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Facile one pot synthesis of N-fused 1,2,4-triazoles via oxidative cyclisation using DDQ

Ashish Bhatt[a], Rajesh K. Singh[b], and Ravi Kant*[a]

[a] *Department of Chemistry, Mewar university, Chittorgarh, (Rajasthan), 312901, India*
[b] *Department of Pharmacy, Mewar university, Chittorgarh, (Rajasthan), 312901, India*
E-mail: itsbhatt2007@yahoo.co.in

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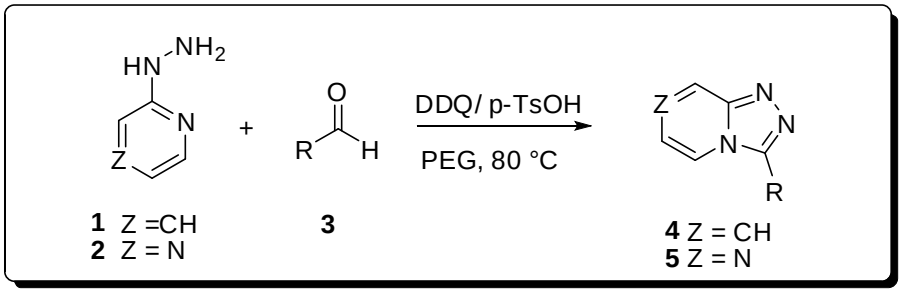
Abstract

A facile and expedient one pot synthesis of N-fused 1,2,4-triazoles from 2-hydrazinopyridines or 2-hydrazinopyrazines and aldehydes is described via oxidative cyclization using DDQ as a safe and convenient oxidizing agent and 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.



Keywords: Polyethylene glycol, DDQ, 1,2,4-triazoles, [1,2,4]triazolo[4,3-a]pyridines, [1,2,4]triazolo[4,3-a]pyrazines

Introduction

Fused aromatic heterocycles are among the most important compound classes in drug discovery and also play a pivotal role in living organisms. In particular, such scaffolds can be found as building blocks for DNA (guanine, adenine) but also in many approved drugs including sildenafil, zolpidem, and trazodone, as well as in medicinal chemistry studies[1–4] [i.e., tyrosine kinase c-Src inhibitors[5,6] or P38α inhibitors; [7] Figure 1].

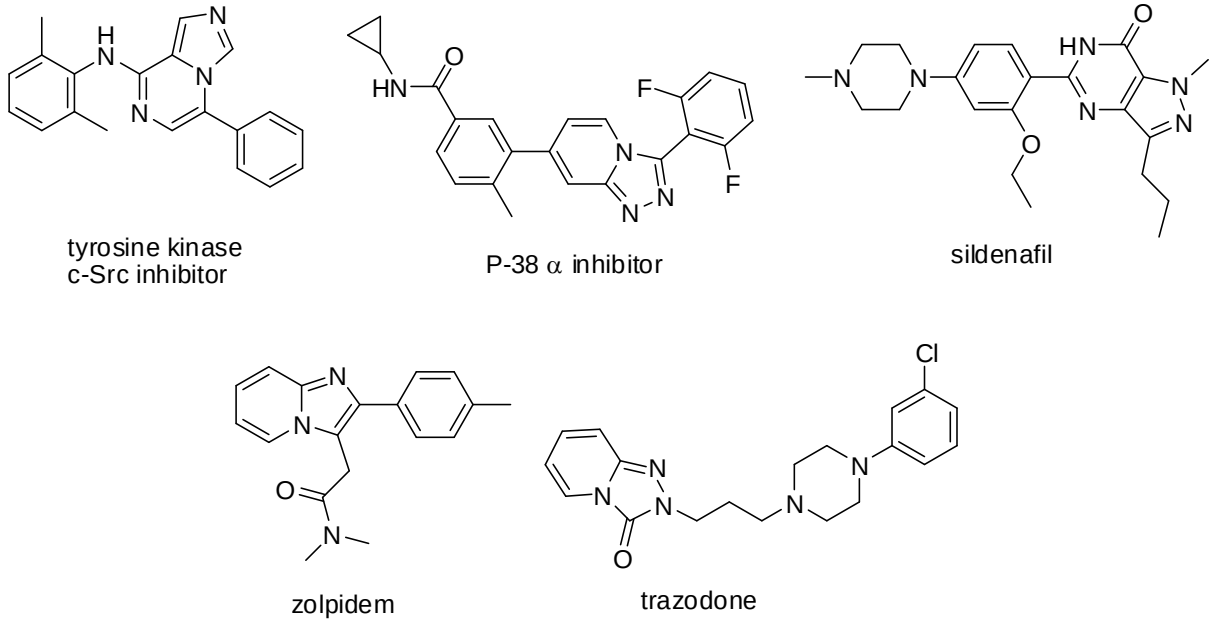
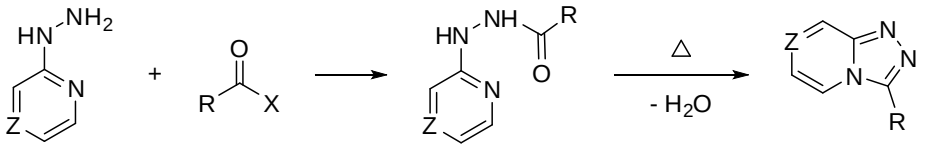


