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ARTICLE

Base free regioselective synthesis of α-triazolylazine derivatives

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A regioselective α-heteroarylation followed by deoxygenation towards the synthesis of variety of azine triazole from simple azine *N*-oxides derivatives and *N*-tosyl-1,2,3-triazoles has been described. The reaction is metal free and base free with lesser reaction time, high yields and a broad substrate scope.

Introduction

(Hetero)aryl substituted azines have wide range of medicinal properties. Pyridotriazoles and quinolinotriazoles[1] are particularly interesting, as they exhibit significant biological properties including control of arthropod tests,[2] substance-related disorders,[3] ATP-competitive inhibition of vascular endothelial growth factor receptors I and II[4] and other biological activities.[5] A number of derivatives of 1-(pyridin-2-yl)-1,2,3-triazole have been used as ligands.[6] In recent years, direct (hetero)arylation has emerged as an attractive alternative to the commonly employed cross coupling reactions as it avoids the preliminary preparation of the metallated or halogenated arene. Several reviews highlight the broad scope of this strategy involving high functional group tolerance, atom economy and mild reaction conditions.[7]
Functionalized azines are to be designed due to their biological importance and though there are significant progress has been achieved in the development of catalytic alkylation, alkenylation and acylation reactions at the pyridine nucleus,[8] the arylation/heteroarylation[9] and alkenylation[10] at pyridine *N*-oxides could be achieved only with transition metal catalysts. The regioselective arylation of azines has been achieved through Pd-catalyzed direct arylation of the corresponding *N*-oxides and *N*-iminopyridinium-ylides.[11] New metal free methods of arylation with regiocontrol are thus invaluable. We report a new C-N bond forming reaction *via* regioselective α-heteroarylation followed by deoxygenation towards the synthesis of variety of azine triazole from simple azine *N*-oxides derivatives and *N*-tosyl-1,2,3-triazole.

Results and discussion

It has been planned to investigate the reactivity of tosyl substituted triazole with pyridine-*N*-oxide in the presence of rhodium catalyst anticipating a [3+3] addition reaction. It can be noticed that such additions are popular towards the construction of six membered rings.[12] Tosyl azide is well known to generate active carbene in presence of Rh complex, which can undergo [3+3] addition reactions.[13] With this idea, tosyl triazole was made to react with pyridine-*N*-oxide **1** in the presence metal catalyst. The selected substrates **1a-y** were prepared by the oxidation of various pyridine with *m*-chloroperbenzoic acid under basic conditions in dichloromethane.[14] The sulfonyl triazole **2** was synthesised by the reaction of 1 eq of tosyl azide and 1.2 eq of phenyl acetylene in the presence of cuprous oxide in water at room temperature.[15] The investigation was started with the reaction between pyridine-*N*-oxide **1a** and sulfonyl triazole **2a** with the hope of getting 3-phenylpyrido[1,2-*b*][1,2,4]oxadiazine moiety *via* formal [3+3] cycloaddition of pyridine **1a** with the sulfonyl triazole **2**, but the reaction did not proceed in the expected pathway. The unexpected product 2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine, **4a** was obtained in 55% yield along with a by-product **5** in 25% yield (Scheme 1). The by-product was identified as 4-phenyl-1*H*-1,2,3-triazole.

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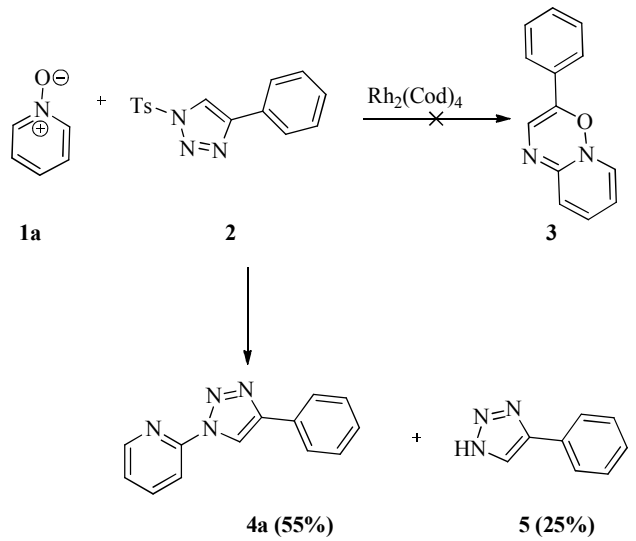
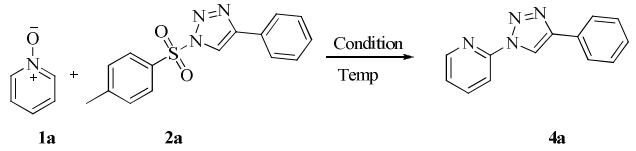


