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Copper-Catalyzed One-Pot Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles from Arylacetic Acids and Hydrazides *via* Dual Oxidation

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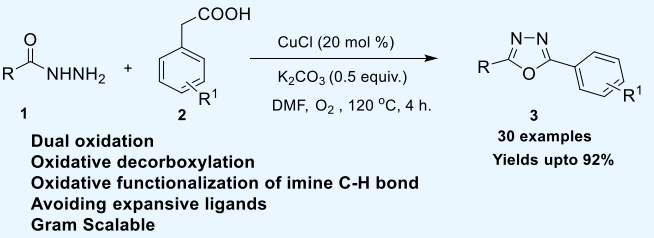
ABSTRACT: A simple and efficient protocol has been developed to access symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles from arylacetic acids and hydrazides *via* copper-catalyzed dual oxidation under an oxygen atmosphere. Oxidative decarboxylation of arylacetic acids and oxidative functionalization of the imine C−H bond are the key steps. This is the first example of the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles through dual oxidation in one-pot. Avoidance of the expensive ligand and high yield of the products are advantageous features of the developed method.



INTRODUCTION

1,3,4-Oxadiazole scaffolds exist ubiquitously in natural products, pharmaceuticals, polymers, and materials.[1] In particular, the compounds that are containing 2,5-disubstituted 1,3,4-oxadiazole motifs exhibit a broad spectrum of biological activities including antimicrobial, anticonvulsant, antidiabetic, antiproliferative, anti-inflammatory, antiallergic, anticancer, antimalarial, antiobesity, antiviral, antidepressant, antihypertensive, antileishmanial, insecticidal, herbicidal, analgesic, antioxidant, immunosuppressant, monoamine oxidase inhibitory, and urease inhibitory activities (Figure 1).[2] On the other hand, these scaffolds are being employed in the development of organic light-emitting diodes (OLEDS), which are utilized in full-color, flat-panel displays.[3] Moreover, some of the conjugated oxadiazoles act as multiphoton absorbing systems.[4]

Owing to their importance in various fields, the exploration of methodologies for the synthesis of 1,3,4-oxadiazoles is being continued by organic chemists.[5] Traditional methods used for the construction of 1,3,4-oxadiazole framework involve the N-acylation of acyl hydrazides or their precursors with either carboxylic acids or their activated derivatives such as acid chlorides,[6] esters,[7] and anhydrides[8] followed by intramolecular cyclodehydration. Alternatively, these compounds can also be constructed by oxidative cyclization of N-acyl hydrazones in the presence of various oxidizing agents such as hypervalent iodines,[9a−e] chloramine T,[9f] ceric ammonium nitrate,[9g] $FeCl_3$,[9h] tetravalent lead reagents,[9i,j] Br_2,[9k] $KMnO_4$ under microwave condition,[9l] Fe(III)/TEMPO,[10] $Cu(OTf)_2$,[11] I_2/K_2CO_3,[12] and isobutyl aldehyde/O_2/PhI[13] (Scheme 1a). These methods are, however, often limited in the requirement of harsh reaction conditions such as the involvement of strong acids in combination with high temperature and utilization of toxic oxidants. Some of these drawbacks have been overcome by the recent developments in metal-catalyzed cross-coupling reactions *via* C−H activation that allow the construction of target heterocyclic compounds under relatively milder conditions. For example, 2,5-disubstituted 1,3,4-oxadiazoles have been synthesized by copper-catalyzed coupling between 1,3,4-oxadiazole with aryl or alkenyl halides (Scheme 1b).[14] Subsequently, He et al. disclosed a metal- and base-free reaction to obtain 2,5-diaryl 1,3,4-oxadiazoles from aryl tetrazoles by N-acylation with aldehydes followed by thermal rearrangement (Scheme 1c).[15] Recently, Li Liu et al. developed a novel approach to assemble 2,5-disubstituted 1,3,4-oxadiazoles from α-oxocarboxylic acids *via* a decarboxylative cyclization by photoredox catalysis using hypervalent (III) iodine as a catalyst (Scheme 1d).[16] Although these methods are impressive, still there are some drawbacks such as the presynthesis of starting materials, long reaction times, expensive ligands, reagents, and low yields. Therefore, facile and simple approaches for accessing an array of 2,5-disubstituted 1,3,4-oxadiazoles from easily available starting materials are highly desirable.

