# Cu–FeCl$_3$-Mediated One-Pot Multicomponent Reaction Leading to *N*-Aryl- and *N*-Alkyltriazoles in Water[1]

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**Abstract:** A concise, convenient and mild route for the one-pot syntheses of *N*-aryl- and *N*-alkyltriazoles in water is reported. The methodology involves the three-component reaction comprising phenylacetylene, sodium azide and aryl/alkyl halide catalyzed by Cu(I) species generated in situ by a redox reaction between FeCl$_3$ and copper metal. Prominent features of our methodology are incorporation of aryl fluoride to generate *N*-aryltriazoles, which are rather scarcely reported, use of water as reaction medium, and avoidance of hazardous aryl azide as a reactant.

**Key words:** multicomponent reaction, triazole, Cu–FeCl$_3$, redox reaction

In recent years there has been growing interest in using specific biologically validated substructures (privileged structures) as starting points for library design.[2] The resulting library can then be used to address a variety of biological targets. One way to increase the structural diversity of a privileged structure is to generate polycyclic rigid templates, which in turn will bear structural analogy to natural products. In view of our continued interest in the development of synthetic strategies for novel polycyclic structures[3] of biological interest, we required polycyclic structures based on *N*-aryltriazole **3**. Triazoles are an important class of compounds, as they form important components in pharmacologically active compounds and are associated with a wide spectrum of activities.[4] These heterocycles function as rigid linking units that can mimic the atom placement and electronic properties of a peptide bond without any susceptibility to hydrolytic cleavage.[5] Perhaps it is due to their ability to mimic certain aspects of a peptide bond, that many derivatives of 1,2,3-triazoles possess varied biological activities, including anti-HIV activity,[4e] selective β3-adrenergic receptor inhibition,[6] antibacterial activity[4d] and potent antihistamine activity.[4a–c]

The synthesis of 1,2,3-triazoles has been generally carried out by Huisgen's 1,3-dipolar cycloaddition reactions in one pot using three-component format.[7] The discovery of 1,4-disubstituted 1,2,3-triazoles under mild conditions was a welcome advance.[8] Perhaps the most powerful click reaction to date,[5a] the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has quickly found many applications in chemistry, biology, and materials science.[9] Since the initial discovery of CuI-catalyzed alkyne–azide coupling, numerous successful examples have been recorded in the literature.[10] Sharpless and co-workers reported Cu(I)-catalyzed ligation of azides with terminal alkynes, whereas Fokin and co-workers developed multicomponent variants in both conventional[11] and microwave irradiation methods.[12] Further reports have varied the reaction conditions, particularly with respect to generation of the active Cu(I) species. Sources of Cu(I) include Cu(I) salts, most commonly copper iodide,[8b] in situ reduction of Cu(II) salts, particularly Cu(II) sulfate,[8a] and comproportionation of Cu(0) and Cu(II).[9] Recent reports suggest that nitrogen-based ligands can stabilize the Cu(I) oxidation state under aerobic, aqueous conditions and in turn promote the desired transformation.[13] Recently, a comprehensive review on Cu(I)-catalyzed click chemistry dealing with both mechanistic as well as synthetic aspects has been described.[10]

However, in general all these reports involved the use of alkyl halide as one of the predominant monomers in contrast to the aryl halide, which is rather scarcely reported.[11c] We envisioned that the synthesis of our target structure *N*-aryltriazole **3** could be affected by replacing alkyl halides with *o*-nitrofluorobenzene in the Cu(I)-catalyzed multicomponent reaction. Our initial experiments with three-component reaction involving alkyne, *o*-nitrofluorobenzene and NaN$_3$ in the presence of Cu(0)/CuSO$_4$ produced final compound **3a** in low yields (Table 1, entry 1). There was no further improvement in yield when NaHCO$_3$ was used as a base, which is known to facilitate the reaction.[9–11]

This led us to develop a modified strategy for the formation of *N*-aryltriazoles by optimizing the redox and reaction conditions (Table 2).