Scheme 1. Attempted reaction of pyridine **1a** and sulfonyltriazole **2a** under catalyst condition

Puzzled by this, the reaction conditions were optimized (Table 1) and it is found under no circumstances, the six membered ring is generated. It was also realized that the presence of metal catalyst or base is not necessary for the reaction to yield **4**. It is found that this is the first report of the *α*-heteroarylation with simultaneous deoxygenative reaction without a catalyst or a base. It should be mentioned that previously stronger bases were employed for the related conversion studied. Nevertheless, this protocol is a new method of preparing triazole at the 2-position of pyridine ring. The advantages of the present method are that it is free from metal catalyst and base with reduced reaction time and high yields. The substrate scope is broadened in the present investigation.

Table 1. Optimization of reaction conditions [a]



Entry	Solvent	Catalyst (mol%)	Base	*t* (°C)	time (h)	Yield of **4a** (%)
1	$CHCl_3$	$Rh_2(Cod)_4$ (20)		90	1.5	55
2	DCE	$Rh_2(OAc)_4$ (20)		90	7	43
3	$CHCl_3$	$Rh_2(OAc)_4$ (20)		90	2.5	52
4	DCE	$Rh_2(OAc)_4$ (20)		rt	18	<2
5	THF	$Ni(COD)_2$ (20)		90	18	NR[b]
6	DCE	CuI (20)		90	12	8
7	Toluene	-[c]		110	6	68
8	Dioxane	-		100	12	<10
9	DCM	-		50	12	48
10	ACN	-		80	12	54
11	Xylene	-		130	12	10
12	DMF	-		140	20	NR[b]
13	DMSO	-		150	20	NR[b]
14	$CHCl_3$	-		80	8	58
15	THF	--		65	18	<5
16	**DCE**	**-**		**95**	**5**	**82**[d]
17	DCE	-		rt	18	<2
18	DCE	-	DIPA	90	12	<5
19	DCE	-	DIPEA	90	12	<5
20	DCE	-	Et_3N	90	12	<2
21	DIPA	-		95	8	62
22	DIPEA	-		95	8	58
23	Et_3N	-		95	8	20

[a] reagent and conditions: pyridine *N*-oxide **1a** (1 mmol), sulfonyltriazole **2a** (1 mmol), solvents (2 mL). [b] No reaction. [c] reactions carried out without catalyst. [d] Isolated yield.

The reaction has led to the formation of a single product **4** in many cases. It must be mentioned that it is certain that the product **4** formed is triazole connected to the pyridine ring at 2 position, but the regiochemistry in the triazole ring has to be established unambiguously. Previously a mixture of regioisomers have been obtained while constructing these skeletons.[16] The NMR features have been analyzed carefully in these cases. A NOESY spectrum of **4c** has also been recorded which gives stronger contour between the triazole ring singlet and the *ortho*-hydrogens of the aryl substituent. All the three isomers **A**, **B** and **C** (Figure 1) will show such contour. **A**, **B** and **C** are quite possible as the reaction is supposed to take place after the generation of free triazolyl anion, which may be resonating between different forms. However, if the regiochemistry of the starting tosyl triazole is to be taken into account, by memory effect and the stability of the triazolyl anion, the isomer **A** may be the favourable one. **B** is sterically hindered and hence its formation is not quite feasible. **C** could be the other regioismer that might have been formed in low yield in some cases.

