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# Ethylene Glycol, an Efficient and Recoverable Medium for Copper-Catalyzed *N*-Arylation of Diazoles under Microwave Irradiation

Ali Sharifi<sup>1</sup>, Nima Ghonouei<sup>1</sup>, M. Saeed Abaee<sup>1</sup>

<sup>1</sup>Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

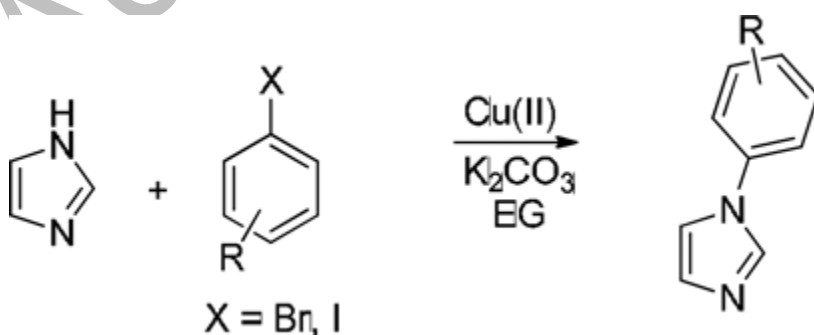
Correspondence: A. Sharifi, Chemistry and Chemical Engineering Research Center of Iran, P.O.Box 14335-186, Tehran, Iran Email: sharifi@ccerci.ac.ir

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## Abstract

Ethylene glycol was used as an efficient and recoverable medium for the reaction of diazoles with aryl iodides and aryl bromides in the presence of CuCl<sub>2</sub> as the catalyst and K<sub>2</sub>CO<sub>3</sub> as the base. Consequently, imidazole, benzimidazole, and pyrazole reacted readily under microwave irradiation to give good to excellent yields of their corresponding *N*-arylated products in relatively short time periods. Apparently, ethylene glycol plays a dual role by activating the catalyst and also providing a homogenous medium for the processes. The reaction medium consisted of the solvent, the base, and the copper salt was recovered and reused successfully in next several reactions.

## Graphical Abstract:



**KEYWORDS:** *N*-Arylation, diazole, ethylene glycol, microwave irradiation

## INTRODUCTION

*N*-Arylation of nitrogen atoms of aromatic heterocycles is a common and frequently practised strategy in synthetic organic chemistry.<sup>[1-2]</sup> The resulting *N*-arylated products have found many applications as biologically<sup>[3-4]</sup> and medicinally<sup>[5-6]</sup> active substances. In this regard, copper-catalyzed reaction of *N*-heterocycles with aryl halides is one of the most straight-forward routes to access these compounds. So far, different sets of copper catalysts, ligands, bases, and solvents have been used to perform *N*-arylation of heterocycles.<sup>[7-8]</sup> Remarkable advances in this area include the use of ligand-free/solvent-free conditions<sup>[9]</sup> and aqueous media.<sup>[10]</sup> Despite these achievements, there is still a demand to design new protocols involving simpler procedures, greener conditions, and less expensive reagents and catalysts.

Ethylene glycol (EG) has found many recent uses as a solvent in organic reactions, because it offers advantages such as low vapor pressure, high chemical and thermal stability, and low flammability.<sup>[11]</sup> Its ability for hydrogen bonding enables EG to bind to substrates and metal ions, and its high polarity makes it a suitable choice as the medium for microwave (MW)-assisted reactions.<sup>[12-14]</sup> In addition, since EG can dissolve both organic and inorganic compounds, it helps provide homogenous conditions for catalytic processes such as many transition metal-catalyzed reactions.<sup>[15-17]</sup> EG has also been used as an auxiliary ligand in copper-catalyzed Ullmann-type<sup>[18]</sup> arylation of primary or secondary amines,<sup>[19]</sup> and in *N*-arylation of  $\beta$ -amino alcohols.<sup>[20]</sup> Moreover, EG is used as

both the reaction solvent and ligand for copper in the amination of aryl bromides with ammonia<sup>[21]</sup> and C–O coupling of aryl bromides with aliphatic diols.<sup>[22]</sup>

In the framework of our studies to design environmentally benign procedures in the field of heterocyclic chemistry,<sup>[23-25]</sup> herein we present the reaction of diazoles with aryl iodides and aryl bromides in EG medium catalyzed by CuCl<sub>2</sub> under MW irradiation.