The redox potential of Cu was compared in the electrochemical series with elements that would facilitate the generation of the Cu(I) species in situ. It was found that use of Fe(III) might assist in improving the generation of Cu(I) in a more effective manner.[14] This phenomenon can be understood by comparing the reduction potential of the redox couples. The reduction potential of Cu(I) to Cu(0) is +0.521 V and Fe(III) to Fe(II) is +0.771 V. Thus, the net potential is positive (+0.25 V) and therefore the reaction may be favorable. Armed with these observations, we carried out the three-component reaction involving alkyne, *o*-nitrofluorobenzene and NaN$_3$ in the presence of Cu–FeCl$_3$ as catalysts in *t*-BuOH–H$_2$O, but the reaction furnished **3a** in 10% isolated yield (Table 1, entry 3). Again NaHCO$_3$

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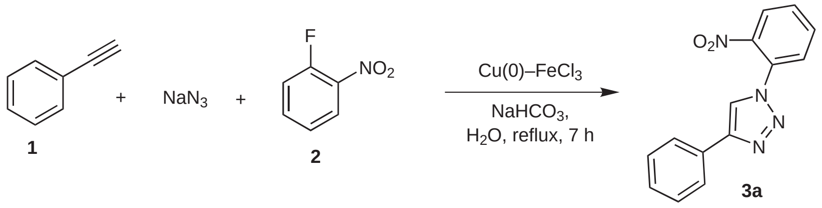
**Table 1** Synthesis of *N*-Aryltriazole (**3a**)

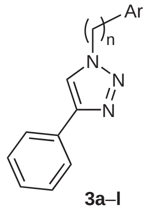


| Entry | Reaction conditions | Solvent | Time (h) | Yield of **3** (%) |
|---|---|---|---|---|
| 1 | Cu–$CuSO_4 \cdot 5H_2O$ | $H_2O$, *t*-BuOH (1:1) | 12 | 35 |
| 2 | Cu–$CuSO_4 \cdot 5H_2O$, $NaHCO_3$ | $H_2O$, *t*-BuOH (1:1) | 12 | 36 |
| 3 | Cu–$FeCl_3$ | $H_2O$, *t*-BuOH (1:1) | 12 | 10 |
| 4 | Cu–$FeCl_3$, $NaHCO_3$ | $H_2O$, *t*-BuOH (1:1) | 7 | 70 |
| 5 | Cu–$FeCl_3$, $NaHCO_3$ | $H_2O$ | 7 | 72[a] |

[a] Formation of 4-phenyl-1,2,3-triazole was observed in 5% isolated yield.

was added as a base and this time to our delight improvement in the yield to 70% was observed (Table 1, entry 4). The Cu(I) catalyst was prepared in situ by the redox reaction of Cu(0) and Fe(III) and the azides were generated in situ from the corresponding halides,[15] whereupon they were captured by copper(I) acetylides, forming the corresponding 1,4-disubstituted 1,2,3-triazoles (Table 1). The cascade of events must have begun with nucleophilic substitution of the halide with the azide **2** to generate the corresponding organoazide **4** derivative, which in turn underwent [3+2]-cycloaddition with alkynes to furnish the title compound **3a** (Figure 1). In order to prove this, sodium azide and phenylacetylene were reacted in the presence of Cu(0)–$FeCl_3$ catalytic system, which furnished 4-phenyl-1,2,3-triazole in 45% isolated yield, hence suggesting the possible reaction pathway depicted in Figure 1.