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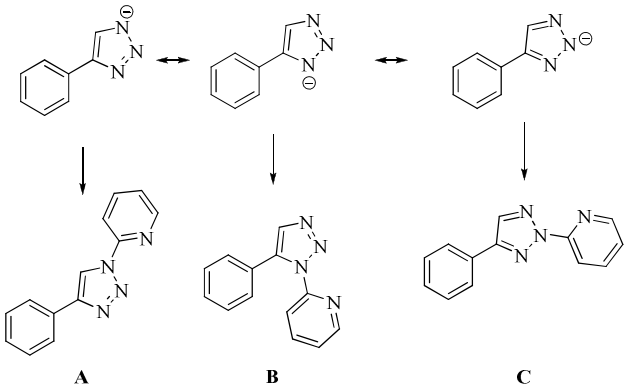

Figure 1. Possible isomers for **4**

In the major/only isomer of **4** prepared in the present investigation, the triazole hydrogen appears at 9.30 ppm (DMSO-d_6). This hydrogen is said to have observed at 8.88 in $CDCl_3$ and 9.37 in DMF for the structure **A**.[17] Hence the above compounds have been said to assume the structure where the 2-pyridyl ring is 1 position and the aryl at 4 position. This is confirmed by two dimensional NMR studies (Figure 2 shows correct assignment based on 2D connectivities for **4c**) and single crystal X-ray analysis of **4d** (Figure 3).

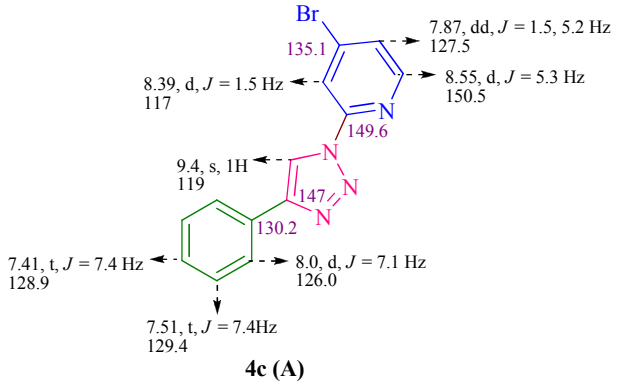

Figure 2 NMR assignments for **4c** (DMSO-d_6)

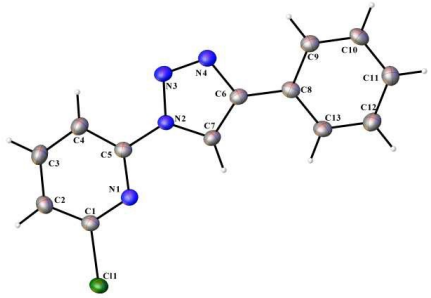

Figure 3 ORTEP diagram of **4d** (CCDC number 1475885)

Interestingly in **4f**, the coupling has occurred *ortho* to methyl in the pyridyl ring and not *para* to methyl (no one hydrogen singlet in the ^{1}H NMR spectrum), though it is sterically placed. Thus the product is 3-methylpyrid-2-yl triazole and not 5-methylpyrid-2-yl triazole. In contrast, in **4g**, the coupling has occurred *para* to acetyl and not *ortho* to acetyl (two singlets and two doublets in the ^{1}H NMR spectrum apart from the singlet of triazole ring). Inductive electron withdrawing could have assisted to have more electron deficiency in the carbon *alpha* to methyl (**4f**), while mesomeric electron withdrawing would have telling effect at the *para* to acetyl group (**4g**), avoiding the steric conjunction, if entered at *ortho* to acetyl.

With **4h**, it seems to be a mixture (81:19). Considerable amount of another regioisomer has been formed and it could not be possible to separate that from the major one. The major isomer has the triazolyl ring hydrogen at 9.4 ppm as in the case of **4a** to **4g**. The minor isomer has the triazolyl singlet appearing at 8.8 ppm. The structure of this minor isomer may be **C**, 2-pyridyl-4-phenyl-2*H*-1,2,3-triazole. This is confirmed with the related isomer **4ja** (vide infra).

In **4f** and **4i**, the triazolyl ring hydrogen is appearing slightly shielded at 9.1 ppm. The presence of *ortho* substituent would have made the triazole ring to go out plane with the pyridyl ring and the deshielding ring current effect may be reduced.

