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# Copper-Catalyzed Direct Synthesis of 1,2,4-Oxadiazoles from Amides and Organic Nitriles by Oxidative N–O Bond Formation

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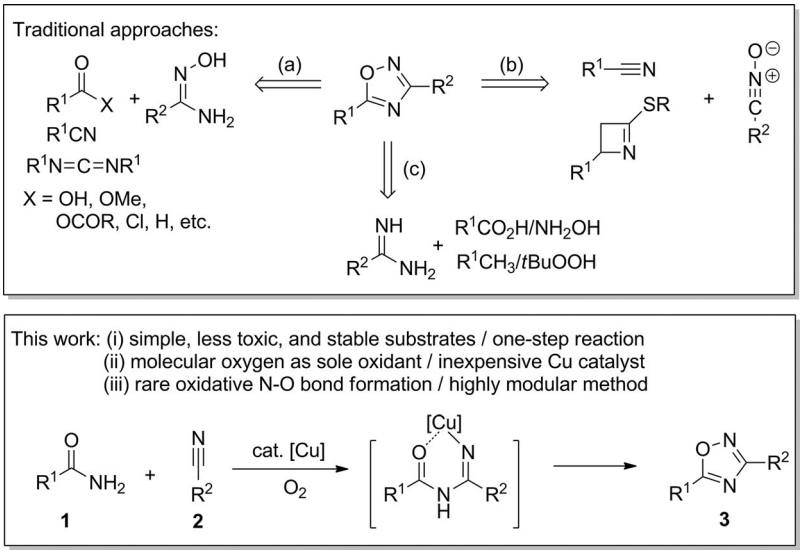
**Abstract:** Herein, we report the first Cu-catalyzed one-step method for the synthesis of 1,2,4-oxadiazoles from stable, less toxic, and readily available amides and organic nitriles by a rare oxidative N–O bond formation using $O_2$ as sole oxidant. This method has a broad substrate scope and a good tolerance for diverse functional groups. Moreover, the synthetic utility of this method is highlighted by the synthesis of biologically active 3,5-disubstituted derivatives.

## Introduction

1,2,4-Oxadiazole is a privileged scaffold, ubiquitous in various bioactive molecules, pharmaceuticals, and functional materials.[1–4] Furthermore, these five-membered heterocycles have been utilized as stable ester or amide bioisosteres in peptide mimetics.[5] Therefore, their synthesis has attracted much attention; thus, various synthetic methods have been developed.[1b,1c] One of the classical methods for the synthesis of 1,2,4-oxadiazoles (Scheme 1a) widely utilizes amidoximes as the starting precursor, prepared by the addition of carcinogenic hydroxylamine to a nitrile compound.[6] Then, the amidoximes are *O*-acylated using activated carboxylic acid derivatives followed by intramolecular dehydration to afford 1,2,4-oxadiazoles. This often requires high temperatures and long reaction times.[6] Recently, microwave-assisted methods or strong acids such as *p*TsOH and $ZnCl_2$ were used to overcome these limitations.[7] Another route for the generation of these heterocycles involves the 1,3-dipolar cycloaddition of nitrile oxides to nitriles or azetine derivatives (Scheme 1b).[8] Recently, *N*-acylamidines obtained from the condensation of amidines with carboxylic acids were used as the intermediates; further tandem reaction with hydroxylamine afforded 1,2,4-oxadiazoles (Scheme 1c).[9a] Moreover, Jiang and co-workers reported the Cu-catalyzed cascade annulation of amidines with methylarenes using *tert*-butyl hydroperoxide as an oxidant.[9b] Despite these diverse meth-




Scheme 1. Outline of our current approach.

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ods,[10] typically multistep processes and harmful reagents are used for the synthesis of diverse 1,2,4-oxadiazoles.

