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Ligand-free CuCl-catalyzed N-Arylation of 1,2,4-triazole with aryl bromides

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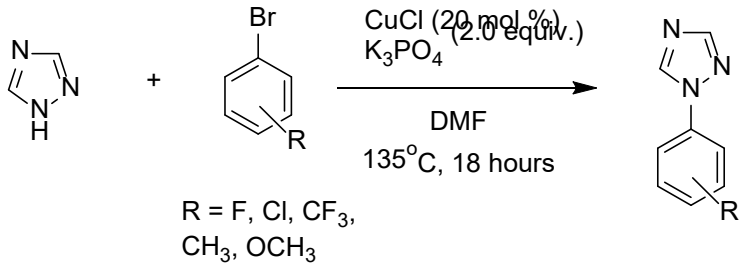

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Abstract: An efficient protocol was developed for the N-arylation of 1,2,4-triazoles using substituted aryl bromides catalyzed by CuCl under ligand-free conditions. This method afforded the products in good to excellent yields (up to 88%) under the optimized conditions.

Key words: triazole, copper(I) chloride, arylation, bromobenzene, ligand-free.

INRODUCTION

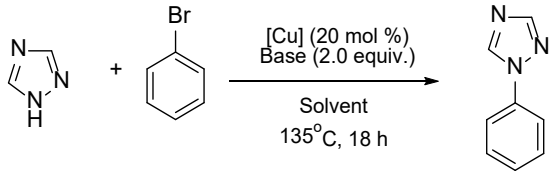
Nitrogen heterocycles are present in many natural products and biologically active pharmaceutical compounds.[1] Triazoles, specifically 1,2,4-triazole, are the most stable compounds among the azoles and used in various application in material[2] and medicinal science.[3] 1,2,4-triazole is also an important pharmacophore, interacting with biological receptors with high affinity due to its high dipole characteristics and rigidity.[4] Along with its heterocyclic derivatives, the triazole shows significant pharmacological activity as a neuroprotectant[5] and contains antimalarial[6] and antiviral[7] activities. Derivatives of 1,2,4-triazoles exhibit applications in the field of material science, showing good emission properties and promise in ionic liquids, agrochemicals, and optoelectronic purposes[8]. With its significant bioactive properties, triazole derivatives can play critical roles in the development of multidrug resistance of chemotherapeutic drugs. [9]

The assembly of N-arylated triazole derivatives has been accomplished by the Ullmann-type cross coupling reactions involving the use of copper catalysts which is a straightforward and inexpensive approach. However, most of the methods require the use of assisting ligands in combination with the copper catalysts to ensure the success of the reactions.[10] In some cases, the ligands must be specifically synthesized for the reaction, which further incurs additional costs and leads to waste generation. Antilla, et al reported the cross-coupling reaction between iodobenzene and 1,2,4-triazole which necessitates the use of dimethylcyclohexane-1,2-diamine as the ligand.[11] The substrate scope for substituted iodobenzene was also limited in the report. Taywade, et al reported two representative N-arylation of 1,2,4-triazole which necessitates the need for specially synthesized pyridine-based ligands.[12] Moreover, the reaction only works well with activating aryl iodides with limited substrate scope for practicality. Song, et al reported the N-arylation of 1,2,4-triazoles under Cu catalysis which required $FeCl_3$ as co-catalyst and trimethoxy silanes as coupling partner with limited substrate scope.[13] In this context, there is also another challenge of using the less toxic and cheaper aryl bromides as electrophilic partners for such cross-coupling reactions. Finally, reports on the Cu-catalysed cross coupling of 1,2,4-triazoles using a variety of substituted bromobenzene under ligand-free conditions has not been reported.

With the importance of triazole derivatives in the pharmaceutical industry, we were motivated to develop more practical and environmentally friendly protocols for the preparation of N-arylated triazoles. Notably, we have recently developed ligand-free protocols for the Cu-catalyzed N arylation of various nitrogen heterocycles with bromobenzene as the electrophilic coupling partners.[14] Based on these precedents; we endeavor to apply the existing catalytic system for the more challenging 1,2,4-triazole substrate to broaden our tools of N-arylation protocols for nitrogen containing nucleophiles using aryl bromides.