Figure 1

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. 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,[8] antimicrobial,[9] antiviral,[10] anti-inflammatory,[11] antiasthmatic,[12] antiproliferative[13] and hypotonic.[14] In addition, they have often been used as bioisosteres of esters and amides, and as dipeptidomimetics in a number of pharmacologically important molecules.[15] 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.[16]

Due to their importance, many efficient methods have been developed to access N-fused 1,2,4-triazoles.[17] Among them, coupling of carboxylic acids or their derivatives with amidrazones, followed by cyclodehydration is the most common explored strategy (Scheme 1).[18] 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 N-fused 1,2,4-triazoles remains desirable.



Scheme-1. General synthesis of N-fused 1,2,4-triazoles.

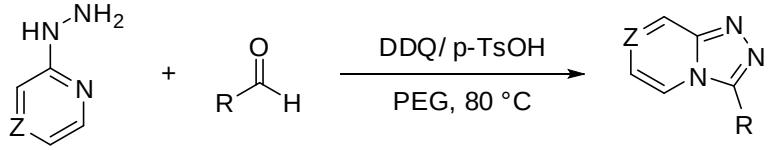
The described oxidative cyclization has previously been reported for the preparation of triazoloquinoxalines.[19–25] Other methods reported in the literature for the cyclization of the triazole ring usually require a combination of NBS and base,[26] refluxing orthoesters,[27,28] acids,[28,29] desulfurization of thiosemicarbazides,[30] or cyclization of hydrazides in polyphosphoric acid (PPA).[28] A couple of examples of oxidative cyclizations using chloramine-T,[31] phenyliodine bis(trifluoroacetate) or iodobenzene diacetate,[32] ceric ammonium nitrate,[33] catalyzed by KI/TBHP,[34] have also been reported.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has attracted significant attention since it was first synthesized by Thiele and Günther in 1906.[35] DDQ is a highly effective oxidizing agent and has been successfully utilized for various organic transformations, including aromatization, deprotection of functional groups, dehydrogenation, cyclisation reaction and potential applications for the formation of carbon-carbon bonds.[36-43]

It should be mentioned that the great advantage of the methodology using DDQ is the fact that the reduced by-product (DDQ-H_2) could be readily removed by filtration and oxidized with MnO_2 in order to recycle back into DDQ. However, it has not been investigated as a reagent in the synthesis of 1,2,4-triazoles until now.

Results and Discussion

Polyethylene glycol (PEG) has been found to be an interesting, ecofriendly solvent in synthetic organic chemistry.[44] It is non-toxic, inexpensive and can function as a non-ionic liquid solvent of low volatility, all of which represent beneficial properties. Various literature describe the use of polyethylene glycol as a reaction medium for the synthesis of 1,2,4- triazoles,[45] 1,2,4-oxadiazoles,[45] 2-(*N*-acyl)aminobenzimidazoles,[46] 2-(*N*-acyl)aminobenzothiazoles[46] and dihydropyridines.[47] In continuation of our studies on developing inexpensive and environmentally benign methodologies for the synthesis of bioactive molecules,[45-47] herein we report a novel, convenient and efficient synthesis of N-fused 1,2,4-triazoles via oxidative cyclization of 2-hydrazinopyridines or 2-hydrazinopyrazines with aldehydes in PEG by using DDQ as an oxidizing agent and p-TsOH as a catalyst (Scheme 2).



