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CuO-Promoted Construction of *N*-2-Aryl-Substituted-1,2,3-Triazoles via Azide-Chalcone Oxidative Cycloaddition and Post-Triazole Arylation

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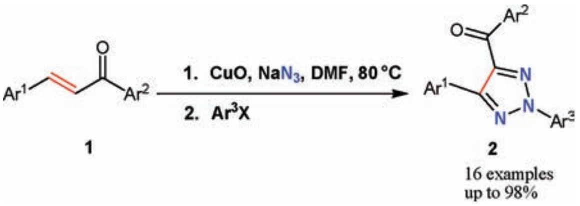
ABSTRACT



An efficient one-pot three-component stepwise approach for the synthesis of *N*-2-aryl-substituted-1,2,3-triazoles has been developed. By using this azide-chalcone oxidative cycloaddition and post-triazole arylation, a series of *N*-2-aryl-substituted-1,2,3-triazoles are readily prepared under mild conditions in excellent yields and high regioselectivity. Both the catalyst and substrates are readily available.

Since the remarkable discovery of Cu-catalyzed-azide-alkyne-cycloaddition (CuAAC, also referred as “click-chemistry”), 1,2,3-triazoles have attracted significant attention as one of the most important heterocycles.[1] Within the past few years, applications of this building block have been extended widely into various research fields,[2] such as chemical biology, material science, and medicinal chemistry. Recently described methods for the catalytic direct functionalization of triazole and its derivatives have also been proven attractive but are mainly limited to the N-1 position,[3] although few methodologies have been reported for the direct functionalization of triazoles at the N-2 position.[4] Traditional routes to prepare 1,2,3-triazoles often suffered from poor regioselectivity, a rather tedious reaction procedure, and a significant amount of expensive and difficult-to-prepare catalysts. 1-Substituted triazoles and the parent unsubstituted compounds can be synthesized by the reaction of organic azides, metal azides, or hydrazoic acid with alkynes respectively. The reaction with alkenes can

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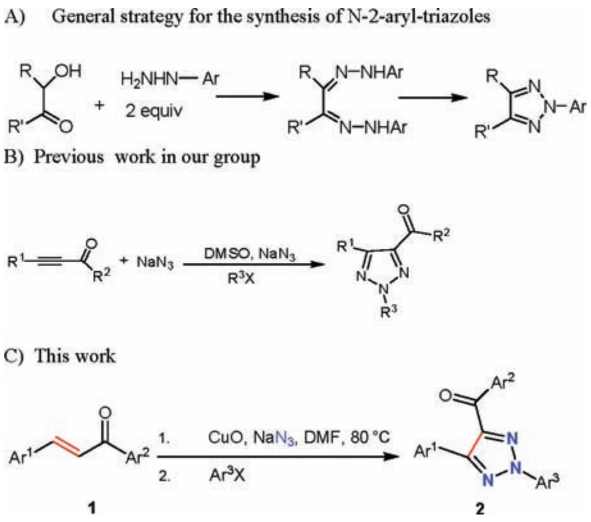
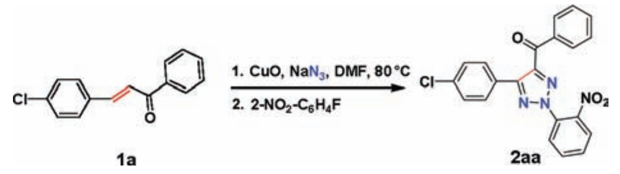
only take place when organic azides exist, mainly because 1,4-conjugate addition and formation of linear adducts are inclined to interact with azide ions and hydrazoic acid.[6]

Scheme 1. *N*-2-Aryl-1,2,3-triazole Synthesis



To date, our group has been working on the investigation of 1,2,3-triazole derivatives in transition metal catalysis.[7] However, the highly regioselective introduction of a substituent at N-2 was not possible via these chemistry methods. The general approach for N-2-aryl triazole is from the hydrazine/α-hydoxyketone condensation[8] as shown in Scheme 1A. We were interested in further investigating the utility of the Cu-based approach for synthesizing triazoles with different substitution patterns, especially those allowing access to the N-2 position. Currently, we had successfully developed a metal- and base-free three-component reaction of ynones, sodium azide, and alkyl halides for regioselectively synthesizing 2,4,5-trisubstituted 1,2,3-triazoles (Scheme 1B).[7b] At the outset of the above-mentioned investigation, we initially envisioned one novel and operationally simple way of regioselectively synthesizing 2,4,5-trisubstituted 1,2,3-triazoles via azide-chalcone oxidative cycloaddition and post-triazole arylation in one pot.