The model reaction for the Cu-catalyzed cross coupling reaction was initiated using 1,2,4-triazole and bromobenzene to determine the effectiveness of various Cu catalysts, base, and solvent for the reaction. The optimisation results are shown in Table 1.

Table 1: Optimisation studies on the Cu-catalysed cross-coupling of 1,2,4-triazole with bromobenzene[a]



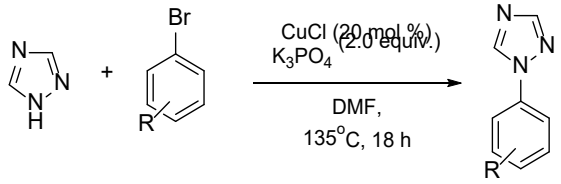
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	K_3PO_4	DMF	65
2	CuBr	K_3PO_4	DMF	59
3	CuCl	K_3PO_4	DMF	71
4	Cu_2O	K_3PO_4	DMF	55
5	CuCl	K_3PO_4	DMSO	57
6	CuCl	K_3PO_4	Water	Trace
7	CuCl	K_3PO_4	t-Butanol	Trace
8	CuCl	K_3PO_4	Toluene	Trace
9	CuCl	Cs_2CO_3	DMF	24
10	CuCl	K_2CO_3	DMF	18
11	CuCl	K_3PO_4	DMF	45[c]
12	CuCl	K_3PO_4	DMF	13[d]

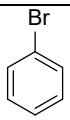
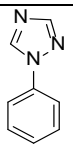
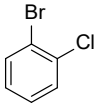
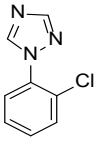
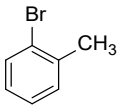
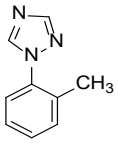
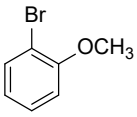
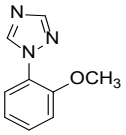
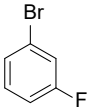
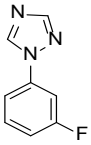
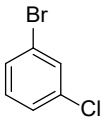
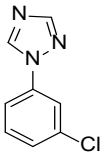
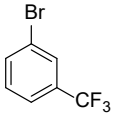
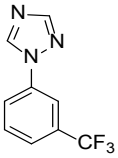
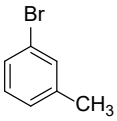
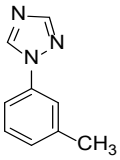
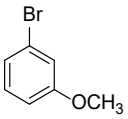
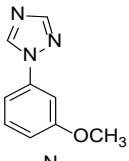
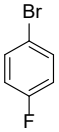
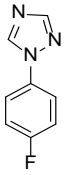
[a]Reactions were carried out with 1.0 equiv. of 1,2,4-triazole, 3.0 equiv. of bromobenzene, 0.2 equiv. of Cu salt, 2.0 equiv. of base and 750 µl solvent at 135 °C for 18h.
[b]Isolated yield.
[c]Reaction was carried out with 2.0 equiv. bromobenzene.
[d]Reaction was carried out at 110°C.

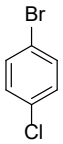
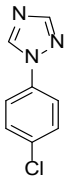
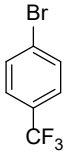
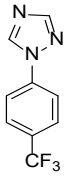
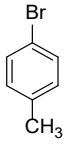
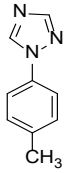
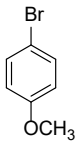
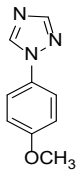
In the screening of Cu metal catalysts, Cu_2O afforded the lowest yield (Table 1, entry 4) proving that Cu(I) halide catalysts are more suitable for the cross-coupling reaction. Among the Cu(I) halides, CuCl produced the best yield of 71% (Table 1, entry 3). The study also demonstrated that both CuI and CuBr were suitable metal salts for the reaction, providing the products in 65% and 59% yields, respectively (entries 1 and 2). As for the solvents screening stage, the more polar solvents DMF and DMSO gave moderate yields with DMF affording the highest product yield at 71% yield. This shows that the ligand-free cross coupling reaction is favored using polar aprotic solvent which probabaly promoted the dissolution of the reactants and subsequently the coupling reaction. Next, we investigated the effect of the bases on the reaction. In this study, both Cs_2CO_3 and K_2CO_3 produced low product yields at 24% and 18% respectively (entries 9 and 10). The optimal base was achieved using K_3PO_4 which afforded the highest yield of 71%. This might be due to the compatibility and basicity of the base that mediated the deprotonation of the proton in the 1,2,4-triazole ring to facilitate the rate of the reductive elimination step in the catalytic cycle. In an attempt to reduce waste and increase the 'greenness' of the reaction, the amount of bromobenzene used was decreased to 2.0 equivalent but the yield was reduced significantly (entry 11). Moreover, reducing the reaction temperature to 110°C to increase practicality of the protocol was futile as it leads to a poor yield to 13% (entry 12). In summary, the optimised condition for the ligand free N-arylation of 1,2,4-triazole is CuCl (20 mol %) as catalyst, DMF (750 µl) as the solvent and K_3PO_4 (2.0 equiv.) as base. This is to be in combination with the use of 4.5 mmol (3.0 equiv.) of aryl bromide and 1.5 mmol (1.0 equiv.) of 1,2,4-triazole at a temperature of 135°C.