**Table 2** Synthesis of *N*-Aryl- and *N*-Alkyltriazole Derivatives Produced via Table 1



**3a–l**

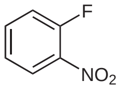
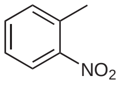
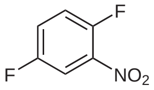
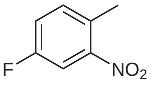
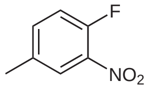
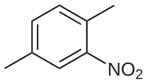
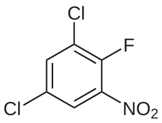
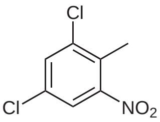
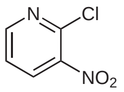
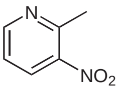
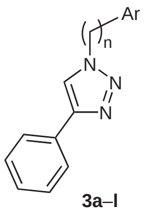
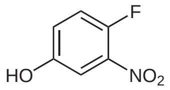
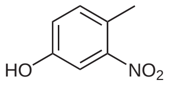
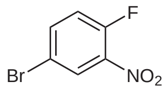
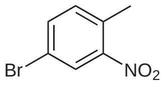
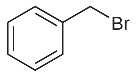
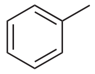
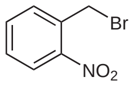
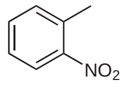
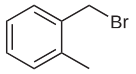
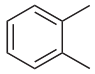
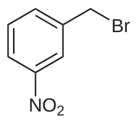
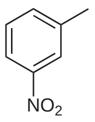
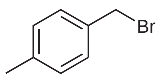
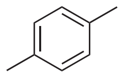
| Entry | Halide | Product | n | Ar | Time (h) | Yield (%)[a] | MS [M$^+$ + 1] (ES) |
|---|---|---|---|---|---|---|---|
| 1 |  | **3a** | 0 |  | 7 | 72 | 267.1 |
| 2 |  | **3b** | 0 |  | 7 | 75 | 285.2 |
| 3 |  | **3c** | 0 |  | 7 | 74 | 281.2 |
| 4 |  | **3d** | 0 |  | 7 | 70 | 335.1 |
| 5 |  | **3e** | 0 |  | 8 | 72 | 268.2 |

**Table 2** Synthesis of *N*-Aryl- and *N*-Alkyltriazole Derivatives Produced via Table 1 (continued)



**3a–l**

| Entry | Halide | Product | n | Ar | Time (h) | Yield (%)[a] | MS [M$^+$ + 1] (ES) |
|---|---|---|---|---|---|---|---|
| 6 |  | **3f** | 0 |  | 8 | 68 | 283.3 |
| 7 |  | **3g** | 0 |  | 7 | 71 | 345.2 |
| 8 |  | **3h** | 1 |  | 2 | 74 | 236.1 |
| 9 |  | **3i** | 1 |  | 2 | 71 | 281.2 |
| 10 |  | **3j** | 1 |  | 2.5 | 69 | 250.1 |
| 11 |  | **3k** | 1 |  | 2 | 75 | 281.2 |
| 12 |  | **3l** | 1 |  | 2.5 | 70 | 250.2 |

[a] Isolated yield.

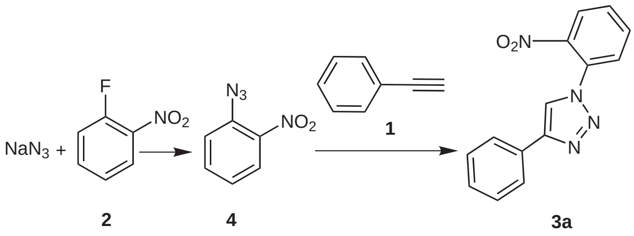


**Figure 1** Proposed reaction pathway.

After successfully optimizing the reaction conditions for the synthesis of *N*-aryltriazole **3**, we next decided to carry out the reaction using water as the sole solvent. Recently, we successfully demonstrated the use of water as solvent for the formation of β-carbolines using the Pictet–Spengler reaction.[16] Water has clear advantages as a solvent because it is cheap, readily available and nontoxic. Moreover, it has been argued that reactants that dislike water tend to come closer (the hydrophobic effect) in order to realize the reaction at a faster rate than in the absence of water.[17] Recently, a Cu(I)-catalyzed three-component reaction to form triazoles using an amine, propargyl halide and aryl azide in water has been reported;[18] however, it suffers from the use of the hazardous aryl azides.