With 3-fluoro-4-chloropyridine-*N*-oxide, the course is different. Here two isomers have been obtained in relatively good yield (38:20) labelled as **4j** and **4ja.** With **4j**, the triazole ring hydrogen comes at 9.4 ppm as with other cases, suggesting the structure to be **A**. In the case of **4ja**, the triazole ring hydrogen appears at 8.8 ppm suggesting the structure to be different. It is found to be **C**, 2-pyridyl-4-aryl-2*H*-1,2,3-triazole. It is possible to grow a single crystal in this case and the single crystal X-ray data confirm the structure (Figure 4).

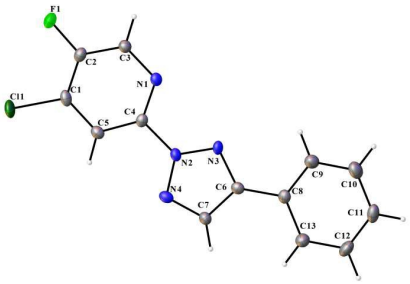

Figure 4. ORTEP diagram of **4ja** (CCDC Number 1475932)

With **4k**, the isomer is found to be 4,5-dimethylpyrid-2-yl triazole and not 3,4-dimethylpyrid-2-yltriazole. There are three one hydrogen singlets in the ^{1}H NMR spectrum proving that the compound is the former and not the latter with the triazole group getting bonded to pyridine at para to the methyl at 3 position and not at ortho to that methyl group. This is surprising as 2-methylpyridine-*N*-oxide has behaved differently giving **4f,** where the triazole group is attached to the C-2 position of the pyridyl ring.

After varying the substitutents in pyridine-*N*-oxide, the scope is extended to fused pyridine ring. With 5-nitroisoquinoline oxide, the reaction goes succesfully coupling with the triazole ring in the 1-position of isoquinoilne and not at the 3-position giving **4l** (four doublets and one triplet). This is not surprising

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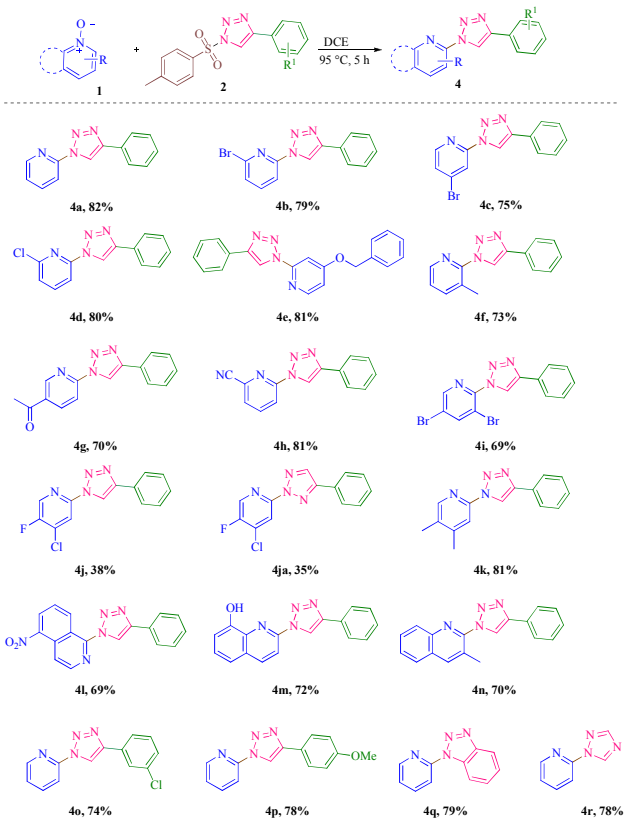
as the nucleophilicity of C-1 position is more compared C-3 position, in spite of the *peri* interaction.[17] Obviously, due to *peri* interaction, the triazole ring goes out of plane feeling an upfield shift for the triazolyl hydrogen, appearing at 8.8 ppm (cf: **4f** and **4i**).