With the optimised conditions established, we proceeded to evaluate the substrate studies using differently substituted aryl bromides to couple with 1,2,4-triazole. The results are tabulated in Table 2.

Table 2: CuCl catalysed N-arylation of 1,2,4-triazole with various substituted bromobenzenes[a]



Entry	ArX	Product		Yield (%)[b]
1			**2a**	71
2			**2b**	20
3			**2c**	14
4			**2d**	34
5			**2e**	76
6			**2f**	88
7			**2g**	84
8			**2h**	46
9			**2i**	55
10			**2j**	62

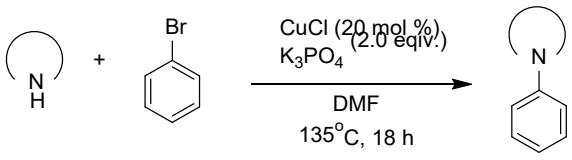
11			**2k**	77
12			**2l**	70
13			**2m**	35
14			**2n**	75

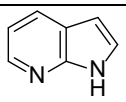
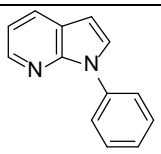
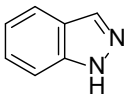
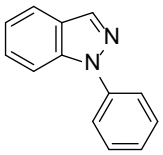
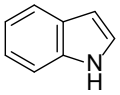
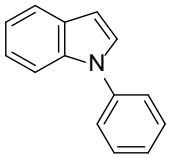
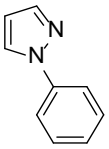
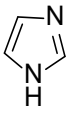
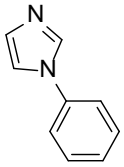
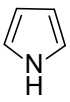
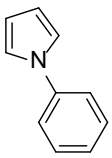
[a]Reactions were carried out with 1.0 equiv. of 1,2,4-triazole, 3.0 equiv. of substituted bromobenzene, 0.2 equiv. of CuCl, 2.0 equiv. of K_3PO_4 and 750 µl DMF at 135 °C for 18h.
[b]Isolated yield.

The aim of reacting 1,2,4-triazole with the various substituted aryl bromides was to analyse the effect of the substituted position and the electronic effect of the substituent have on the reaction yields. A deduction can be made that substituent in the meta and para positions gave significantly higher yield than their ortho substituted counterparts. A likely reason is due to steric hindrance at the ortho-position, hampering the oxidation addition step. Moreover, the yields produced by the bigger ortho positioned -CF_3 and -CH_3 substituted aryl bromides are lower than the other substituents in the same position. Between the various aryl bromides, the reaction yields with the other halide substituents in both meta and para gave comparable yields. Overall, this substrate study generated promising results, with the reaction yields ranging from moderate to excellent.

The promising results from the initial substrate studies prompted us to broaden the generality of the protocol through the reactions of bromobenzene and 1-bromo-3-chlorobenzene with various nitrogen heterocycles. Based on the results in Table 3, a wide range of yields, between 26% to 93% were produced in the reactions between bromobenzene and the various substituted heterocycle. Good yields were obtained when indazole, pyrazole and imidazole were employed as the nitrogen nucleophiles probably due to the presence of the α- and β- effects of the second nitrogen atom in the ring system.