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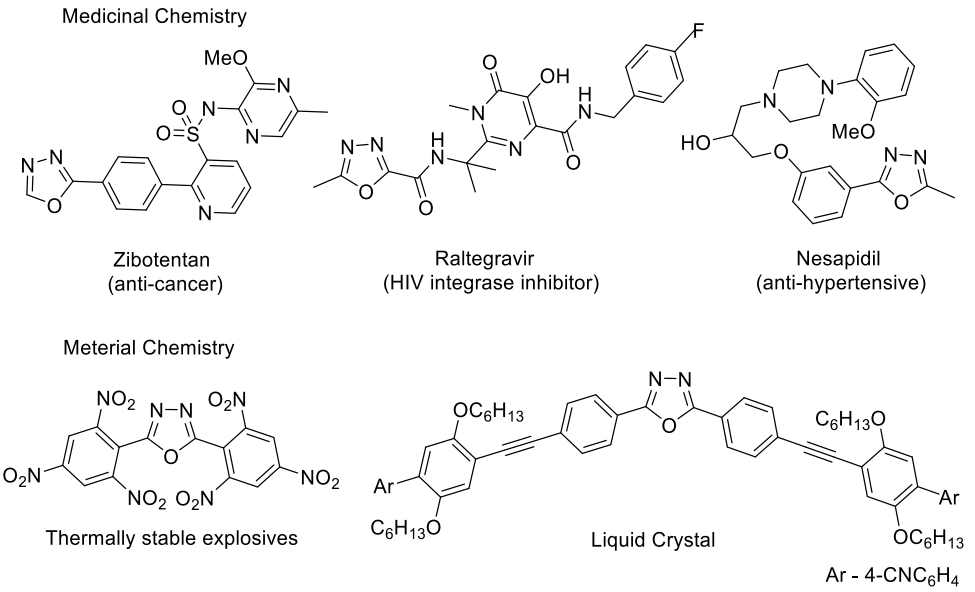
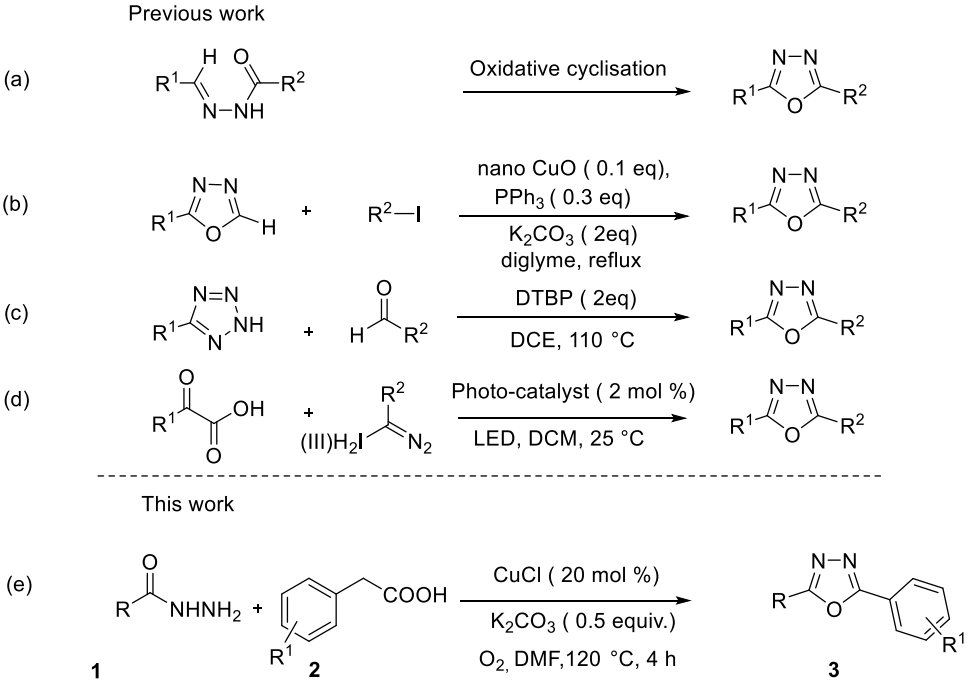