There are a few examples in the literature for using copper(II) in Ullmann-type reactions since it is generally believed that Cu(II) is less reactive in these types of reactions. The difference between Cu(I) and Cu(II) ions in copper-catalyzed cross coupling reactions is that Cu(I) can directly enter the reaction cycle as the active species, but Cu(II) must first convert to Cu(I) via the action of a nucleophile in the reaction medium.<sup>[26]</sup> In the case of our experiment, we believe that the nucleophilic hydroxyl groups on EG provides the necessary conditions for the conversion to Cu(I) species in the presence of the base.

Search in the literature shows existence of a single article where the use of EG as the ligand for Cu(I) catalyzed Ullmann-type reactions in an ionic liquid has been unsuccessful.<sup>[27]</sup> We believe that in the present work the use of Cu(II)/EG conditions combined with MW irradiation has substantially improved the conditions so that the desired reaction takes place conveniently. The study also shows that there is no need for the reactions to add extra ligands or solvents, since EG both activates the copper ion and provides a homogenizing medium for the reaction by dissolving the starting materials as well as the base and the copper species. In addition, after a simple extraction of the

products by ether, the reaction medium could be recovered and reused efficiently in the next runs.

## RESULTS AND DISCUSSION

First, we monitored the effect of different sets of conditions on the model reaction of imidazole with 4-iodoanisole in EG as shown in Table 1. By using  $\text{CuCl}_2$  as the copper source and  $\text{K}_2\text{CO}_3$  as the base, the desired *N*-arylated product was formed in 50% yield after 24 hours of heating at 130 °C, while no trace of the *O*-arylated EG was observed (entry 1). When the amount of  $\text{CuCl}_2$  was increased to 10 mol%, a better yield of the product was obtained (entry 2), but no improvements was observed with further addition of the catalyst amount (entry 3). Literature survey show precedence for MW irradiation to improve the scope of the Ullmann-type reactions.<sup>[28]</sup> When we repeated the reaction under MW conditions, it took only 30 minutes at 300 W to obtain 95% of the target product (entry 4). When we used lower ratios of imidazole:4-iodoanisole (entries 5-6) or took two equivalents of the base, only decreased yields of the isolated product was obtained (entry 7).

The effect of different Cu(I) and Cu(II) salts was also studied (entries 8-11). As it is obvious from the results, while all attempted Cu(II) salts gave comparable results, Cu(I) species were not as efficient and led to lower yields within the same time periods. This was in agreement with the previous observations by Chae et al in the *O*-arylation of EG,<sup>[22]</sup> where they attributed the enhanced reactivity of the Cu(II) salts to higher stabilization and solubility of these salts in EG medium. The low yield of the reaction in

the absence of EG, or when EG was used in stoichiometric amounts, proved the determining role of EG in the process (entries 12-13).

Next, we employed the optimized conditions (Table 1, entry 4) to examine the generality of the procedure. Table 2 summarizes the results for the reactions of imidazole, benzimidazole, and pyrazole with different aryl halides. Aryl bromides reacted under the optimized conditions, but their respective reaction times were longer and in some cases relatively lower yields were obtained (entries 1-2, 13). Aryl halides with *p*- or *m*-substitutions did not interfere with the reaction, but *o*-substituted derivatives gave only trace of the expected products. The electronic nature of the substitutions on the aryl halide also affected the outcome of the reaction. Thus, while electron-donating substituents such as methyl or methoxy groups were successfully used (entries 2-4, 9-11), electron deficient counterparts resulted in lower conversions and complex mixtures were formed.

As it is obvious from Table 2, imidazole reacted more readily with iodobenzene than benzimidazole and pyrazole did (entries 1, 9, 13). Also, the *O*-arylation of EG was not observed in any of the reactions. The generally accepted catalytic cycle for the reaction is depicted in Figure 1.<sup>[29]</sup> The first step involves the coordination of the nucleophile to the copper species in the presence of the base. The observed reactivity order (imidazole > benzimidazole > pyrazole >> EG) can be explained by considering both the relative acidities of the Nu-H bonds (Nu = diazole or EG) and the nucleophilicity of the resulting anion. Greater N-H acidities would favor easier coordination of the nucleophile to the

central Cu ion, and a more nucleophilic anion would favor the reductive elimination step, and the formation of the product.<sup>[30-31]</sup> Thus, EG would not bind to copper in the presence of diazoles because of the lower acidity of the O-H bond compared to those of heterocyclic N-H bonds.