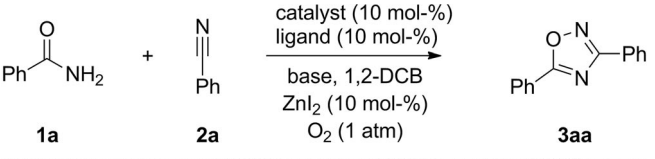
Despite the synthetic and medicinal utility of oxa–aza heterocycles containing N–O bonds, the direct oxidative bond formation between nitrogen and oxygen atoms are scarce and typically requires strong oxidants.[11] Among the recently reported transition-metal-catalyzed or transition-metal-free syntheses of nitrogen heterocycles involving oxidative N–N coupling,[12] the synthesis of 1,2,4-triazoles by a Cu-catalyzed addition and oxidative cyclization of amidines with aryl nitriles developed by Nagasawa and Ueda is noteworthy.[13] However, to the best of our knowledge, the direct synthesis of 1,2,4-oxadiazoles from amides and organic nitriles by direct N–O bond formation has not been reported. The development of efficient methods for the synthesis of complex organic molecules from simple substrates is always demanding and challenging. In this study, we report a Cu-catalyzed direct method for the synthesis of 1,2,4-oxadiazoles from readily available and simple starting precursors, amides, and organic nitriles.

## Results and Discussion

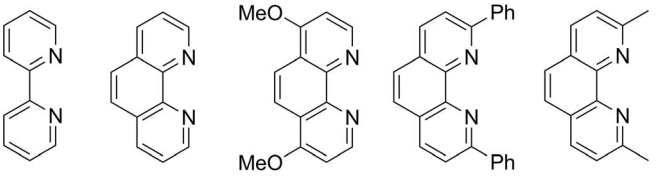
First, the reaction conditions were optimized (Table 1) for the direct synthesis of 1,2,4-oxadiazole using benzamide (**1a**; 1.2 equiv.) and benzonitrile (**2a**; 1.0 equiv.). The initial screening to obtain 1,2,4-oxadiazole using various transition-metal catalysts was unsuccessful (see Supporting Information, Table S2). To our delight, the desired product was obtained when CuI/1,10-phenanthroline (**L2**) and $ZnI_2$ were used in 1,2-dichlorobenzene at 120 °C under $O_2$, albeit in 2 % GC yield (Table 1, Entry 1). The addition of a base slightly increased the yield (Entry 2). Among the bases screened, $K_2CO_3$ was the best, resulting in 22 % yield (see also Table S3). Then, various nitrogen ligands were screened; bathophenanthroline (**L4**) increased the yield up to 36 % compared to other ligands (Entries 3–6). When air was used instead of $O_2$, 15 % GC yield was obtained; attempts to use other oxidants including benzoyl peroxide, $K_2S_2O_8$, and $PhI(OAc)_2$ were unsuccessful (see Table S4). The reaction did not proceed in other solvents such as toluene, *N*,*N*-dimethylformamide, and dimethyl sulfoxide (Table S5). Interestingly, when the temperature was increased up to 130 °C without $ZnI_2$, the yield significantly increased to 60 % (Entry 7). A further increase in temperature to 150 °C did not affect the yield (Entry 8). The reaction profile was relatively clean after the addition of MS (4 Å) in the GC analysis. A further improvement in the yield was observed when the amounts of benzamide (**1a**) and benzonitrile (**2a**) were changed to 1 and 2 equiv., respectively (Entry 9). Gratifyingly, the addition of $ZnI_2$ increased the isolated yield up to 92 % (Entry 10). In the presence of a $Cu^{II}$ salt, 60 % yield was obtained (Entry 11). Without a Cu catalyst, no product formation was observed (Entry 12). Therefore, Entry 10 was selected for the optimal reaction conditions.

Then, the substrate scope and generality of the method under the optimized reaction conditions were investigated using various organic nitriles containing diverse functional groups (Scheme 2). The results demonstrate broad substrate scope with **1a** as a partner, and the corresponding 1,2,4-oxadiazoles

Table 1. Optimization of the reaction conditions.[a]