The reaction takes with equal ease in quinoline system as well (**4m**). The substrate scope has also been extended by introducing the substituents in the 4-aryl ring of triazole (**4o** and **4p)**. The starting triazole sulphonyl compounds for **4q** and **4r** have been prepared by reported procedure.[18]

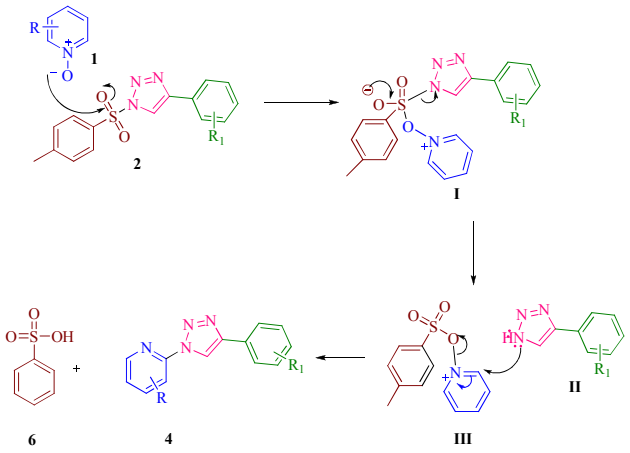
Scheme 2 Scope of the substrates (**4a-4r)**



[a]Reaction conditions: **1** (1mmol), **2** (1mmol), DCE (2 mL), 95 ºC, 5 h. Isolated yields refer to **1**

The plausible mechanism of the reaction is provided in Scheme 3. It must be admitted that the reaction is not taking place with alkyl azides.

Scheme 3 Plausible mechanism for *α*-heteroarylation of pyridine *N*-oxide



Conclusions

We have presented a new C-N bond forming reaction *via* regioselective *α*-heteroarylation followed by deoxygenation towards the synthesis of variety of azinetriazole from simple azine *N*-oxides derivatives and *N*-tosyl-1,2,3-triazoles. The reaction is metal free and base free with lesser reaction time, high yields and a broad substrate scope. Out of the synthesised compounds, **4b, 4c, 4e-n** & **4q** are new.

Experimental section

General consideration

The melting points reported in the work are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. The ^{1}H and ^{13}CNMR spectra of the new compounds were measured at 400 MHz or 300 MHz and 100 MHz or 75 MHz (mentioned in respective NMR data itself) respectively using Bruker NMR instrument in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in parts per million (δ), coupling constants (*J* values) are reported in Hertz (Hz) relative to tetramethylsilane. Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), m (multiplet) dd (doublet of doublets), bs (broad singlet). Infrared spectra were recorded on a FT-IR instrument and only major peaks are reported in cm.$^{-1}$ Column chromatography was carried out in silica gel (60−120 mesh) using petroleum ether-ethyl acetate as eluent.

General procedure for the preparation of 4

To a solution of pyridine-*N*-oxide **1** (1 mmol) in 1,2-dichloroethane (2 mL) was added sulfonyl triazole **2** (1 mmol). The reaction was stirred magnetically reflux at 95 °C for the indicated time (Table 1). After completion of the reaction (monitored by TLC), the product was extracted with ethyl acetate (15 mL) and purified by column chromatography (silica gel) using ethyl acetate/petroleum ether mixture as a gradient elution to afford product (**4a-r**).

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2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4a [1,6f,199]

Isolated yield 0.19 g (82%); off white solid; M.pt. 128-130°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.39 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.56 - 7.59 (m, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 8.12 - 8.19 (m, 2H), 8.63 (d, *J* = 7.6 Hz, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 114.2, 118.7, 124.8, 126.1, 128.9, 129.4, 130.4, 140.6, 147.9, 149.0, 149.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H: 7.35 - 7.40 (m, 2H), 7.49 (t, *J* = 7.2 Hz), 7.94 - 7.97 (m, 3H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.53 - 8.54 (m, 1H), 8.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 113.8, 116.8, 123.5, 125.9, 128.4, 128.9, 130.3, 139.1, 148.1, 148.5, 149.3; IR (ATR KBr cell, cm^{-1}) 1053, 1560, 3078, 3125.

2-Bromo-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4b

Isolated yield 0.14 g (79%); off white solid; M.pt. 180-182°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.40 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.05 - 8.10 (m, 3H), 8.20 (d, *J* = 8 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 113.6, 118.9, 126.1, 128.8, 128.9, 129.4, 130.2, 140.2, 143.3, 147.8, 148.8; IR (ATR KBr cell, cm^{-1}) 550, 1280, 3042, 3145. LC-MS calcd. m/z 301, found 302 [(M+1)]$^+$. Anal. Calcd for $C_{13}H_9BrN_4$: C, 51.85; H, 3.01; N, 18.60; Found: C, 51.80; H, 2.98; N, 18.54.