One of the advantages associated with conducting reactions in EG is that the reaction medium could be recycled and reused in next experiments. This persuaded us to investigate the feasibility of recovering and reusing the medium in the model reaction between imidazole and 4-iodoanisole. Thus, after extracting the product with diethyl ether, the reaction medium was recovered by removing the volatile portion under reduced pressure and reused successfully in next several runs without further addition of the base or the catalyst. Table 3 shows the results for successful recycling of the catalyst.

In summary, we have introduced EG as an efficient medium for the Cu(II)-catalyzed reactions of aryl iodides and bromides with diazoles under MW irradiation. The catalyst system is inexpensive and readily available. The selectivity for *N*-alkylation, short reaction times, high yields of the products, and the ability to recover the catalyst are among the advantages of the current method.

## EXPERIMENTAL

All reagents and solvents were commercially available and used as received. Progress of the reactions was monitored by TLC using silica gel coated plates and EtOAc/petroleum ether mixture (1:1) as the eluent. MW-assisted reactions were carried out in a Milestone

Microsynth<sup>®</sup> instrument. Melting points are uncorrected and are obtained by Buchi Melting Point 530. <sup>1</sup>H NMR (500 MHz) spectra were obtained on a FT-NMR Bruker Ultra Shield<sup>TM</sup> instrument as CDCl<sub>3</sub> solutions and the chemical shifts are expressed as  $\delta$  units with Me<sub>4</sub>Si as the internal standard. All products were known and their identity was confirmed by the comparison of their melting points and their <sup>1</sup>H NMR data with those of authentic compounds available in the literature.

**General Procedure For MW-Assisted CuCl<sub>2</sub>-Catalyzed Preparation Of 1c (Table 2, Entry 3)**

Imidazole (0.13 gr, 2.0 mmol), CuCl<sub>2</sub> (0.0134 gr, 0.1 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.41 gr, 3.0 mmol) were added to EG (2.0 mL) and the mixture was stirred thoroughly. Then, 4-iodoanisole (0.23 gr, 1.0 mmol) was added and the reaction vessel was capped. The reaction mixture was irradiated at 300 W in the MW instrument for 30 minutes. After completion of the reaction, water (30.0 mL) was added to the mixture and the organic portion was extracted with diethyl ether (3  $\times$  10 mL). The combined ethyl acetate layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude product was purified via a silica gel column using EtOAc/petroleum ether mixtures (1:1) as the eluent to yield a white solid. 0.22 gr, 95%, m.p: 52-55 °C (found), 57 °C (literature);<sup>[32]</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  7.80 (s, 1H); 7.26 (m, 1H); 7.12 (s, 1H); 7.11 (s, 1H); 6.86 (m, 1H); 6.81 (m, 2H); 3.74 (s, 3H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$  159.2, 136.0, 130.8, 130.0, 123.3, 119.0, 115.2, 55.8 ppm.



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**Table 1.** Optimization of the reaction conditions

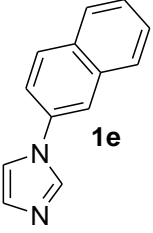
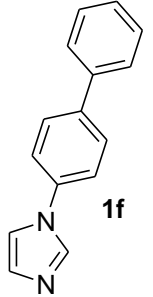
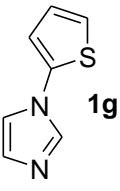
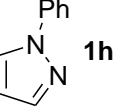
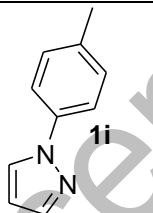
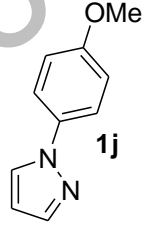
| Entry | Imidazole:PhX | Catalyst (mol%)           | Conditions            | Time   | Yield (%) <sup>a</sup> |
|-------|---------------|---------------------------|-----------------------|--------|------------------------|
| 1     | 2.0:1.0       | CuCl <sub>2</sub> (5)     | 120 °C                | 24 h   | 50                     |
| 2     | 2.0:1.0       | CuCl <sub>2</sub> (10)    | 120 °C                | 24 h   | 71                     |
| 3     | 2.0:1.0       | CuCl <sub>2</sub> (20)    | 120 °C                | 24 h   | 75                     |
| 4     | 2.0:1.0       | CuCl <sub>2</sub> (10)    | MW, 300W              | 30 Min | 95                     |
| 5     | 1.0:1.0       | CuCl <sub>2</sub> (10)    | MW, 300W              | 30 Min | 70                     |
| 6     | 1.0:1.1       | CuCl <sub>2</sub> (10)    | MW, 300W              | 30 Min | 65                     |
| 7     | 2.0:1.0       | CuCl <sub>2</sub> (10)    | MW, 300W <sup>b</sup> | 30 Min | 60                     |
| 8     | 2.0:1.0       | Cu(OAc) <sub>2</sub> (10) | MW, 300W              | 30 Min | 80                     |
| 9     | 2.0:1.0       | CuBr <sub>2</sub> (10)    | MW, 300W              | 30 Min | 85                     |
| 10    | 2.0:1.0       | CuI (10)                  | MW, 300W              | 30 Min | 50                     |
| 11    | 2.0:1.0       | CuCl (10)                 | MW, 300W              | 30 Min | 60                     |
| 12    | 2.0:1.0       | CuCl <sub>2</sub> (10)    | MW, 300W <sup>c</sup> | 30 Min | 5>                     |
| 13    | 2.0:1.0       | CuCl <sub>2</sub> (10)    | MW, 300W <sup>d</sup> | 30 Min | 30                     |