1a 2a 3aa



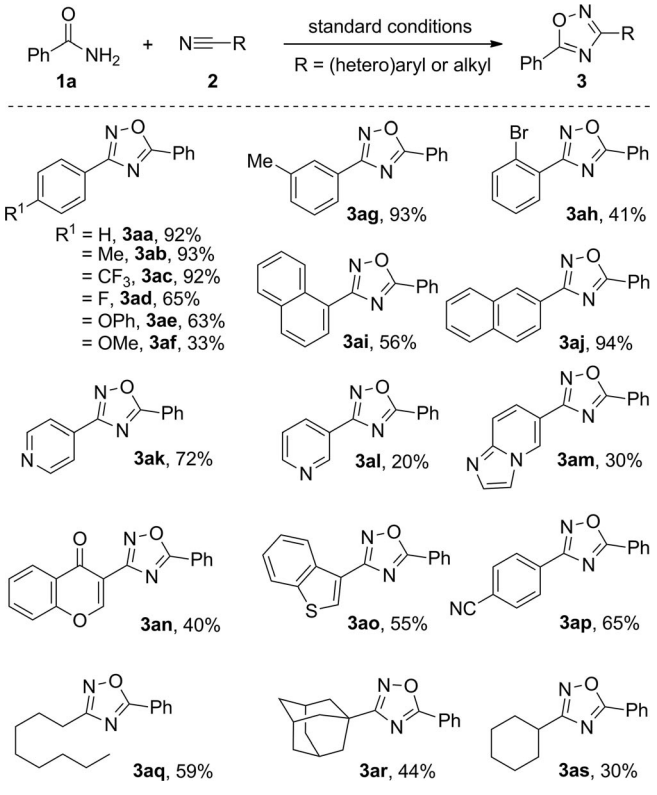

L1 L2 L3 L4 L5

| Entry | Catalyst | Ligand | Base | *T* [°C] | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | CuI | **L2** | – | 120 | 2 |
| 2 | CuI | **L2** | $K_2CO_3$ | 120 | 22 |
| 3 | CuI | **L1** | $K_2CO_3$ | 120 | 25 |
| 4 | CuI | **L3** | $K_2CO_3$ | 120 | 22 |
| 5 | CuI | **L4** | $K_2CO_3$ | 120 | 36 |
| 6 | CuI | **L5** | $K_2CO_3$ | 120 | 2 |
| 7 | CuI | **L4** | $K_2CO_3$ | 130 | 60[c,d] |
| 8 | CuI | **L4** | $K_2CO_3$ | 150 | 64[c,d] |
| 9 | CuI | **L4** | $K_2CO_3$ | 130 | 68[c,d,e] |
| 10 | CuI | **L4** | $K_2CO_3$ | 130 | 92[c,e] |
| 11 | $Cu(OTf)_2$ | **L4** | $K_2CO_3$ | 130 | 60 |
| 12 | – | **L4** | $K_2CO_3$ | 130 | – |

[a] Reaction conditions: **1a** (1.2 equiv.), **2a** (1.0 equiv., 0.2 mmol), catalyst (10 mol-%), ligand (10 mol-%), base (2.0 equiv.), $ZnI_2$ (10 mol-%) in 1,2-dichlorobenzene (1,2-DCB, 1 mL) under $O_2$ (1 atm) for 24 h. [b] GC yield with *n*-dodecane as an internal standard. [c] MS (4 Å), isolated yield. [d] Without $ZnI_2$. [e] **1a** (1.0 equiv.) and **2a** (2.0 equiv.).

(**3**) were generally obtained in moderate to excellent yields (up to 94 %). The reactions of substrates bearing electron-withdrawing and electron-donating *para* substituents on the aromatic ring of benzonitrile, such as methyl (**2b**), trifluoromethyl (**2c**), fluoro (**2d**), and phenoxy (**2e**) groups, afforded the corresponding products in good yields (Scheme 2; **3ab**–**3ae**). In the case of 4-methoxybenzonitrile (**2f**), only 33 % yield was obtained (**3af**), probably because of the reduced electrophilicity of the cyano group by the strong electron-donating methoxy group. The detailed reaction mechanism will be discussed further below. To our delight, the reactions of *ortho*-/*meta*-substituted benzonitriles afforded the corresponding products in good to moderate yields (**3ag** and **3ah**). When 1-cyanonaphthalene (**2i**) and naphthalene-2-carbonitrile (**2j**) were treated with benzamide (**1a**), products **3ai** and **3aj** were obtained in 56 % and 94 % yields, respectively. The reactions with heterocyclic nitriles such as isonicotinonitrile (**2k**), nicotinonitrile (**2l**), and imidazo[1,2-*a*]pyridine-6-carbonitrile (**2m**) afforded the corresponding products (**3ak**–**3am**), indicating the broad substrate scope of the protocol. The reactions of 3-cyanochromone (**2n**) and benzo[*b*]thiophene-3-carbonitrile (**2o**) also afforded the corresponding products in moderate yields (**3an** and **3ao**). Interestingly, in the reaction of 1,4-dicyanobenzene, one cyano group survived, thus affording **3ap** in 65 % yield. Next, the reactivities of different aliphatic nitriles with benzamide (**1a**) were

