,5-trisubstituted 1,2,4-triazoles in good to excellent yields. Benzaldehydes with electron-donating groups such as 4-tolualdehyde (**2b**) and 4-anisaldehyde (**2c**) gave the desired products in very good yields (Table 2, entries 3 and 4). An aromatic aldehyde with an electron-withdrawing group, 4-bromobenzaldehyde (**2d**), gave the corresponding triazole **3e** in 97% yield (Table 2, entry 5). However, the use of 4-nitrobenzaldehyde (**2e**) did not lead to the desired product (Table 2, entry 6). The heteroaryl aldehyde, 3-formylpyridine (**2h**), reacted smoothly, affording the desired product **3i** in good yield (Table 2, entry 9). Aliphatic aldehydes including propanal (**2f**) and cyclohexanal (**2g**) underwent the addition reaction to give the corresponding products **3g** and **3h** in 89% and 90% yields, respectively (Table 2, entries 7 and 8).

Table 2 Synthesis of 3,4,5-Trisubstituted 1,2,4-Triazoles from Different Amidrazones and Aldehydes



1 **2** **3**

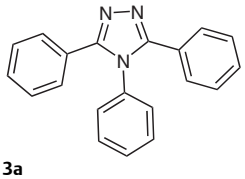
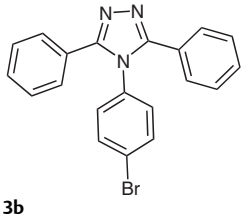
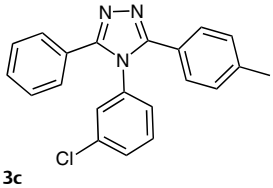
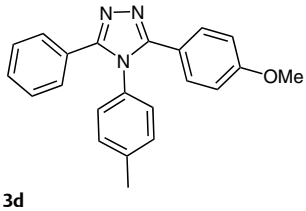
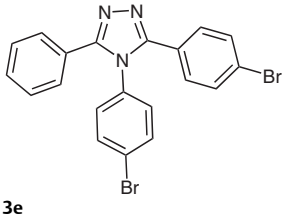
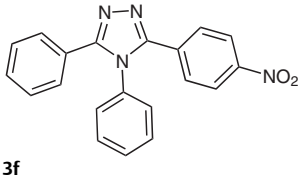
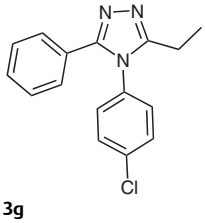
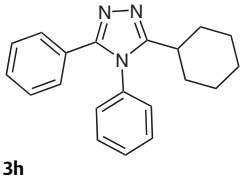
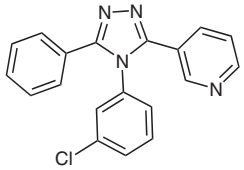
Entry	R	R^1	Product	Time (h)	Yield (%)[a]
1	Ph	Ph (**2a**)	 **3a**	1	96
2	4-BrC_6H_4	Ph (**2a**)	 **3b**	1	95
3	3-ClC_6H_4	4-MeC_6H_4 (**2b**)	 **3c**	1.5	94

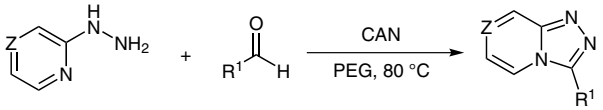
Table 2 (continued)

Entry	R	R^1	Product	Time (h)	Yield (%)[a]
4	4-MeC_6H_4	4-$MeOC_6H_4$ (**2c**)	 **3d**	1.5	93
5	4-BrC_6H_4	4-BrC_6H_4 (**2d**)	 **3e**	1	97
6	Ph	4-$O_2NC_6H_4$ (**2e**)	 **3f**	–	–
7	4-ClC_6H_4	*n*-Pr (**2f**)	 **3g**	2	89
8	Ph	Cy (**2g**)	 **3h**	2	90
9	3-ClC_6H_4	3-pyridyl (**2h**)	 **3i**	2	88

[a] Yield of isolated product after column chromatography.