Scheme 2. Synthesis of N-fused 1,2,4-triazoles.

Our preliminary investigation began with the reaction of 2-hydrazinopyridine (**1a**) and benzaldehyde (**3a**) in the presence of DDQ (1equiv.) and a catalytic amount of *p*-TsOH (2 mol%) in ethanol at 80 °C. We were delighted to observe the formation of the desired product **4a**, albeit in a low yield of 65% (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 N-fused 1,2,4-triazoles, we then focused on the quantity of DDQ and *p*-TsOH. An increase in the amount of DDQ (from 1equiv. to 2equiv.) and *p*-TsOH (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 80% to 95% (Table 1, entry 7). Further increasing the quantity of DDQ to 3equiv. and *p*-TsOH (10 mol%) led to a decrease in the yield to 70% (Table 1, entry 8). Therefore, we decided to perform the subsequent reactions of the 2-hydrazinopyridines or 2-hydrazinopyrazines with different aldehydes in the presence of DDQ (2 equiv.) and *p*-TsOH (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).

Mechanism:

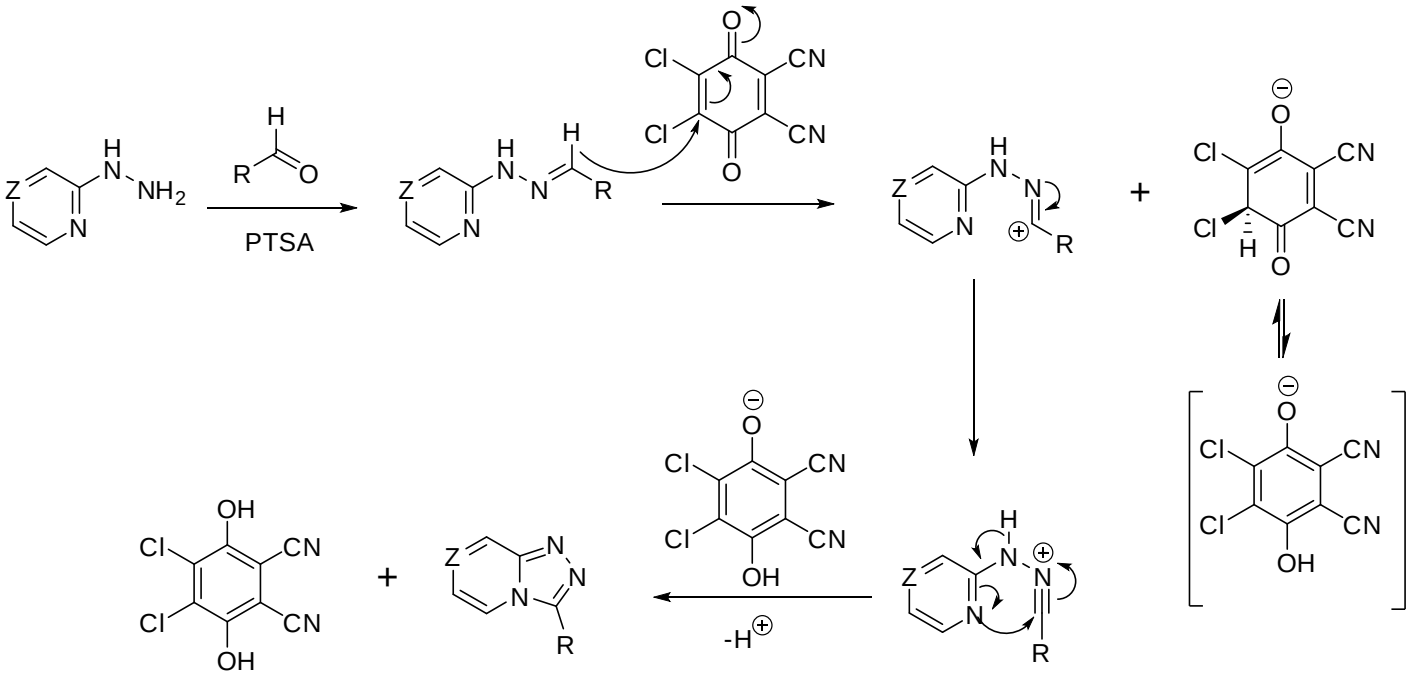
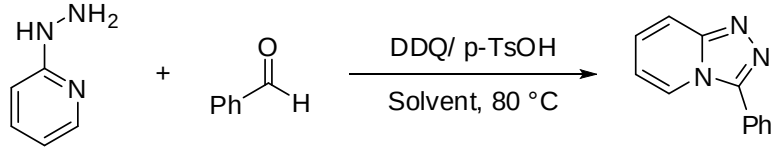