4-Bromo-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4c

Isolated yield 0.13 g (75%); off white solid; M.pt.118-120°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.41 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.44 Hz, 2H), 7.87 (dd, *J* = 1.48 Hz, 5.2 Hz, 1H), 8.04 (d, *J* = 7.36 Hz, 2H), 8.39 (d, *J* = 1.48 Hz, 1H), 8.55 (d, *J* = 5.32 Hz, 1H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 117.2, 119.0, 126.1, 127.8, 128.9, 129.4, 130.2, 135.2, 147.8, 149.6, 150.5; IR (ATR KBr cell, cm^{-1}) 570, 1280, 3100, 3126. LC-MS calcd. m/z 301, found 302 [(M+1)]$^+$. Anal. Calcd for $C_{13}H_9BrN_4$: C, 51.85; H, 3.01; N, 18.60; Found: C, 51.80; H, 2.94; N, 18.53.

2-Chloro-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4d [6f]

Isolated yield 0.16 g (80%); off white solid; M.pt.136-138°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.40 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.69 (dd, *J* = 1.6 Hz, 6.8 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.15 - 8.21 (m, 2H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 113.3, 119.0, 125.0, 126.1, 129.0, 129.4, 130.2, 143.8, 147.9, 148.7, 149.5; IR (ATR KBr cell, cm^{-1}) 682, 733, 1474, 1593, 3131.

4-(Benzyloxy)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4e

Isolated yield 0.13g (81%); off white solid; M.pt. 155-157°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 5.36 (s, 2H), 7.20 - 7.22 (m, 1H), 7.37 - 7.52 (m, 8H), 7.74 (d, *J* = 2 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 2H), 8.44 (d, *J* = 5.6 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 70.5, 100.3, 112.3, 119.0, 126.0, 128.5, 128.8, 128.9, 129.1, 129.4, 130.4, 136.1, 147.6, 150.5, 150.6, 167.2; IR (ATR KBr cell, cm^{-1}) 1580, 3080, 3125; LC-MS calcd. m/z 328, found 329 [(M+1)]$^+$. Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06; Found: C, 73.11; H, 4.84; N, 17.03.

3-Methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4f

Isolated yield 0.16 g (73%); off white solid; M.pt. 148-150°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 2.44 (s, 3H), 7.40 (t, *J* = 3.8 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.56 - 7.59 (m, 1H), 8.00 - 8.05 (m, 3H), 8.51 - 8.52 (m, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 18.5, 122.1, 125.5, 125.9, 128.2, 128.7, 129.5, 130.7, 142.3, 146.6, 147.0, 148.2; IR (ATR KBr cell, cm^{-1}) 1476, 1537, 2998, 3120; LC-MS calcd. m/z 236, found 237 [(M+1)]$^+$. Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71; Found: C, 71.12; H, 5.09; N, 23.64.

1-(6-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyridin-3-yl)ethanone 4g

Isolated yield 0.13 g (70%); off white solid; M.pt. 198-200°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 2.69 (s, 3H), 7.51 - 7.56 (m, 3H), 8.05 - 8.23 (m, 3H), 8.58 - 8.81 (m, 2H), 9.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 27.5, 114.0, 126.8, 129.4, 129.7, 130.1, 131.8, 136.2, 139.8, 150.2, 150.5, 152.6, 196.7; IR (ATR KBr cell, cm^{-1}) 1402, 1570, 1645, 2384, 3042; LC-MS calcd. m/z 264, found 265[(M+1)]$^+$. Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20; Found: C, 68.11; H, 4.55; N, 21.15.

6-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)picolinonitrile 4h

Isolated yield 0.17 g (81%); off white solid; M.pt. 176-178°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.39 (t, *J* = 7.2 Hz, 1H), 7.46 - 7.53 (m, 2H), 8.03 - 8.06 (m, 2H), 8.19 (d, *J* = 7.6 Hz, 1H), 8.35 - 8.41 (m, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 116.5, 118.2, 125.9, 126.5, 128.6, 129.0, 129.9, 131.6, 135.4, 141.9, 148.0, 149.5; IR (ATR KBr cell, cm^{-1}) 1570, 2928, 3042; LC-MS calcd.m/z 247, found 248 [(M+1)]$^+$. Anal. Calcd for $C_{14}H_9N_5$: C, 68.01; H, 3.67; N, 28.32; Found: C, 67.99; H, 3.60; N, 28.27.