Encouraged by these promising results, we turned our attention toward the synthesis of N-fused 1,2,4-triazoles such as [1,2,4]triazolo[4,3-*a*]pyridines and [1,2,4]triazolo[4,3-*a*]pyrazines. Gratifyingly, following the above protocol, we were able to prepare triazolopyridines and triazolopyrazines very efficiently using 2-hydrazinopyridines and 2-hydrazinopyrazines, respectively. Table 3 shows the scope of the aldehydes employed, demonstrating that aromatic, aliphatic and heteroaromatic substituents furnished the expected adducts in and efficient manner. However, the electron-deficient aromatic aldehyde, 4-nitrobenzaldehyde (**2e**), was not a suitable substrate for this process (Table 3, entry 5).

Table 3 Synthesis of Various [1,2,4]Triazolo[4,3-*a*]pyridines and [1,2,4]Triazolo[4,3-*a*]pyrazines



4 Z = CH
6 Z = N

2

5 Z = CH
7 Z = N

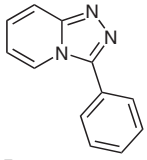
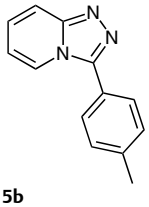
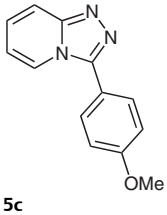
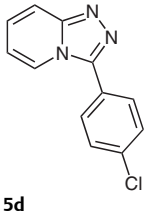
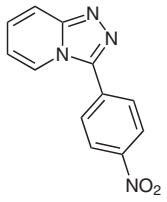
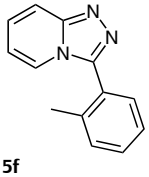
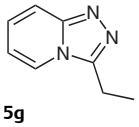
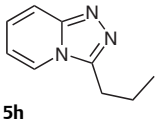
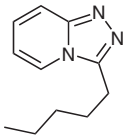
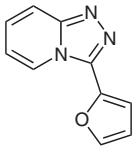
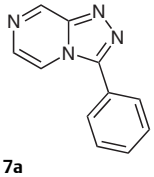
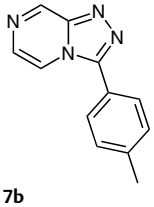
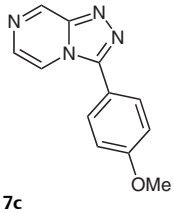
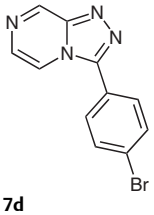
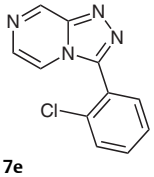
Entry	R^1	Product	Time (h)	Yield (%)[a]
1	Ph (**2a**)	 **5a**	1.5	97
2	4-MeC_6H_4 (**2b**)	 **5b**	1.5	95
3	4-$MeOC_6H_4$ (**2c**)	 **5c**	1.5	94
4	4-ClC_6H_4 (**2i**)	 **5d**	1	98
5	4-$O_2NC_6H_4$ (**2e**)	 **5e**	–	–
6	2-MeC_6H_4 (**2j**)	 **5f**	1.5	96
7	*n*-Pr (**2f**)	 **5g**	2	88

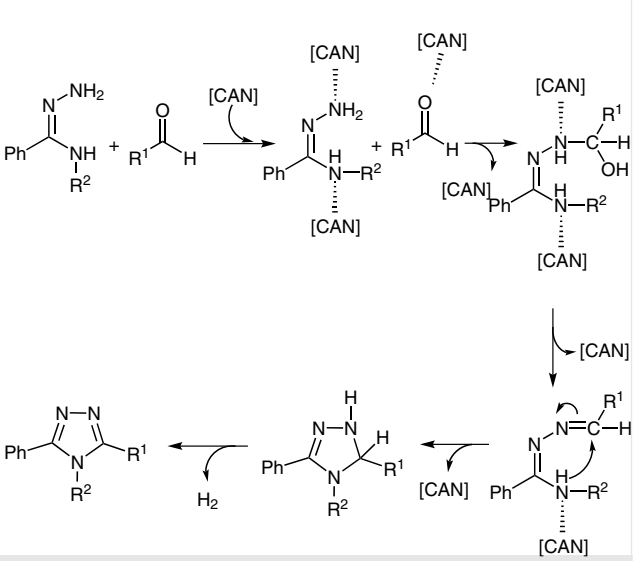
Table 3 (continued)