Table 3: CuCl catalysed N-arylation of various nitrogen heterocycles with bromobenzene[a]

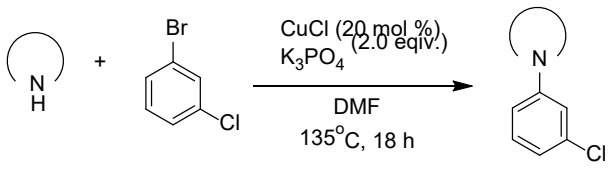


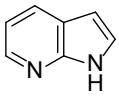
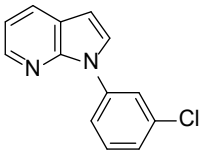
Entry	N-Het	Product		Yield(%)[b]
1			**3a**	26
2			**3b**	78[c]
3			**3c**	31[c]
4			**3d**	78
5			**3e**	93
6			**3f**	28[c]

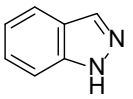
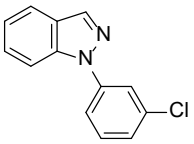
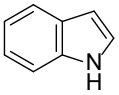
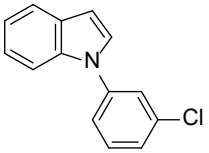
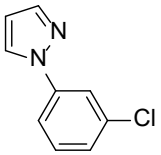
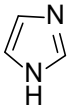
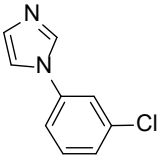
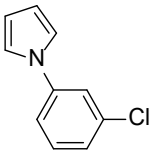
[a]Reactions were carried out with 1.0 equiv. of substituted N3-heterocycles, 3.0 equiv. of bromobenzene, 0.2 equiv. of CuCl, 2.0 equiv. of K_3PO_4 and 750 µl DMF at 135 °C for 18h.
[b]Isolated yield.
[c]Reactions were carried out with 1.0 equiv. of bromobenzene and 3.0 equiv. of substituted N-heterocycles.

Next, 1-bromo-3-chlorobenzene was chosen to further expand the scope of the reaction protocol as it gave the highest yield amongst the other aryl bromides as shown in Table 2. The yields produced by reacting various nitrogen heterocycles and 1-bromo-3-chlorobenzene are summarised in Table 4.

Table 4: CuCl-catalysed N-arylation of various nitrogen heterocycles with 1-bromo-3-chlorobenzene[a]



Entry	N-Het	Product		Yield (%)[b]
1			**4a**	72

2			**4b**	61[c]
3			**4c**	80[c]
4			**4d**	98
5			**4e**	55
6			**4f**	61[c]

[a]Reactions were carried out with 1.0 equiv. of substituted N-heterocycles, 3.0 equiv. of 1-bromo-3-chlorobenzene, 0.2 equiv. of CuCl, 2.0 equiv. of K_3PO_4 and 750 µl DMF at 135 °C for 18h.
[b]Isolated yields of the products after flash column chromatography.
[c]Reactions were carried out with 1.0 equiv. of 1-bromo-3-chlorobenzene and 3.0 equiv. of substituted N-heterocycles.

The reactions generally generated moderate yields between 55% to 80% except for pyrazole which produced an excellent yield of 98%. These results reflected a great promise in successfully expanding the scope of Cu-catalysed cross-coupling reactions between various nitrogen heterocycles and aryl bromides. Comparing the yields obtained in Table 3 and Table 4, there is a general trend of increased yields when using 1-bromo-3-chlorobenzene instead of bromobenzene. This is because of the additional inductive effect of chlorine in the meta position which activated the aryl bromides for the cross-coupling reactions.

In conclusion, an efficient method for the cross-coupling of 1,2,4-triazole with various substituted bromobenzene using CuCl as the catalyst has been demonstrated.[15] These reactions were carried under ligand-free conditions and moderate to good product yields were obtained under relatively mild reaction conditions. This study also showed that a good substrate scope was achieved with a diverse range of 1,2,4-triazole and substituted aryl bromides having different electronic and steric properties. This method has the potential to find widespread applications in both pharmaceutical and material industries due to its practicality and experimental simplicity.

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Supporting Information

Supporting Information for this article is available online.

Conflict of Interest

The authors declare no conflict of interest.