Figure 1. Active compounds containing 1,3,4-oxadiazole scaffolds.

Scheme 1. Recent Progress in the Synthesis of 1,3,4-Oxadiazoles



Recently, transition-metal-catalyzed decarboxylative coupling of carboxylic acids, in particular, C(sp^3) arylacetic acids, has been employed as an effective tool in organic synthesis to forge various heterocyclic compounds[17] because arylacetic acids are highly stable compared to aldehydes and release a nontoxic byproduct (CO_2). Moreover, arylacetic acids are cheap, commercially available, nontoxic, and easy to handle, thus making it advantageous to be used as an ideal starting material. Recently, our group reported the synthesis of 2,4,6 triphenyl pyridines using oxime acetates and arylacetic acids via oxidative decarboxylative cyclization.[18] As a continuous study on this field, we visualized that 2,5-disubstituted 1,3,4-oxadiazoles could be synthesized from aryl hydrazides and arylacetic acids *via* dual oxidation using oxygen as the sole terminal oxidant. This reaction involves copper-catalyzed oxidative decarboxylation coupling followed by the oxidative functionalization of the imine C−H bond (Scheme 1e). To the best of our knowledge, this protocol has not been reported to date.

RESULTS AND DISCUSSION

Initially, we began our investigation by employing the reaction of hydrazide **1a** (0.7 mmol) and arylacetic acid **2a** (0.7 mmol) with the catalytic system of CuI (20 mol %) and K_2CO_3 (0.3 mmol, 0.5 equiv) in dimethylformamide (DMF) (2.0 mL) at 120 °C for 4 h under an oxygen atmosphere. To our delight, the target product **3a** was obtained with a 74% yield (Table 1, entry 1). To improve the yield of **3a**, we examined different