Entry	R^1	Product	Time (h)	Yield (%)[a]
8	*n*-Bu (**2k**)	 **5h**	2	88
9	*n*-Hex (**2l**)	 **5i**	2	87
10	2-furyl (**2m**)	 **5j**	2.5	91
11	Ph (**2a**)	 **7a**	2	89
12	4-MeC_6H_4 (**2b**)	 **7b**	2	89
13	4-$MeOC_6H_4$ (**2c**)	 **7c**	2	87
14	4-BrC_6H_4 (**2d**)	 **7d**	1.5	93
15	2-ClC_6H_4 (**2n**)	 **7e**	1.5	88

[a] Yield of isolated product after column chromatography

To check the reusability of polyethylene glycol, a mixture of *N*-phenylbenzamidrazone (**1a**), benzaldehyde (**2a**) and ceric ammonium nitrate in polyethylene glycol was stirred at 80 °C for one hour. After the completion of the reaction (monitored by TLC), the mixture was extracted with diethyl ether (3 × 20 mL). The retained polyethylene glycol phase was reused three consecutive times with only a slight variation in the yields of the obtained products (96%, 94% and 92%).

According to the literature,[18] a plausible mechanism has been proposed for this oxidative cyclization reaction as shown in Scheme 3. It is clear that ceric ammonium nitrate acts as both a Lewis acid and an oxidant.



Scheme 3 A plausible mechanism for the preparation of 3,4,5-trisubstituted 1,2,4-triazoles

In summary, we have developed a new, mild and efficient approach for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles and N-fused 1,2,4-triazoles via oxidative cyclization of amidrazones with aldehydes using polyethylene glycol as the solvent and employing ceric ammonium nitrate as the catalyst. The advantages of this procedure are the use of an environmentally benign solvent and cheap oxidant, the wide scope of the reactants and satisfactory product yields, which should make it a useful addition to previously reported strategies.

Standard substrates and reagents were obtained from commercial suppliers and were used without further purification. TLC analysis was performed on Merck silica gel 60 F_{254} plates. Column chromatography was performed on Merck silica gel (100–200 mesh). Melting points were recorded on an Equiptronics capillary digital melting point apparatus. IR spectra were obtained using a Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer and referenced to Me_4Si (δ = 0 ppm). Mass spectra were recorded on an Agilent 1100 LC/MSD. Elemental analyses were obtained using an Elementar Vario EL III analyzer.

3,4,5-Triphenyl-4*H*-1,2,4-triazole (3a);[15] Typical Procedure

A mixture of amidrazone **1a** (1.00 g, 0.0047 mol), benzaldehyde (**2a**) (0.50 g, 0.0047 mol), PEG-300 (5 mL) and CAN (5 mol%) was heated at 80 °C for 1 h (Table 2). After completion of the reaction as monitored by TLC, the mixture was cooled to r.t. and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 30 mL) and aq $NaHCO_3$ solution (2 × 30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (EtOAc–hexane, 1:1) to afford pure **3a**.

Yield: 1.35 g (96%); off-white solid; mp 287–289 °C.

IR (KBr): 3014, 1632, 1498, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 6 H), 7.30–7.19 (m, 7 H), 7.09–7.06 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 135.2, 129.9, 129.5, 128.9, 128.8, 128.3, 127.8, 126.9.

LC–MS: *m*/*z* = 298 [M + H]$^+$.

Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.72; H, 5.11; N, 14.11.

4-(4-Bromophenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (3b)[15]

Yield: 1.23 g (95%); light gray solid; mp 236–238 °C.

IR (KBr): 3031, 1638, 1492, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.41–7.36 (m, 5 H), 7.34–7.26 (m, 5 H), 7.00 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 134.2, 133.2, 129.8, 129.3, 128.9, 128.5, 126.7, 123.6.

LC–MS: *m*/*z* = 376 [M + H]$^+$.

Anal. Calcd for $C_{20}H_{14}BrN_3$: C, 63.84; H, 3.75; N, 11.17. Found: C, 63.81; H, 3.80; N, 11.15.

4-(3-Chlorophenyl)-3-phenyl-5-(*p*-tolyl)-4*H*-1,2,4-triazole (3c)[15]

Yield: 1.32 g (94%); off-white solid; mp 197–199 °C.

IR (KBr): 3031, 2933, 1641, 1470, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.28 (m, 9 H), 7.16–7.11 (m, 3 H), 7.06–7.03 (m, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 153.5, 134.0, 133.2, 129.5, 129.2, 128.44, 128.41, 126.9, 123.7, 26.0.