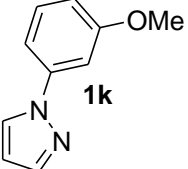
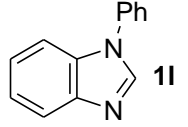
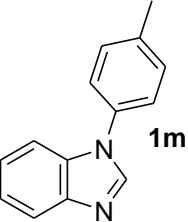
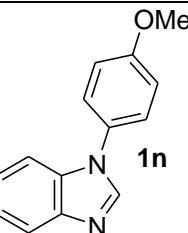
<sup>a</sup>Isolated yields;<sup>b</sup>Two equivalents of K<sub>2</sub>CO<sub>3</sub> was used;<sup>c</sup>Solvent-free conditions;<sup>d</sup>Two equivalents of EG was used

**Table 2.** Reaction of diazoles with different aryl halides



| Entry | Product       | X  | Time (Min) | Yield (%) <sup>a,b</sup> |
|-------|---------------|----|------------|--------------------------|
| 1     | <br><b>1a</b> | I  | 30         | 90                       |
|       |               | Br | 60         | 85                       |
| 2     | <br><b>1b</b> | I  | 30         | 82                       |
|       |               | Br | 60         | 78                       |
| 3     | <br><b>1c</b> | I  | 30         | 95                       |
| 4     | <br><b>1d</b> | Br | 30         | 80                       |

|    |  |    |    |    |
|----|--|----|----|----|
| 5  | <br><b>1e</b>   | Br | 90 | 95 |
| 6  | <br><b>1f</b>   | Br | 90 | 60 |
| 7  | <br><b>1g</b>   | I  | 30 | 90 |
| 8  | <br><b>1h</b> | I  | 30 | 75 |
| 9  | <br><b>1i</b> | I  | 30 | 80 |
| 10 | <br><b>1j</b> | I  | 30 | 90 |

|    |   |    |     |    |
|----|---|----|-----|----|
| 11 | <br><b>1k</b>  | Br | 30  | 95 |
| 12 | <br><b>1l</b>  | I  | 0.5 | 86 |
|    |   | Br | 1   | 20 |
| 13 | <br><b>1m</b>  | I  | 1.5 | 40 |
|    |   | Br | 1.5 | 20 |
| 14 | <br><b>1n</b> | I  | 1.5 | 38 |

<sup>a</sup>Isolated yields

<sup>b</sup>Reaction conditions: diazole (2.0 mmol), aryl halide (1.0 mmol), CuCl<sub>2</sub> (0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (3.0 mmol), MW irradiation (300 W).

**Table 3.** Successful recycling of the catalyst

| Entry | Run             | Yield (%) <sup>a</sup> |
|-------|-----------------|------------------------|
| 1     | 1 <sup>st</sup> | 95                     |
| 2     | 2 <sup>nd</sup> | 88                     |
| 3     | 3 <sup>rd</sup> | 80                     |
| 4     | 4 <sup>th</sup> | 70                     |

<sup>a</sup>GC yields



**Figure 1.** The general catalytic cycle