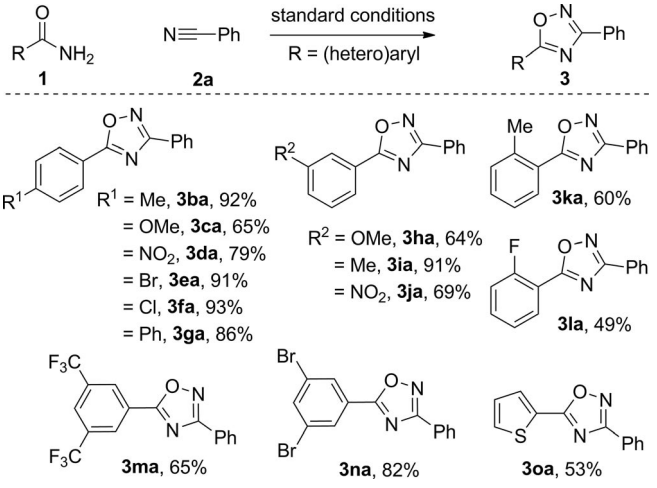
investigated. When nonanenitrile (**2q**) was used, a good yield of the product **3aq** was obtained. Adamantanecarbonitrile (**2r**) and cyclohexanecarbonitrile (**2s**) were less reactive, resulting in 44 % and 30 % yields, respectively (**3ar** and **3as**). These results indicate that aromatic nitriles are more reactive. The inductively donating aliphatic groups may lead to a decrease in the electrophilicity, resulting in less reactive aliphatic nitriles towards the nucleophilic attack of amides.




Scheme 2. Synthesis of 1,2,4-oxadizoles from diverse organic nitriles. Standard conditions: amide **1** (1.0 equiv., 1.0 mmol), organic nitrile **2** (2.0 equiv., 2.0 mmol), CuI (10 mol-%), **L4** (10 mol-%), $K_2CO_3$ (2.0 equiv.), $ZnI_2$ (10 mol-%), MS (4 Å) (300 mg) in 1,2-DCE (2.0 mL) at 130 °C under $O_2$ (1 atm) for 24 h.

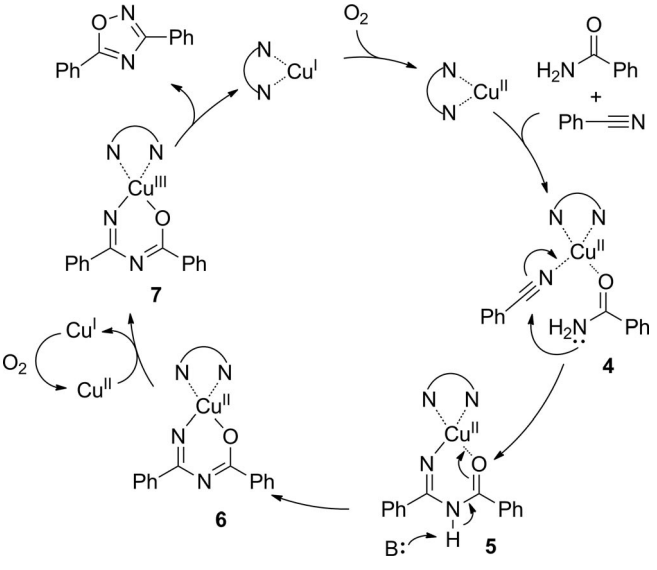
Then, the reactivities of various amides with benzonitrile (**2a**) were investigated (Scheme 3). The reactions of aryl amides bearing various *para*-substituted functional groups such as methyl (**1b**), methoxy (**1c**), nitro (**1d**), halo (**1e** and **1f**), and phenyl (**1g**) proceeded smoothly. The reactions of *meta*- or *ortho*-substituted aryl amides bearing methoxy (**1h**), methyl (**1i**/**1k**), nitro (**1j**), and fluoro (**1l**) groups afforded the corresponding products in moderate to good yields. The reactions of 3,5-bis(trifluoromethyl)benzamide (**1m**) and 3,5-dibromobenzamide (**1n**) with benzonitrile (**2a**) afforded the corresponding products **3ma** and **3na** in good yields. Finally, the heterocyclic thiophene-2-carboxamide (**1o**) reacted well with benzonitrile (**2a**) to afford **3oa** in 53 % yield.