Table 1. Optimization Studies[a]



entry	Cu	*T* (°C)	equiv	solvent	yield[b] (%)
1	$CuCl_2$	80	1	DMF	21
2	$Cu(OAc)_2$	80	1	DMF	none
3	$Cu(acac)_2$	80	1	DMF	trace
4	CuI	80	1	DMF	none
5	**CuO**	**80**	**1**	**DMF**	**93**
6	CuO	80	1	DMA	79
7	CuO	80	1	DMSO	67
8	CuO	rt	1	DMF	none
9	CuO	120	1	DMF	71
10	none	80	none	DMF	none
11	CuO	80	0.2	DMF	80
12	CuO	80	0.5	DMF	61
13	CuO	80	2	DMF	76

[a] All of the reactions were carried out with substrate **1a** (0.2 mmol), NaN_3 (0.2 mmol), and 1 equiv of CuO in the solvent (2 mL) at 80 °C under air for 24 h first, then $2\text{-}NO_2\text{-}C_6H_4F$ (0.2 mmol) was added to the mixture, and the reaction continued for 6 h. [b] Isolated yields.

With this goal, we initiated our studies by choosing 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**1a**) as a model substrate with different Cu sources and solvents at varied temperature (Table 1). The reaction was conducted in DMF at 80 °C in the presence of 1 equiv of $CuCl_2$ under air for 24 h first, then $2\text{-}NO_2\text{-}C_6H_4F$ was added to the mixture, and the reaction continued for 6 h providing the desired product **2aa** (Figure 1) only in 21% yield (Table 1, entry 1). This inspired us to examine the optimal conditions for the reaction in order to obtain more satisfactory results. The catalytic activity of the

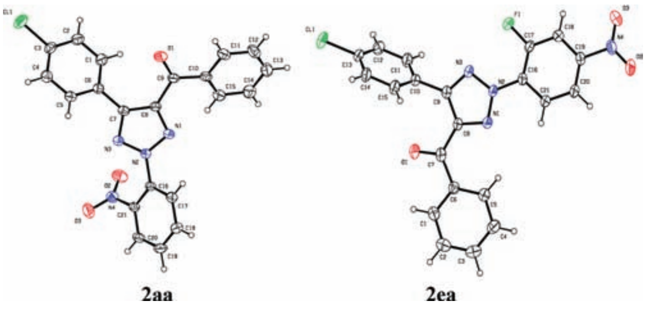

2aa **2ea**

Figure 1. X-ray crystal structures of **2aa** and **2ea**.

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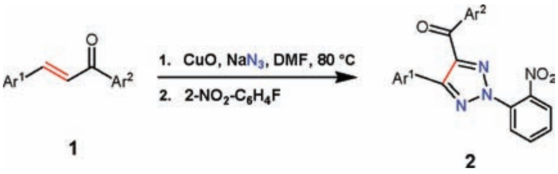
different copper sources such as $Cu(OAc)_2$, $Cu(acac)_2$, CuI, and CuO were tested (Table 1, entries 1−5). Among these tested copper sources, CuO was found to be superior and resulted in a 93% yield. The effect of the solvent was also investigated; changing the solvent from DMA to DMSO failed to improve the yield of the product (Table 1, entries 6−7). Although no anticipated product was observed at room temperature, no improvement was achieved when the reaction was conducted at 120 °C. In addition, neither increasing nor decreasing the loading of CuO gave any obvious improvement in the yields.

After obtaining the optimized reaction conditions, a variety of chalcones were used as substrates to investigate the scope of the reaction as shown in Table 2.

Table 2. Substrate Scope of Chalcones[a]



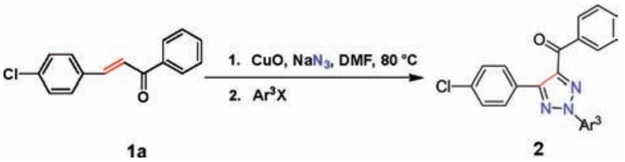
entry	Ar^1	Ar^2	yield[b] (%)	product
1	$4\text{-}ClC_6H_4$	C_6H_5	93	**2aa**
2	$4\text{-}NO_2C_6H_4$	C_6H_5	85	**2ab**
3	$4\text{-}FC_6H_4$	C_6H_5	75	**2ac**
4	$4\text{-}CH_3C_6H_4$	C_6H_5	71	**2ad**
5	$3,4\text{-}(CH_3)_2C_6H_3$	C_6H_5	65	**2ae**
6	C_6H_5	$4\text{-}CH_3OC_6H_4$	72	**2ah**
7	C_6H_5	C_6H_5	76	**2af**
8	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3OC_6H_4$	28	**2ag**
9	C_6H_5	$4\text{-}NO_2C_6H_4$	90	**2ai**
10	C_6H_5	$4\text{-}ClC_6H_4$	92	**2aj**
11	C_6H_5	$4\text{-}BrC_6H_4$	90	**2ak**
12	$4\text{-}CH_3OC_6H_4$	$4\text{-}NO_2C_6H_4$	97	**2al**
13	$4\text{-}ClC_6H_4$	$4\text{-}CH_3OC_6H_4$	83	**2am**
14	Fc	C_6H_5	0	**2an**

