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Graphical Abstract

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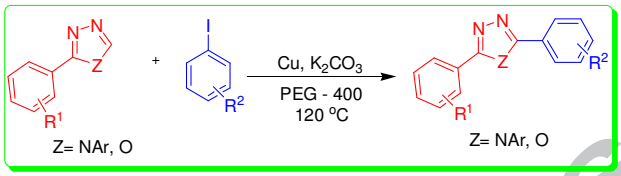

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Ligand-free copper(0) catalyzed direct C-H arylation of 1,2,4-triazoles and 1,3,4-oxadiazoles with aryl iodides in PEG-400

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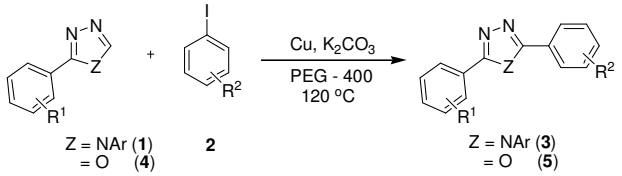
ABSTRACT

A ligand-free copper catalyzed approach has been developed to the synthesis of 3,4,5-triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles by the direct arylation of corresponding 3,4-diaryl-1,2,4-triazoles and 2-aryl-1,3,4-oxadiazoles with aryl iodides using PEG-400 as reaction medium. The procedure is experimentally simple and free from addition of external chelating ligands or co-catalysts.

3,4,5-Triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles are well known to exhibit a wide range of biological activities including anti-bacterial,[1] anti-inflammatory,[2] anti-tumour,[3] anti-tubercular,[4] tyrosinase inhibitory,[5] and cytotoxic[6] activities. Besides their biological properties, these π-conjugated scaffolds find applications in the field of material science.[7] Due to their unique optoelectronic properties these scaffolds have been exploited in the development of organic light emitting diodes (OLEDs) and utilized in energy efficient, full-color, flat-panel displays.[8] Certain suitably conjugated oxadiazoles are also known to perform as multiphoton absorbing systems.[8b]

In outlook of their biological and optoelectronic properties, numerous methods have been reported for their synthesis.[9] Generally, 3,4,5-triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles are synthesized by the cyclodehydration of corresponding *N*-acylamidrazones[10] and diacylhydrazines[11] respectively. Recently, transition-metal catalyzed direct arylation of heterocyclic C-H bonds has received significant attention in organic synthesis because of their potential for diverse transformation into a variety of useful derivatives.[12] 3,4,5-Triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles are synthesized by the direct arylation of 1,2,4-triazoles and 1,3,4-oxadiazoles using CuI/1,10-phenanthroline(phen) catalytic system.[13] However, this method has some drawbacks such as requirement of organic ligands which make it difficult for the separation and purification after the reaction and use of expensive organic solvents. Therefore, there is a need to develop more economical, ligand-free, eco-friendly and potential alternative methods for the synthesis of 3,4,5-triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles.

On the other hand, poly(ethylene glycols) (PEGs) are known to be nontoxic, less volatile, thermally stable, eco-friendly, and inexpensive media for various organic reactions.[14] Inspired by these advances and in continuation of our work[15] in development of environmentally benign methodologies for various biologically active heterocycles using PEG as a reaction medium, herein, we report a ligand-free copper catalyzed direct arylation of 3,4-diaryl-1,2,4-triazoles and 2-aryl-1,3,4-oxadiazoles using aryl iodides and PEG-400 as reaction medium (**Scheme 1**).



Scheme 1. Synthesis of 3,4,5-triaryl-1,2,4-triazoles (**3**) and 2,5-diaryl-1,3,4-oxadiazoles (**5**)

Initially, 3,4-diphenyl-4*H*-1,2,4-triazole (**1a**) was treated with iodobenzene (**2a**) in the presence of a catalytic amount of copper powder (20 mol%) and K_2CO_3 (2.5 equiv) in diglyme at 120 °C. To our delight, the desired product **3a** was formed, albeit in a low

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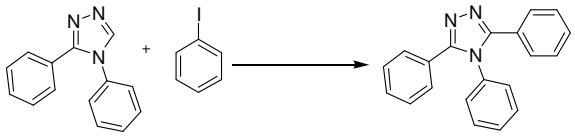
yield of 18% (**Table 1, entry 1**) after 24 h. Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents and bases were screened and the results are summarized in **Table 1**. It was found that PEG-400 was the most superior solvent and K_2CO_3 was the most effective base in terms of the reaction time and yield of the product (**Table 1, entry 6**). Once we had established suitable solvent and base, we then focused on the quantity of copper powder. By decreasing the quantity of copper powder from 20 mol% to 10 mol% the yield was dropped to 80% even after prolonged reaction time also (**Table 2, entry 12**). In contrast, no improvement of the yield was observed by increasing the catalyst loading (**Table 2, entry 13**). The effect of temperature on the reaction was also investigated. Faster reactions occurred on increasing the temperature but the product yields were not satisfactory (**Table 1, entries 14**). The progress of the reactions was monitored by TLC analysis (using EtOAc-hexane as the eluents).