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

Isolated yield 0.10 g (69%); off white solid; M.pt. 128-130°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.41 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 8.86-8.89 (m, 2H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 116.7, 122.3, 122.9, 126.0, 128.9, 129.5, 130.3, 146.1, 146.6, 146.9, 149.5; IR (ATR KBr cell, cm^{-1}) 557, 1462, 1552, 1949, 3129. LC-MS calcd. m/z 380, found 381 [(M+1)]$^+$. Anal. Calcd for $C_{13}H_8Br_2N_4$: C, 41.09; H, 2.12; N, 14.74; Found: C, 41.02; H, 2.09; N, 14.70.

4-Chloro-5-fluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4j

Isolated yield 0.07 g (38%); off white solid; M.pt. 158-160°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.40 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 8.02 (d, *J* = 7.6 Hz, 2H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.83 (s, 1H), 9.35 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 116.3, 126.7, 129.1, 129.7, 131.1, 132.5, 135.6, 137.9, 147.2, 150.1, 154.5; IR (ATR KBr cell, cm^{-1}) 1128, 1570, 3071; LC-MS calcd. m/z 274, found 275 [(M+1)]$^+$. Anal. Calcd for $C_{13}H_8ClFN_4$: C, 56.84; H, 2.94; N, 20.40; Found: C, 56.78; H, 2.91; N, 20.35.

4-Chloro-5-fluoro-2-(4-phenyl-2*H*-1,2,3-triazol-2-yl)pyridine 4ja

Isolated yield 0.03 g (20%); off white solid; M.pt. 170-172°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.47 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 2H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.73 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 116.4, 119.2, 126.1, 129.0, 129.5, 130.2, 133.0, 138.2, 145.6,

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147.2, 154.8; IR (ATR KBr cell, cm^{-1}) 700, 1135, 1499, 3012; LC-MS calcd. m/z 274, found 275 $[(M+1)]^+$. Anal. Calcd for $C_{13}H_8ClFN_4$: C, 56.84; H, 2.94; N, 20.40; Found: C, 56.80; H, 2.92; N, 20.36.

4,5-Dimethyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyridine 4k

Isolated yield 0.16 g (81%); off white solid; M.pt. 148-150^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 2.31 (s, 3H), 2.41 (s, 3H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.99 (s, 1H), 8.03 (d, *J* = 7.2 Hz, 2H), 8.35 (s, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 16.1, 19.6, 114.4, 118.6, 126.0, 128.8, 129.4, 130.6, 133.7, 147.4, 147.5, 148.5, 150.4; IR (ATR KBr cell, cm^{-1}) 1041, 1466, 1601, 3173; LC-MS calcd. m/z 250, found 251 $[(M+1)]^+$. Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38; Found: C, 71.93; H, 5.60; N, 22.31.

5-Nitro-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)isoquinoline 4l

Isolated yield 0.12g (69%); off white solid; M.pt.188-190^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.49 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 8 Hz, 1H), 8.04 (t, *J* = 8.4 Hz, 2H), 8.52 (d, *J* = 7.6 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.75 (d, *J* = 6.8 Hz, 1H), 8.79 (d, *J* = 6 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 118.0, 122.7, 126.7, 128.6, 129.5, 129.6, 129.7, 129.9, 130.5, 132.7, 135.2, 144.4, 145.4, 149.7, 149.9; IR (ATR KBr cell, cm^{-1}) 1520, 1625, 3106. LC-MS calcd.m/z 317, found 318 $[(M+1)]^+$. Anal. Calcd for $C_{17}H_{11}N_5O_2$: C, 64.35; H, 3.49; N, 22.07; Found: C, 64.31; H, 3.41; N, 22.01.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)quinolin-8-ol 4m