Table 1. Optimization of the reaction conditions



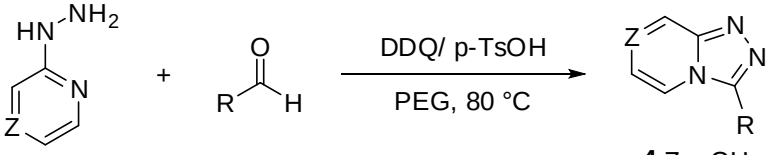
1a **3a** **4a**

Entry	Solvent	DDQ (equiv.)	p-TsOH (mol%)	Time (h)	Yield (%)
1	EtOH	1	2	3.5	65
2	1,4-dioxane	1	2	3.5	50
3	MeCN	1	2	4	48
4	PEG-300	1	2	2	80
5	Toluene	1	2	4	50
6	PEG-300	1.5	5	1.5	90
7	PEG-300	2	5	1	95
8	PEG-300	3	10	0.5	70

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 N-fused 1,2,4-triazoles in good to excellent yields. Benzaldehydes with electron-donating groups such as *p*-tolualdehyde (**3b**) and *p*-anisaldehyde (**3f**) gave the desired products in very good yields (Table 2, entries 2 and 6). An aromatic aldehyde with an electron withdrawing group, 4-chlorobenzaldehyde (**3d**), gave the corresponding triazole **4d** in 90% yield (Table 2, entry 4). However, the use of 4-nitrobenzaldehyde (**3h**) did not lead to the desired product (Table 2, entry 8). The heteroaryl aldehyde, 4-formylpyridine (**3k**), reacted smoothly, affording the desired product **4k** in good yield (Table 2, entry 11).

To check the reusability of polyethylene glycol, a mixture of 2-hydrazinopyridine (**1a**), benzaldehyde (**3a**) and DDQ 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 (92%, 90% and 87%).

Table 2. Synthesis of various [1,2,4]triazolo[4,3-*a*]pyridines and [1,2,4]triazolo[4,3-*a*]pyrazines



1 Z =CH
2 Z = N

3

4 Z = CH
5 Z = N

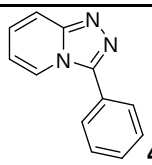
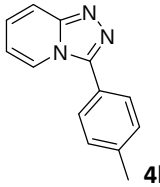
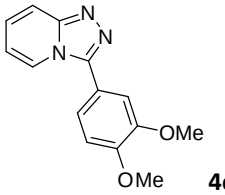
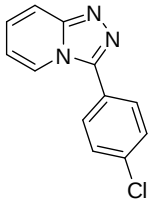
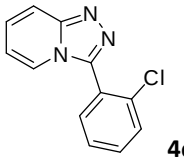
Entry	R	Product	Time (h)	Yield (%)
1	Ph **3a**	 **4a**	1	95
2	4-MeC_6H_4 **3b**	 **4b**	1	97
3	3,4-OMeC_6H_3 **3c**	 **4c**	1.5	85
4	4-ClC_6H_4 **3d**	 **4d**	1	90
5	2-ClC_6H_4 **3e**	 **4e**	1	83