Interestingly, the three-component click chemistry when carried out in water using Cu(0)–FeCl$_3$ as a source of Cu(I), furnished **3** in good isolated yield. In our subsequent experiments,[19] we conducted a broader investigation of this reaction in water by utilizing a variety of *o*-fluoronitrobenzenes and alkyl halides with the aim to synthesize both *N*-aryl- and *N*-alkyltriazoles (Table 1). Both *o*-fluoronitrobenzenes and alkyl halides furnished **3** with equal ease. The crude *N*-derivatized triazoles were purified on silica gel column furnishing pure compounds in 68–75% isolated yields. HPLC and MS analyses of the crude products showed presence of 4-phenyl-1,2,3-triazole in less than 8% yield.

In summary, we have developed a mild and efficient protocol for the synthesis of *N*-aryl- and *N*-alkyltriazoles using three-component click chemistry. The use of Fe(III) to generate Cu(I) has been reported for the first time for the synthesis of *N*-aryltriazoles. Studies are in progress to use the functionalized *N*-aryltriazoles for the preparation of polyheterocyclic structures via C–C bond formation.

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## References and Notes

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(19) **General Procedure for the Preparation of 1-(2-Nitrophenyl)-4-phenyl-1*H*-[1,2,3]triazole (3a)**: 1-Fluoro-2-nitrobenzene (2.0 mmol), phenylacetylene (2.2 mmol), sodium azide (2.2 mmol) and $NaHCO_3$ (2.2 mmol) were suspended in $H_2O$ (10 mL) in a 50-mL round-bottomed flask equipped with a small magnetic stirring bar. To this was added copper powder (100 mg) and ferric chloride (100 mg). The mixture was then heated to reflux for 7 h. The reaction mixture was cooled and EtOAc (50 mL) was added. The suspension was passed through a bed of celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried ($Na_2SO_4$) and concentrated to afford a residue, which was purified by silica gel chromatography using hexane–EtOAc (70:30) as eluent to afford **3a** as a yellow solid. Yield: 72%; mp 144–145 °C. IR (KBr): 1604, 1534, 1351 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 8.12$ (dd, $J = 1.2$, 7.9 Hz, 1 H, ArH), 8.09 (s, 1 H, ArH), 7.91–7.94 (m, 2 H, ArH), 7.81–7.84 (m, 1 H, ArH), 7.69–7.76 (m, 2 H, ArH), 7.46–7.51 (m, 2 H, ArH), 7.40–7.43 (m, 1 H, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 148.54$, 144.60, 134.01, 130.91, 130.41, 129.96, 129.11, 128.81, 128.03, 126.15, 125.73, 121.18. MS (ES$^+$): $m/z = 267.1$ [M$^+$ + 1]. Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 63.26; H, 3.57; N, 21.40.
1-(4-fluoro-2-nitrophenyl)-4-phenyl-1*H*-[1,2,3]triazole (**3b**): Yield: 75%; mp 178–180 °C. IR (KBr): 1601, 1523, 1347 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO): $\delta = 9.14$ (s, 1 H, ArH), 8.28 (dd, $J = 2.4$, 8.0 Hz, 1 H, ArH), 8.04–8.08 (m, 1 H, ArH), 7.89–7.94 (m, 3 H, ArH), 7.51 (t, $J = 7.2$ Hz, 2 H, ArH), 7.27–7.42 (m, 1 H, ArH), $^{13}$C NMR (75.5 MHz, DMSO): $\delta = 147.08$, 144.75, 129.78, 129.60, 129.03, 128.43, 125.79, 125.37, 122.91, 121.60, 121.30, 113.80, 113.42. MS (ES$^+$): $m/z = 285.2$.