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(15) **General Procedure for the N-arylation of 1,2,4-triazoles**

CuCl (0.030g, 0.30mmol, 20 mol %), K_3PO_4 (0.637g, 3.0mmol, 2.0 equiv.), 1,2,4-triazole (0.104g, 1.5mmol, 1.0 equiv.), 750 µl of dimethylformamide (DMF) and bromobenzene (529 µl, 4.5mmol, 3.0 equiv.) were added in order into a reaction vial, The vial was sealed tightly with a screw cap and reaction mixture was pre-mixed for 5 minutes at room temperature. Using a silicon oil bath, the reaction mixture was subsequently stirred, in a closed system, under air, at 135°C for 18 hours. Thereafter, the reaction mixture was cooled to room temperature and diluted with 3 x 10 mL of dichloromethane. The mixture was dried by the addition of anhydrous Na_2SO_4 and filtered. The filtrate was collected, and the

solvent removed under vacuum. The crude product was collected and purified by silica gel column chromatography, to afford the product. Using ^{1}H and ^{13}C NMR spectroscopic analysis and elemental analysis, the identity and structure of the product was determined.

1-phenyl-1*H*-1,2,4-triazole (2a)

1H NMR (400MHz $CDCl_3$): δ = 8.56 (s, 1H), δ = 8.11 (s, 1H), δ = 7.68 (d, J = 8.4Hz, 2H), δ = 7.52 (t, J = 7.8Hz, 2H), δ = 7.41 (t, J = 7.4Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.6, 140.9, 137.0, 129.8, 128.3, 120.1; Anal. Calcd: C, 66.19; H, 4.86; N, 28.95; Found: C, 65.75; H, 5.05; N, 28.73

1-(2-chlorophenyl)-1*H*-1,2,4-triazole (2b)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.53 (s, 1H), δ = 8.13 (s, 1H), δ = 7.55 – 7.59 (m, 2H), δ = 7.41 – 7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.3, 144.5, 134.8, 130.8, 130.4, 128.6, 128.0, 127.6; Anal. Calcd: C, 53.50; H, 3.37; N, 23.40; Found: C, 53.43; H, 3.50; N, 23.02

1-(2-methylphenyl)-1*H*-1,2,4-triazole (2c)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.26 (s, 1H), δ = 8.13 (s, 1H), δ = 7.31 – 7.40 (m, 4H), δ = 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.2, 143.8, 136.2, 133.9, 131.6, 129.7, 126.9, 126.1, 17.9; Anal. Calcd: C, 67.90; H, 5.70; N, 26.40; Found: C, 67.35; H, 5.75; N, 26.40

1-(2-methoxyphenyl)-1*H*-1,2,4-triazole (2d)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.74 (s, 1H), δ = 8.07 (s, 1H), δ = 7.77 (d, J = 8.2Hz, 1H), δ = 7.36 (t, J = 7.9Hz, 1H), δ = 7.09 (t, J = 8.2Hz, 2H), δ = 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 151.3, 151.0, 144.7, 129.1, 124.6, 121.4, 112.2, 56.0; Anal. Calcd: C, 61.70; H, 5.18; N, 23.99; Found: C, 61.90; H, 5.25; N, 24.10

1-(3-fluorophenyl)-1*H*-1,2,4-triazole (2e)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.56 (s, 1H), δ = 8.09 (s, 1H), δ = 7.34 – 7.62 (m, 3H), δ = 7.06 – 7.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.8, 141.0, 123.2, 118.3, 115.2, 115.0, 108.0, 107.7; Anal. Calcd: C, 58.89; H, 3.71; N, 25.76; Found: C, 47.86; H, 3.34; N, 20.91

1-(3-chlorophenyl)-1*H*-1,2,4-triazole (2f)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.56 (s, 1H), δ = 8.11 (s, 1H), δ = 7.73 (t, J = 2.2Hz, 1H), δ = 7.57 – 7.59 (m, 1H), δ = 7.45 (t, J = 8.0Hz, 1H), δ = 7.36 – 7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.9, 140.9, 137.9, 135.7, 130.9, 128.3, 120.4, 117.9; Anal. Calcd: C, 53.50; H, 3.37; N, 23.40; Found: C, 53.94; H, 3.53; N, 23.31