Table 2. Continued

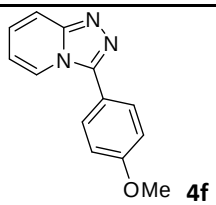
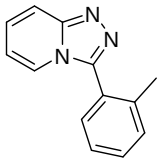
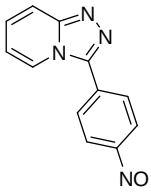
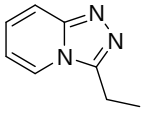
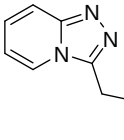
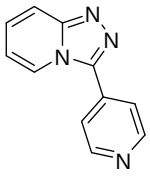
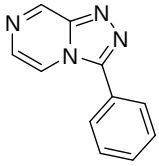
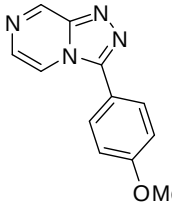
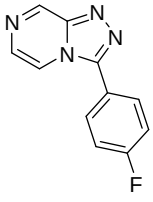
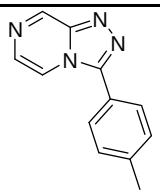
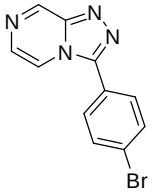
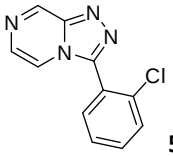
Entry	R	Product	Time (h)	Yield (%)
6	4-OMeC_6H_4 **3f**	 **4f**	1	98
7	2-MeC_6H_4 **3g**	 **4g**	0.5	95
8	4-$NO_2C_6H_4$ **3h**	 **4h**	--	--
9	C_2H_5 **3i**	 **4i**	0.5	93
10	C_3H_7 **3j**	 **4j**	0.5	90
11	4-pyridyl **3k**	 **4k**	1.5	80
12	Ph **3a**	 **5a**	0.5	92
13	4-OMeC_6H_4 **3f**	 **5b**	1	95
14	4-F C_6H_4 **3j**	 **5c**	1	85

Table 2. Continued

Entry	R	Product	Time (h)	Yield (%)
15	4-MeC_6H_4 **3b**	 **5d**	0.5	94
16	4-BrC_6H_4 **3k**	 **5e**	1.5	87
17	2-ClC_6H_4 **3e**	 **5f**	1	90

Conclusions

In summary, we have developed a new, mild and efficient approach for the synthesis of N-fused 1,2,4-triazoles via oxidative cyclization of amidrazones with aldehydes using polyethylene glycol as the solvent and employing DDQ as an oxidizing agent and *p*-TsOH 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.

Experimental Section

General. Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and mass of the synthesized compounds was checked by LCMS . ^{1}H NMR spectral was recorded in $CDCl_3$ /DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively.

General procedure for the one-pot synthesis of N-fused 1,2,4-triazoles (4a-4k, 5a-5f). To a stirred solution of 2-hydrazinopyridines **1a-k** or 2-hydrazinopyrazines **2a-f** (1equiv.) and aldehyde **3a-k** (1equiv.) in polyethylene glycol (PEG) (10 mL) were added *p*-TsOH (5 mol%)) and DDQ (2 equiv.). The mixture was stirred at reflux until the starting material was completely consumed (monitored by TLC, 1h) and then cooled down to room temperature. After filtration and evaporation of solvent from the filtrate, the resulting residue was purified by silica gel column chromatography (EtOAc/Hexane, 3:7 v/v), affording the pure *N*-fused 1,2,4-triazole derivative, [1,2,4]triazolo[4,3-a]pyridines **4a-k** & [1,2,4]triazolo[4,3-a]pyrazines **5a-f**.