Isolated yield 0.13 g (72%); off white solid; M.pt. 156-158^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.49 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 8 Hz, 2H), 8.04 (t, *J* = 8.4 Hz, 2H), 8.52 (d, *J* = 7.6 Hz, 1H), 8.69 (d, *J* = 8.4 Hz, 1H), 8.75 (d, *J* = 6.8 Hz, 1H), 8.79 (d, *J* = 6 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 112.6, 113.3, 118.4, 119.3, 122.8, 123.7, 125.9, 129.0, 129.6, 130.5, 136.5, 144.0, 146.1, 147.7, 153.5; IR (ATR KBr cell, cm^{-1}) 1598, 3045, 3200. LC-MS calcd. m/z 288, found 289 $[(M+1)]^+$. Anal. Calcd for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43; Found: C, 70.79; H, 4.14; N, 19.40.

3-Methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinoline 4n

Isolated yield 0.13 g (70%); off white solid; M.pt. 148-150^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 2.58 (s, 3H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.85 (t, *J* = 8 Hz, 1H), 8.06 (t, *J* = 7.6 Hz, 4H), 8.58 (s, 1H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 19.2, 122.3, 126.0, 126.1, 127.8, 128.4, 128.5, 128.7, 128.8, 129.5, 130.6, 130.8, 141.2, 145.0, 146.6, 148.2; IR (ATR KBr cell, cm^{-1}) 1496, 1599, 2923. LC-MS calcd. m/z 286, found 287 $[(M+1)]^+$. Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.50; H, 4.93; N, 19.57; Found: C, 75.46; H, 4.86; N, 19.53.

2-(4-(3-Chlorophenyl)-1H-1,2,3-triazol-1-yl)pyridine 4o [6f]

Isolated yield 0.20 g (74%); off white solid; M.pt. 138-140^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.44 (d, *J* = 8 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.57 - 7.60 (m, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.11 - 8.18 (m, 2H), 8.64 (d, *J* = 4.4 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 114.3, 119.6, 124.6, 125.0, 125.7, 128.6, 131.4, 132.6, 134.3, 140.6, 146.3, 148.9, 149.4; IR (ATR KBr cell, cm^{-1}) 774, 1400, 1590, 3108.

2-(4-(4-Methoxyphenyl)-1H-1,2,3-triazol-1-yl)pyridine 4p [6f]

Isolated yield 0.21 g (78%); off white solid; M.pt. 110-112^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 3.82 (s, 3H), 7.06 (t, *J* = 8.8 Hz, 2H), 7.56 - 7.59 (m, 1H), 7.97 (t, *J* = 8.4 Hz, 2H), 8.12 - 8.19 (m, 2H), 8.64 (t, *J* = 4.8 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 55.7, 114.2, 114.8, 117.7, 123.0, 124.7, 127.5, 140.6, 147.6, 149.1, 149.4, 159.9; IR (ATR KBr cell, cm^{-1}) 1437, 1476, 1645, 3085.

1-(Pyridin-2-yl)-1*H*-benzo[*d*][1,2,3]triazole 4q

Isolated yield 0.16 g (79%); off white solid; M.pt. 108-110^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.53 - 7.58 (m, 2H), 7.70 - 7.74 (m, 1H), 8.17 (td, *J* = 1.6 Hz, 7.2 Hz, 1H), 8.21 (d, *J* = 8 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.58 (d, *J* = 7.6 Hz, 1H), 8.70 - 8.72 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 114.8, 114.9, 120.1, 123.6, 125.8, 129.7, 131.3, 140.4, 146.5, 149.2, 151.2; IR (ATR KBr cell, cm^{-1}) 1579, 2380, 3141. LC-MS calcd. m/z 196, found 197 $[(M+1)]^+$. Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55; Found: C, 67.29; H, 4.08; N, 28.51.

2-(1*H*-1,2,4-Triazol-1-yl)pyridine 4r [16]

Isolated yield 0.12g (78%); off white solid; M.pt.84-86^{0}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H: 7.49 (t, *J* = 5.2 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 8.09 (t, *J* = 7.2 Hz, 1H), 8.29 (s, 1H), 8.54 (d, *J* = 4.4 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C: 113.3, 124.1, 140.5, 142.4, 149.1, 149.3, 153.4; IR (ATR KBr cell, cm^{-1}) 1448, 1556, 3121.

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Base free regioselective synthesis of α-triazolylazine derivatives

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Graphical abstract