1-(3-trifluoromethylphenyl)-1*H*-1,2,4-triazole (2g)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.63 (s, 1H), δ = 8.14 (s, 1H), δ = 7.99 (s, 1H), δ = 7.88 – 7.91 (m, 1H), δ = 7.63 – 7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 153.1, 141.0, 137.4, 132.7, 132.4, 130.6, 124.9, 123.0, 117.1; Anal. Calcd: C, 50.71; H, 2.84; N, 19.71; Found: C, 51.01; H, 2.98; N, 19.62

1-(3-methylphenyl)-1*H*-1,2,4-triazole (2h)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.53 (s, 1H), δ = 8.09 (s, 1H), δ = 7.50 (s, 1H), δ = 7.44 (d, J = 7.4Hz, 1H), δ = 7.37 (t, J = 7.8Hz, 1H), δ = 7.20 (d, J = 7.0Hz, 1H), δ = 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.6, 140.9, 140.1, 137.0, 129.6, 129.0, 120.8, 117.1; Anal. Calcd: C, 67.90; H, 5.70; N, 26.40; Found: C, 66.99; H, 5.48; N, 26.18

1-(3-methoxyphenyl)-1*H*-1,2,4-triazole (2i)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.54 (s, 1H), δ = 8.09 (s, 1H), δ = 7.39 (t, J = 8.3Hz, 1H), δ = 7.21 – 7.25 (m, 2H), δ = 6.93 (d, J = 7.5Hz, 1H), δ = 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.7, 152.6, 141.0, 138.1, 130.6, 114.0, 111.9, 106.1, 55.6; Anal. Calcd: C, 61.70; H, 5.18; N, 23.99; Found: C, 61.84; H, 5.14; N, 23.97

1-(4-fluorophenyl)-1*H*-1,2,4-triazole (2j)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.49 (s, 1H), δ = 8.09 (s, 1H), δ = 7.62 – 7.66 (m, 2H), δ = 7.19 (t, J = 8.3Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.7, 141.0, 132.9, 122.2, 122.0, 121.5, 116.9, 116.6; Anal. Calcd: C, 58.89; H, 3.71; N, 25.76; Found: C, 56.46; H, 3.91; N, 24.24

1-(4-chlorophenyl)-1*H*-1,2,4-triazole (2k)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.53 (s, 1H), δ = 8.10 (s, 1H), δ = 7.63 (d, J = 8.8Hz, 2H), δ = 7.48 (d, J = 8.8Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.8, 140.9, 135.5, 134.0, 130.0, 121.3; Anal. Calcd: C, 53.50; H, 3.37; N, 23.40; Found: C, 53.71; H, 3.73; N, 23.63

1-(4-trifluoromethylphenyl)-1*H*-1,2,4-triazole (2l)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.64 (s, 1H), δ = 8.13 (s, 1H), δ = 7.77 – 7.85 (dd, J = 24.0Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 153.1, 141.0, 139.5, 130.4, 130.0, 127.2, 124.9, 122.3, 119.9; Anal. Calcd: C, 50.71; H, 2.84; N, 19.71; Found: C, 50.90; H, 3.35; N, 19.87

1-(4-methylphenyl)-1*H*-1,2,4-triazole (2m)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.49 (s, 1H), δ = 8.06 (s, 1H), δ = 7.52 (d, J = 7.5Hz, 2H), δ = 7.27 (d, J = 8.1Hz, 2H), δ = 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 152.5, 140.8, 138.3, 134.7, 130.3, 120.1, 21.1; Anal. Calcd: C, 67.90; H, 5.70; N, 26.40; Found: C, 66.56; H, 5.43; N, 26.87

1-(4-methoxyphenyl)-1*H*-1,2,4-triazole (2n)

^{1}H NMR (400MHz $CDCl_3$): δ = 8.44 (s, 1H), δ = 8.06 (s, 1H), δ = 7.54 – 7.56 (dd, J = 8.9Hz, 2H), δ = 6.98 – 7.00 (dd, J = 8.9Hz, 2H), δ = 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.5, 152.4, 140.8, 130.5, 121.9, 144.9, 55.6; Anal. Calcd: C, 61.70; H, 5.18; N, 23.99; Found: C, 58.22; H, 4.67; N, 23.90