LC–MS: *m*/*z* = 346 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.90; H, 4.70; N, 12.12.

3-(4-Methoxyphenyl)-5-phenyl-4-(*p*-tolyl)-4*H*-1,2,4-triazole (3d)[15]

Yield: 1.40 g (93%); light gray solid; mp 200–202 °C.

IR (KBr): 3034, 2935, 1608, 1071, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 2 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.33–7.26 (m, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 154.7, 154.5, 139.6, 132.8, 130.4, 130.1, 129.3, 128.7, 128.3, 127.6, 127.3, 119.5, 113.8, 55.2, 21.2.

LC–MS: *m*/*z* = 342 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.37; H, 5.67; N, 12.29.

3,4-Bis(4-bromophenyl)-5-phenyl-4*H*-1,2,4-triazole (3e)

Yield: 1.51 g (97%); light gray solid; mp 180–182 °C.

IR (KBr): 3027, 1638, 1489, 833 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.40 (d, *J* = 6.4 Hz, 3 H), 7.35–7.29 (m, 2 H), 7.26 (d, *J* = 6.4 Hz, 2 H), 7.02 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 153.6, 133.9, 133.3, 131.8, 130.1, 129.2, 129.1, 128.8, 128.5, 126.3, 125.5, 124.5, 123.9.

LC–MS: *m*/*z* = 453 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.77; H, 2.97; N, 9.22.

4-(4-Chlorophenyl)-3-ethyl-5-phenyl-4*H*-1,2,4-triazole (3g)[15]

Yield: 1.02 g (89%); off-white solid; mp 136–138 °C.

IR (KBr): 3036, 2957, 1634, 1489, 826 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 8.0 Hz, 2 H), 7.39–7.26 (m, 5 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 2.66 (q, *J* = 7.2 Hz, 2 H), 1.28 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 153.8, 134.0, 133.3, 129.6, 128.9, 128.5, 128.3, 126.8, 123.7, 19.0, 11.7.

LC–MS: *m*/*z* = 284 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 67.70; H, 5.01; N, 14.78.

3-Cyclohexyl-4,5-diphenyl-4*H*-1,2,4-triazole (3h)[15]

Yield: 1.29 g (90%); light gray solid; mp 147–149 °C.

IR (KBr): 3028, 2935, 1637, 1468, 833 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 3 H), 7.49–7.38 (m, 2 H), 7.29–7.23 (m, 3 H), 7.22–7.19 (m, 2 H), 2.53–2.50 (m, 1 H), 1.89–1.75 (m, 6 H), 1.68–1.64 (m, 1 H), 1.31–1.15 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 153.6, 135.1, 129.9, 129.6, 129.2, 128.4, 128.3, 127.6, 127.2, 34.7, 31.6, 26.0, 25.6.

LC–MS: *m*/*z* = 304 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.16; H, 7.01; N, 13.82.

3-[4-(3-Chlorophenyl)-5-phenyl-4*H*-1,2,4-triazol-3-yl]pyridine (3i)

Yield: 1.19 g (88%); light gray solid; mp 200–202 °C.

IR (KBr): 3029, 1597, 1485, 838 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.63 (t, *J* = 4.0 Hz, 2 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.51 (d, *J* = 8.4 Hz, 1 H), 7.45–7.40 (m, 4 H), 7.37–7.20 (m, 3 H), 7.20 (s, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 152.0, 150.5, 148.8, 135.9, 135.8, 135.6, 131.0, 130.3, 130.0, 128.6, 128.5, 127.7, 125.9, 125.8, 123.2, 122.9.

LC–MS: *m*/*z* = 333 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{13}ClN_4$: C, 68.57; H, 3.94; N, 16.84. Found: C, 68.56; H, 3.99; N, 16.83.

3-Phenyl[1,2,4]triazolo[4,3-*a*]pyridine (5a)[19]

Yield: 1.71 g (97%); off-white solid; mp 171–173 °C.

IR (KBr): 3030, 1631, 1494, 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 6.8 Hz, 1 H), 7.84 (dd, *J* = 5.6, 6.4 Hz, 3 H), 7.60–7.52 (m, 3 H), 7.27 (dd, *J* = 6.8, 9.2 Hz, 1 H), 6.88 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 146.7, 130.2, 129.3, 128.2, 126.9, 126.7, 122.6, 116.9, 114.2.