Table 1. Optimization of reaction conditions to **3a**[a]



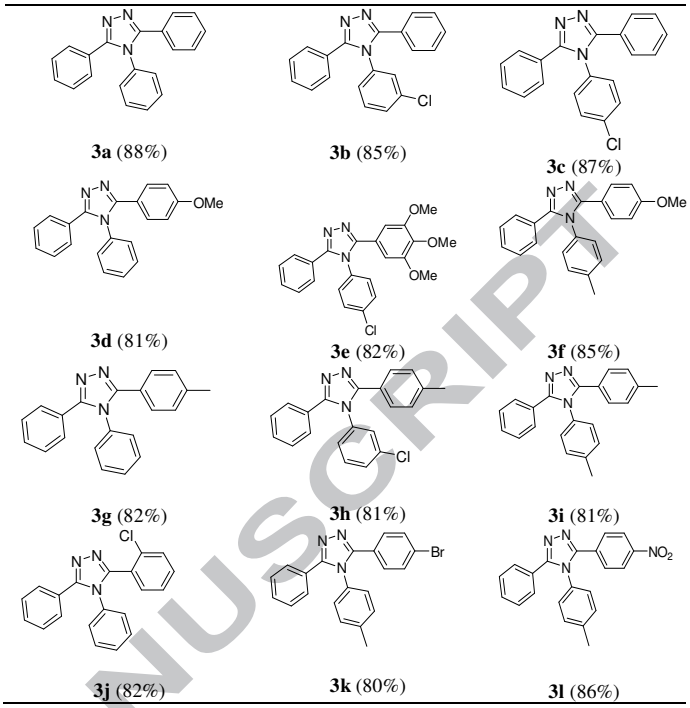
1a **2a** **3a**

Entry	Catalyst (mol %)	Base	Solvent	Temp (^oC)	Time (h)	Yield (%)[b]
1	20	K_2CO_3	Diglyme	120	24	18
2	20	K_2CO_3	Toluene	reflux	24	trace
3	20	K_2CO_3	Dioxane	reflux	24	25
4	20	K_2CO_3	DMSO	120	24	27
5	20	K_2CO_3	DMF	120	24	39
6	20	K_2CO_3	PEG-400	120	12	88
7	20	K_3PO_4	PEG-400	120	24	14
8	20	KO^{t}Bu	PEG-400	120	24	9
9	20	KOH	PEG-400	120	24	trace
10[c]	20	K_2CO_3	PEG-400	rt	36	-
11[d]	20	K_2CO_3	PEG-400	120	12	24
12	10	K_2CO_3	PEG-400	120	30	80
13	30	K_2CO_3	PEG-400	120	12	88
14	20	K_2CO_3	PEG-400	150	8	82

(a) Reaction conditions: 3,4-diphenyl-4*H*-1,2,4-triazole (1.0 equiv.), iodobenzene (1.2 equiv.), base (2.5 equiv.), solvent (5 vol.).
(b) Isolated yield.
(c) Reaction performed at room temperature.
(d) Reaction was performed in air.

Subsequently, with the optimal conditions in hand,[16] we examined the structural diversity of the various aryl iodides as the coupling partners. Notably, a wide variety of functionalities regardless of the electronic nature of the substituents were compatible with the reaction conditions. For example, chloro and bromo substituents (**Table 2, entries 3j and 3k**), electron-donating groups such as methoxy (**Table 2, entry 3d and 3f**) and methyl (**Table 2, 3g-3i**) and electron-withdrawing groups including a nitro substituent on the aromatic ring (**Table 2, entry 3l**) were well tolerated in direct C-H arylation of 1,2,4-triazoles. Interestingly, steric bulk of the aryl iodides didn't affect the reactivity, and 82% yield of the product was achieved with 2-chloro iodobenzene (**Table 2, entry 3j**). Only aryl iodides are effective coupling partners, with aryl bromides and chlorides giving little or no product. This result suggests that this method should be useful for the chemoselective arylation at iodide-substituted centers when other halogen substituents are present (**Table 2**, **3j and 3k**). To further probe the scope of the reaction, a range of 1,2,4-triazoles were converted into corresponding products with excellent yields under the established conditions (**Table 2, entries 3a-3c and 3e**). All the synthesized compounds are well characterized by advanced spectroscopic analysis (^{1}H NMR, ^{13}C NMR and Mass).are well characterized by advanced spectroscopic analysis (^{1}H NMR, ^{13}C NMR and Mass).