3-Phenyl-[1,2,4]triazolo[4,3-*a*]pyridine (4a). Mp 171–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.28 (d, *J* 6.8 Hz, 1H), 7.82 (dd, *J* 6.4, 5.6 Hz, 3H), 7.60-7.52 (m, 3H), 7.27 (dd, J 6.8, 9.2 Hz, 1H), 6.86 (t, *J* 6.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 150.5, 146.7, 130.2, 129.3, 128.2, 126.9, 126.7, 122.6, 116.9, 114.17. LCMS: *m/z* = 196 $[M+H]^+$. 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-(*p*-Tolyl)-[1,2,4]triazolo[4,3-*a*]pyridine (4b). Mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* 7.2 Hz, 1H), 7.85 (d, *J* 9.2 Hz, 1H), 7.75 (d, *J* 8.0 Hz, 2H), 7.42 (d, *J* 8.0 Hz, 2H), 7.30-7.26 (m, 1H), 6.88-6.84 (m, 1H), 2.48 (s, 3H). ^{13}C NMR (400 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. LCMS: *m/z* = 210 $[M+H]^+$. 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-(3,4-Dimethoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine (4c). Mp 136–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.52 (m, 1H), 7.81 (m, 1H), 7.42-7.36 (m, 3H), 7.16 (t, *J* 4.4 Hz, 1H), 6.99-6.87 (m, 1H), 3.81 (s, 6H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 150.6, 150.2, 149.6, 146.5, 128.1, 124.4, 121.3, 119.3, 116.0, 114.6, 112.6, 112.1, 56.1. LCMS: *m/z* = 256 $[M+H]^+$. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.81; H, 5.11; N, 16.41.

3-(4-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyridine (4d). Mp 196–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.57 (d, *J* 7.2 Hz, 1H), 7.94 (d, *J* 8.8 Hz, 2H), 7.86 (d, *J* 9.2 Hz, 1H), 7.69 (d, *J* 8.4 Hz, 2H), 7.46-7.42 (m, 1H), 7.04 (t, *J* 7.2 Hz, 1H). ^{13}C NMR (400 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. LCMS: *m/z* = 230 $[M+H]^+$. 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-Chlorophenyl)-[1,2,4]triazolo[4,3-*a*]pyridine (4e). Mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* 6.8 Hz, 1H), 7.82 (d, *J* 8.8 Hz, 1H), 7.38 (d, *J* 8.4 Hz, 2H), 7.32-7.25 (m, 3H), 6.84 (t, *J* 6.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 163.2, 151.1, 141.5, 133.4, 130.38, 130.35, 126.9, 123.2, 122.1, 116.9, 116.7, 114.3; LCMS: *m/z* = 230 $[M+H]^+$; Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.70; H, 3.61; N, 18.29.

3-(4-Methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (4f). Mp 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* 1.2 Hz, 1 H), 7.80–7.75 (m, 3H), 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 (400 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. LCMS: *m/z* = 226 $[M + H]^+$. 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-(*o*-Tolyl)[1,2,4]triazolo[4,3-*a*]pyridine (4g). Mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.76 (m, 2H), 7.45–7.35 (m, 4H), 7.30–7.26 (m, 1H), 6.83–6.79 (dd, *J* 0.4, 6.4 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (400 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. LCMS: *m/z* = 210 $[M + H]^+$. 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 (4i). Mp 121-123 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.89 (d, *J* 8.0 Hz, 1H), 7.72 (d, *J* 8.0 Hz, 1H), 7.27–7.20 (m, 1H), 6.83 (t, *J* 8.0 Hz, 1H), 1.92 (q, *J* 8.2 Hz, 2H), 1.05 (t, *J* 8.0 Hz, 3H). ^{13}C NMR (400MHz, $CDCl_3$): δ = 149.6, 146.7, 129.5, 121.8, 116.5, 113.3, 20.0, 13.7. LCMS: *m/z* =148 $[M+H]^+$. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.25; H, 6.14; N, 28.52.

3-Propyl[1,2,4]triazolo[4,3-*a*]pyridine (4j). Mp 122-124 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.90 (d, *J* 8.0 Hz, 1H), 7.73 (d, *J* 8.0 Hz, 1H), 7.24–7.20 (m, 1H), 6.83 (t, *J* 8.0 Hz, 1H), 3.04 (t, *J* 8.0 Hz, 2H), 1.92 (m, 2H), 1.05 (t, *J* 8.0 Hz, 3H). ^{13}C NMR (400MHz, $CDCl_3$): δ = 149.7, 146.7, 126.6, 121.9, 116.6, 113.5, 26.4, 20.0, 13.8. LCMS: *m/z* =162 $[M+H]^+$. Calcd for $C_{11}H_8N_4$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.03; H, 6.84; N, 26.03.