LC–MS: *m*/*z* = 196 $[M + H]^+$.

Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.76; H, 4.76; N, 21.48.

3-(4-Tolyl)[1,2,4]triazolo[4,3-*a*]pyridine (5b)

Yield: 1.80 g (95%); off-white solid; mp 110–112 °C.

IR (KBr): 3026, 2916, 1629, 1494, 744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.2 Hz, 1 H), 7.85 (d, *J* = 9.2 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.30–7.26 (m, 1 H), 6.88–6.84 (m, 1 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 146.8, 140.4, 129.9, 128.1, 126.9, 123.7, 122.6, 116.7, 114.0, 21.4.

LC–MS: *m*/*z* = 210 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.58; H, 5.41; N, 20.01.

3-(4-Methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (5c)[19]

Yield: 1.92 g (94%); off-white solid; mp 122–124 °C.

IR (KBr): 3031, 2981, 1613, 1498, 1130, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 1.2 Hz, 1 H), 7.80–7.75 (m, 3 H), 7.28–7.24 (m, 1 H), 7.11 (dd, *J* = 2.0, 6.0 Hz, 2 H), 6.85 (m, 1 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 149.9, 146.0, 129.8, 127.7, 123.9, 118.9, 115.7, 114.8, 114.3, 55.5.

LC–MS: *m*/*z* = 226 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.29; H, 4.99; N, 18.62.

3-(4-Chlorophenyl)[1,2,4]triazolo[4,3-*a*]pyridine (5d)[19]

Yield: 2.00 g (98%); off-white solid; mp 196–199 °C.

IR (KBr): 3039, 1633, 1473, 826 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.57 (d, *J* = 7.2 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 2 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.46–7.42 (m, 1 H), 7.04 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 150.5, 145.5, 135.1, 130.3, 129.7, 128.5, 125.9, 124.4, 116.1, 115.0.

LC–MS: *m*/*z* = 230 $[M + H]^+$.

Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.71; H, 3.59; N, 18.28.

3-(2-Tolyl)[1,2,4]triazolo[4,3-*a*]pyridine (5f)

Yield: 1.82 g (96%); off-white solid; mp 148–150 °C.

IR (KBr): 3028, 2921, 1626, 1498, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.76 (m, 2 H), 7.45–7.35 (m, 4 H), 7.30–7.26 (m, 1 H), 6.83–6.79 (dd, *J* = 0.4, 6.4 Hz, 1 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 146.2, 138.5, 133.8, 130.6, 130.5, 130.2, 127.0, 126.2, 125.5, 122.6, 116.5, 19.6.

LC–MS: *m*/*z* = 210 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.61; H, 5.33; N, 20.06.

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

Yield: 1.18 g (88%); light orange solid; mp 121–123 °C.

IR (KBr): 3041, 2981, 1631, 1489 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.27–7.20 (m, 1 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 1.92 (q, *J* = 8.2 Hz, 2 H), 1.05 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 146.7, 129.5, 121.8, 116.5, 113.3, 20.0, 13.7.

LC–MS: *m*/*z* = 148 $[M + H]^+$.

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.27; H, 6.20; N, 28.53.

3-Propyl[1,2,4]triazolo[4,3-*a*]pyridine (5h)

Yield: 1.29 g (88%); light orange solid; mp 122–124 °C.

IR (KBr): 3044, 2983, 1627, 1482 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.24–7.20 (m, 1 H), 6.83 (t, *J* = 8.0 Hz, 1 H), 3.04 (t, *J* = 8.0 Hz, 2 H), 1.92 (m, 2 H), 1.05 (t, *J* = 8.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 146.7, 126.6, 121.9, 116.6, 113.5, 26.4, 20.0, 13.8.

LC–MS: *m*/*z* = 162 $[M + H]^+$.

Anal. Calcd for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.04; H, 6.95; N, 26.04.

3-Pentyl[1,2,4]triazolo[4,3-*a*]pyridine (5i)

Yield: 1.50 g (87%); light orange solid; mp 111–114 °C.

IR (KBr): 3040, 2980, 1632, 1504 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 6.8 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.18 (m, 1 H), 6.79 (t, *J* = 6.8 Hz, 1 H), 3.01 (t, *J* = 7.6 Hz, 2 H), 1.85 (t, *J* = 6.8 Hz, 2 H), 1.37–1.32 (m, 4 H), 0.85 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 146.9, 126.5, 121.9, 116.5, 113.5, 31.4, 26.2, 24.4, 22.2, 13.8.