Table 2. Synthesis of 3,4,5-triaryl-1,2,4-triazoles **(3)**[a]

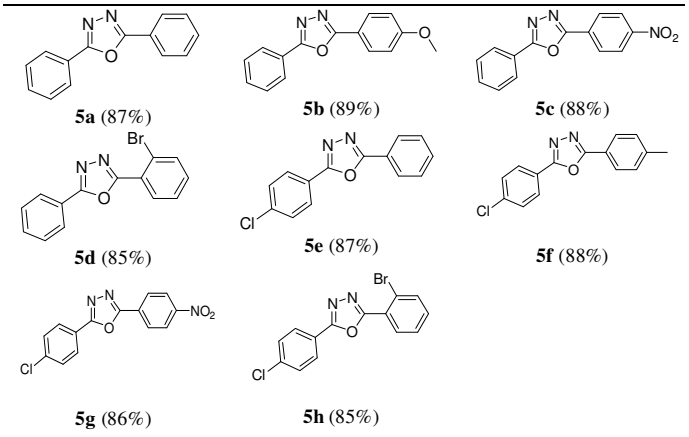


3a (88%) **3b** (85%) **3c** (87%)
3d (81%) **3e** (82%) **3f** (85%)
3g (82%) **3h** (81%) **3i** (81%)
3j (82%) **3k** (80%) **3l** (86%)

(a) Reaction conditions: 3,4-diaryl-1,2,4-triazole (**1**) (1.0 equiv.), iodobenzene (**2**) (1.2 equiv.), copper powder (0.2 equiv.), base (2.5 equiv.), solvent (5 vol.) and temperature 120 ^{o}C. Reported yields are isolated yields.

Motivated by this result, next we undertook the direct arylation of 1,3,4-oxadiazoles by taking 2-phenyl-1,3,4-oxadiazole as a representative example under the optimized conditions. Fortunately, we were able to synthesize various 2,5-diaryl-1,3,4-oxadiazoles (**5a-5h**) in reasonably high yields (85-89%) following the above protocol and the results are presented in **Table 3**.

Table 3. Synthesis of 2,5-diaryl-1,3,4-oxadiazoles[a]



5a (87%) **5b** (89%) **5c** (88%)
5d (85%) **5e** (87%) **5f** (88%)
5g (86%) **5h** (85%)

(a) Reaction conditions: 2-aryl-1,3,4-oxadiazole (**4**) (1.0 equiv), iodobenzene (**2**) (1.2 equiv.), copper powder (0.2 equiv), base (2.5 equiv.), solvent (5 vol.) and temperature 120 ^{o}C. Reported yields are isolated yields.

In summary, we have developed a ligand-free copper powder catalyzed direct arylation of 3,4-diaryl-1,2,4-triazoles and 2-aryl-1,3,4-oxadiazoles with aryl iodides in PEG-400. The present method allows a wide range of aryl iodides as arylating reagents and provides an easy access to a variety of 3,4,5-triaryl-1,2,4-triazoles and 2,5-diaryl-1,3,4-oxadiazoles. The use of inexpensive copper powder, simple experimental procedure and free from addition of external ligands or co-catalyst are the major advantages of this method.

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Supplementary Information

Supplementary information associated with general experimental procedure, characterization data and ^{1}H, ^{13}C NMR and Mass spectra of all new compounds.

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16. **General experimental procedure for the synthesis of 3 and 5:** Copper powder (0.2 equiv) and K_2CO_3 (2.5 equiv) were added to a solution of 3,4-diaryl-1,2,4-triazole (**1**) or 2-aryl-1,3,4-oxadiazole (**4**) (1.0 equiv) and iodobenzene (**2**) (1.2 equiv) in PEG-400 (5 vol.). The reaction mixture was stirred at 120 ^{o}C under nitrogen atmosphere for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature and partitioned between water and ethyl acetate. The organic and aqueous layers were then separated and aqueous layer was extracted with ethyl acetate twice. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude compound. The crude was further purified by silica gel chromatography using EtOAc/hexane as eluents to furnish the desired product **3** or **5**.
4-(3-Chlorophenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (3b): Mp: 278-280 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03-7.05 (m, 1H), 7.14 (s, 1H), 7.26-7.45 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): 126.13, 126.47, 127.90, 128.53, 128.76, 129.86, 129.93, 130.85, 135.49, 136.23, 154.61; LCMS: *m/z* = 332 $[M+H]^+$; Anal. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66 Found: C, 72.38; H, 4.30; N, 12.64.
2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (5c): Mp: 220 - 222 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 - 7.60 (m, 3H), 8.14 - 8.17 (m 2H), 8.32 (d, *J* = 8.8 Hz, 2H), 8.45 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 123.5, 125.0, 127.4, 128.5, 129.4, 129.9, 132.8, 149.6, 163.2, 165.3; LCMS: *m/z* = 268 $[M+H]^+$; Anal. Calcd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72 Found: C, 62.88; H, 3.44; N, 15.70.