Based on the previous reports[13,14] and our experimental results, a reaction mechanism is proposed. The reaction proceeds by the addition of the amide to the benzonitrile followed by N–O bond formation to afford the 1,2,4-oxadiazole (Scheme 4). First, $Cu^{I}$ is oxidized to $Cu^{II}$ by molecular oxygen and forms



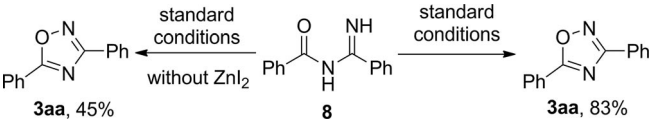

Scheme 3. Synthesis of 1,2,4-oxadizoles from diverse amides under standard conditions.

complex **4** by coordinating with substrates. The nucleophilic addition of the amide to the benzonitrile, activated by a Lewis acidic $Cu^{II}$ species, affords $Cu^{II}$ complex **5**.[14e] The removal of the proton with a base followed by the rearrangement affords $Cu^{II}$ chelate complex **6**. Then, $Cu^{III}$ complex **7** is formed by the disproportionation of $Cu^{II}$ with molecular oxygen, thus reoxidizing $Cu^{I}$ to $Cu^{II}$.[14a,14d] Finally, the reductive elimination affords the desired product and regenerates the catalytic cycle.

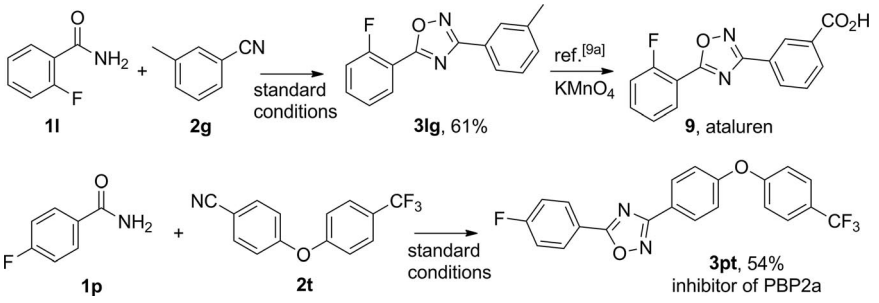



Scheme 4. Proposed reaction mechanism.

To support the proposed reaction mechanism, intermediate **8** was synthesized and subjected to standard reaction conditions; **3aa** was obtained in 83 % yield (Scheme 5). This clearly




Scheme 5. Mechanistic studies by using intermediate **8**.




Scheme 6. Syntheses of biologically active 1,2,4-oxadiazole derivatives.

indicates the involvement of intermediate **5** in the proposed catalytic cycle. When intermediate **8** was subjected to the optimized reaction conditions without $ZnI_2$, the yield of **3aa** dramatically decreased (45 %), indicating the probable role of $ZnI_2$ during the reductive elimination step or disproportionation of $Cu^{II}$; yet the role of $ZnI_2$ as a Lewis acid promoting the nucleophilic addition cannot be completely ruled out.

To highlight the synthetic utility of this Cu-catalyzed oxidative cyclization, biologically active 1,2,4-oxadiazole derivatives were synthesized (Scheme 6). The reaction of 2-fluorobenzamide (**1l**) with *m*-tolunitrile (**2g**) afforded **3lg** in 61 % yield; this can be converted into ataluren (**9**),[9a] a drug for the treatment of cystic fibrosis.[15] Recently, Chang and co-workers synthesized and studied the oxadiazole derivative **3pt**, a new class of non-β-lactam antibiotics that inhibits the penicillin-binding protein (PBP) 2a.[16] When 4-fluorobenzamide was treated with **2t** under optimized reaction conditions, product **3pt** was obtained in 54 % yield.

## Conclusions

A new method was developed for the synthesis of 1,2,4-oxadiazoles by a Cu-catalyzed reaction through a rare oxidative N–O bond formation, and $O_2$ was used as the sole oxidant, thus avoiding the synthesis of starting precursors or to use of strong oxidants, typically required in previous methods. The method also showed a broad substrate scope and a good tolerance for diverse functional groups. Considering the ready availability of stable starting precursors, inexpensive reagents, and the one-step synthesis, a convenient and highly modular 1,2,4-oxadiazole synthesis was developed.

## *Acknowledgments*

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**Keywords:** Copper · Heterocycles · 1,2,4-Oxadiazoles · Homogeneous catalysis · Cyclization

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