LC–MS: *m*/*z* = 190 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99; N, 22.20. Found: C, 69.79; H, 8.02; N, 22.19.

3-(Furan-2-yl)[1,2,4]triazolo[4,3-*a*]pyridine (5j)

Yield: 1.54 g (91%); off-white solid; mp 132–134 °C.

IR (KBr): 3039, 1631, 1420, 1082 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.75 (d, *J* = 8.0 Hz, 1 H), 8.01 (d, *J* = 4.0 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.47–7.42 (m, 1 H), 7.29 (t, *J* = 4.0 Hz, 1 H), 7.29–7.08 (m, 1 H), 6.79 (dd, *J* = 1.6, 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.7, 145.0, 142.0, 139.1, 128.5, 124.9, 116.0, 115.3, 112.4, 111.0.

LC–MS: *m*/*z* = 186 $[M + H]^+$.

Anal. Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.84; H, 3.90; N, 22.68.

3-Phenyl[1,2,4]triazolo[4,3-*a*]pyrazine (7a)[19]

Yield: 1.57 g (89%); off-white solid; mp 161–163 °C.

IR (KBr): 3036, 1614, 1450, 707 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.44 (s, 1 H), 8.18 (d, *J* = 5.0 Hz, 1 H), 7.97–7.91 (m, 2 H), 7.77–7.57 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.5, 146.6, 144.8, 130.5, 130.0, 129.7, 128.1, 125.9, 117.1.

LC–MS: *m*/*z* = 197 $[M + H]^+$.

Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.29; H, 4.22; N, 28.49.

3-(4-Tolyl)[1,2,4]triazolo[4,3-*a*]pyrazine (7b)

Yield: 1.69 g (89%); off-white solid; mp 164–166 °C.

IR (KBr): 3091, 2978, 1660, 1427, 815 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* = 1.6 Hz, 1 H), 8.60 (dd, *J* = 1.6, 4.8 Hz, 1 H), 7.95 (d, *J* = 4.8 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.1, 146.0, 144.6, 140.8, 130.3, 129.7, 128.4, 123.3, 117.4, 21.5.

LC–MS: *m*/*z* = 211 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.51; H, 4.88; N, 26.61.

3-(4-Methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyrazine (7c)

Yield: 1.77 g (87%); off-white solid; mp 148–150 °C.

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

^1H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, *J* = 1.6 Hz, 1 H), 8.19 (dd, *J* = 1.6, 4.8 Hz, 1 H), 7.91 (d, *J* = 4.8 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 145.8, 145.0, 130.23, 130.20, 129.6, 129.0, 127.9, 115.2, 56.5.

LC–MS: *m*/*z* = 227 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.68; H, 4.52; N, 24.71.

3-(4-Bromophenyl)[1,2,4]triazolo[4,3-*a*]pyrazine (7d)

Yield: 2.30 g (93%); off-white solid; mp 168–171 °C.

IR (KBr): 3039, 1628, 1502, 818 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* = 1.2 Hz, 1 H), 8.62 (dd, *J* = 1.6, 4.8 Hz, 1 H), 7.95 (d, *J* = 4.8 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.0, 145.9, 144.3, 132.4, 130.29, 130.25, 125.1, 124.1, 117.2.

LC–MS: *m*/*z* = 276 $[M + H]^+$.

Anal. Calcd for $C_{11}H_7BrN_4$: C, 48.02; H, 2.56; N, 20.37. Found: C, 48.00; H, 2.64; N, 20.34.

3-(2-Chlorophenyl)[1,2,4]triazolo[4,3-*a*]pyrazine (7e)

Yield: 1.82 g (88%); off-white solid; mp 164–165 °C.

IR (KBr): 3033, 1636, 1484, 744 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* = 1.6 Hz, 1 H), 8.66 (d, *J* = 1.2 Hz, 1 H), 8.44 (s, 1 H), 8.15–8.03 (m, 2 H), 7.50–7.47 (m, 1 H), 7.41–7.35 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.0, 142.4, 137.1, 135.9, 132.57, 132.54, 131.3, 130.7, 130.2, 127.9, 126.9.

LC–MS: *m*/*z* = 231 $[M + H]^+$.

Anal. Calcd for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.24; H, 3.19; N, 24.25.

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