[a] All of the reactions were carried out with chalcones (0.2 mmol), NaN_3 (0.2 mmol), and 1 equiv of CuO in DMF (2 mL) at 80 °C for 24 h under air first, then $2\text{-}NO_2\text{-}C_6H_4F$ (0.2 mmol) was added to the mixture, and the reaction continued for 6 h. [b] Isolated yields.

Generally, chalcones with electron-withdrawing substituents on Ar^1 and/or Ar^2 led to higher yields (Table 2, entries 1−3, 10−13). In contrast, chalcones with electron-donating substituents gave lower but still acceptable yields (Table 2, entries 4−7). Notably, when the chalcone bearing two electron-donating groups was employed, the yield dropped to 28% (Table 2, entry 8). In addition, replacing the aryl group of Ar^1 of **1a** with ethynyl ferrocene (**Fc**) gave no desirable product.

To further explore the generality and scope of this protocol, several aryl halides were also investigated. As illustrated in Table 3, when the highly electron-deficient aryl halides were used, the reactions were conducted sluggishly and regioselectively produced the corresponding 2,4,5-trisubstituted 1,2,3-triazoles with excellent yields (Table 3, entries 1, 3−5). When $2\text{-}NO_2\text{-}C_6H_4Cl$ and the electron-rich aryl chlorides $2\text{-}CH_3\text{-}C_6H_4Cl$ were explored, the reactions did not yield any desired products (Table 3, entries 2 and 6). The structure of compound **2ea** was unambiguously confirmed by X-ray analysis (Figure 1).

Table 3. Substrate Scope of Aryl Halides[a]

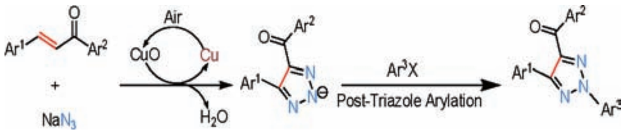


entry	Ar^3X	yield[b] (%)	product
1	$2\text{-}NO_2\text{-}C_6H_4F$	93	**2aa**
2	$2\text{-}NO_2\text{-}C_6H_4Cl$	none	**2ba**
3	$2, 4\text{-}diNO_2\text{-}C_6H_3Cl$	98	**2ca**
4	$2, 5\text{-}diF\text{-}C_6H_3NO_2$	79	**2da**
5	$3, 4\text{-}diF\text{-}C_6H_3NO_2$	88	**2ea**
6	$2\text{-}CH_3\text{-}C_6H_4Cl$	none	**2fa**

[a] All of the reactions were carried out with **1a** (0.2 mmol), NaN_3 (0.2 mmol), and 1 equiv of CuO in the DMF (2 mL) at 80 °C for 24 h under air first, then aryl halide Ar^3X (0.2 mmol) was added to the mixture, and the reaction continued for 6 h. [b] Isolated yields.

To probe the mechanism of this transformation, reactions of **1a** in the presence of 0.2 equiv of CuO under air and in the absence of CuO under air were investigated respectively. We were surprised to find that the latter reaction did not afford any expected product. We therefore postulated that CuO acted not only as the oxidant but also as an initiator to trigger this catalytic process, and then Cu was oxidized to CuO by air. On the basis of the above results, a plausible reaction pathway for the oxidative dehydrogenative coupling is illustrated in Scheme 2.

Scheme 2



In conclusion, the combination of azide-chalcone oxidative cycloaddition and post-triazole arylation presented herein is a powerful approach in diversity-oriented, multiple component condensation sequences. To the best of our knowledge, this is an efficient example of the selective preparation of N-2 triazole compounds with clear characterization of the different N-isomers. With the continuously growing interest in 1,2,3-triazoles, we believe this strategy will greatly benefit researchers in various fields. Application of this general concept to the construction of other triazole-containing scaffolds with potential biological activity is currently under investigation in our group and will be reported in due course.

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Supporting Information Available. Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.