3-(Pyridin-4-yl)-[1,2,4]triazolo[4,3-*a*]pyridine (4k). Mp 176-178 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ = 8.88 (d, J 6.0 Hz, 2H), 8.48 (d, J 7.2 Hz, 1H), 7.92 (d, J 9.6 Hz, 1H), 7.85 (d, J 6.0 Hz, 2H), 7.46 (d, J 9.6 Hz, 1H), 7.01-6.91 (m, 1H). ^{13}C NMR (400MHz, $CDCl_3$): δ = 151.3, 150.9, 144.1, 133.5, 126.9, 122.2, 122.1, 116.9, 113.7. LCMS: *m/z* =197 $[M+H]^+$. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.32; H, 4.14; N, 28.54.

3-Phenyl-[1,2,4]triazolo[4,3-*a*]pyrazine (5a). Mp 161-163 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.44 (s, 1H), 8.18 (d, *J* 5.0 Hz, 1H), 7.97-7.83 (m, 2H), 7.77-7.55 (m, 4H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 147.5, 146.6, 144.8, 132.3, 130.0, 129.7, 128.1, 124.3, 117.4. LCMS: m/z = 197 $[M+H]^+$. 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-Methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (5b). Mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.39 (d, *J* 1.6 Hz, 1H), 8.19 (dd, *J* 1.6, 4.8 Hz, 1H), 7.91 (d, *J* 4.8 Hz, 1H), 7.75 (d, *J* 8.0 Hz, 2H), 7.26 (d, *J* 8.0 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 147.3, 145.8, 145.0, 130.2, 130.2, 129.6, 129.0, 127.9, 115.2, 56.5. LCMS: *m/z* = 227 $[M+H]^+$. 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-Fluorophenyl)-[1,2,4]triazolo[4,3-*a*]pyrazine (5c). Mp 177–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.48 (d, *J* 1.2 Hz, 1H), 8.62 (dd, *J* 1.6, 4.8 Hz, 1H), 8.00-7.93 (m, 3H), 7.71-7.69 (m, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 163.5, 152.3, 141.3, 139.9, 136.1, 132.0, 130.4, 128.4, 115.9. LCMS: *m/z* = 215 $[M+H]^+$. Calcd for $C_{11}H_7N_4F$: C, 61.68; H, 3.29; N, 26.16. Found: C, 61.66; H, 3.25; N, 26.11.

3-(*p*-Tolyl)[1,2,4]triazolo[4,3-*a*]pyrazine (5d). Mp 164–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* 1.6 Hz, 1H), 8.60 (dd, *J* 1.6, 4.8 Hz, 1H), 7.95 (d, *J* 4.8 Hz, 1H), 7.87 (d, *J* 8.0 Hz, 2H), 7.47 (d, *J* 8.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (400 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. LCMS: m/z = 211 $[M + H]^+$. 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-Bromophenyl)[1,2,4]triazolo[4,3-*a*]pyrazine (5e). Mp 168–171 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* 1.2 Hz, 1H), 8.62 (dd, *J* 1.6, 4.8 Hz, 1H), 7.95 (d, *J* 4.8 Hz, 1H), 7.87 (d, *J* 8.0 Hz, 2H), 7.47 (d, *J* 8.0 Hz, 2H). ^{13}C NMR (400 MHz, DMSO-d_6): δ = 146.0, 145.9, 144.3, 132.4, 130.29, 130.25, 125.1, 124.1, 117.2. LCMS: *m/z* = 276 $[M + H]^+$. 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 (5f). Mp 164–165 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.47 (d, *J* 1.6 Hz, 1H), 8.66 (d, *J* 1.2 Hz, 1H), 8.44 (s, 1H), 8.15–8.03 (m, 2H), 7.50–7.47 (m, 1H), 7.41–7.35 (m, 1H). ^{13}C NMR (400 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. LCMS: *m/z* = 231 $[M + H]^+$. 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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