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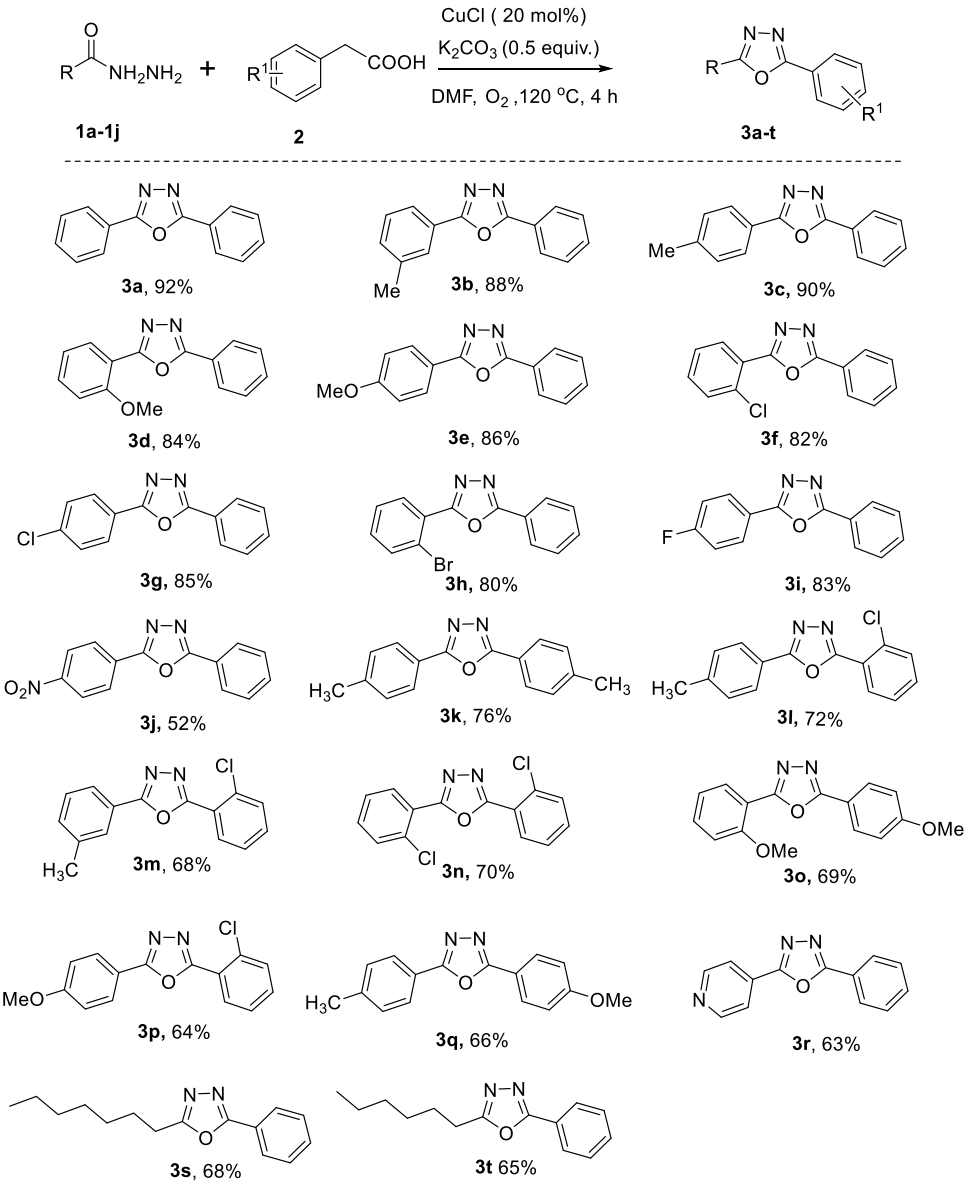
Scheme 2. Scope of Hydrazides and Arylacetic Acids[a,b]



[a]Reaction conditions: **1a** (0.7 mmol), **2a** (0.7 mmol), CuCl (20 mol%), K_2CO_3 (0.5 equiv), and DMF (2.0 mL), 120 °C, under an oxygen atmosphere, 4 h. [b]Isolated yields.

copper catalysts such as $CuCl_2$, CuBr, $Cu(OAc)_2$, and CuCl (Table 1, entries 2−4) and found that CuCl was the best choice and provided a 92% yield (Table 1, entry 5). It was also observed that no desired product could be obtained in the absence of copper catalysts (Table 1, entry 6). Subsequently, various oxidants such as DTBP, PIDA, and TBHP were tested; these results illustrated that oxygen displayed the best ability in the transformation (Table 1, entries 7−9). We also performed the reaction in air without any additional oxidant, but only 22% of **3a** was observed (Table 1, entry 10). Further, other bases including $NaHCO_3$, Cs_2CO_3, and Na_2CO_3 were tested, and K_2CO_3 was proven to be the most effective base (Table 1, entries 11−13). This investigation also revealed that the base was very crucial for this reaction and no desired product was observed in the absence of base (Table 1, entry 14). The screening of different solvents such as DMSO, dioxane, and toluene indicated that DMF was a suitable solvent (Table 1, entries 15−17). The yield of **3a** was decreased when either the increase of the catalyst was from 20 to 30 mol % or the decrease of the catalyst was to 10 mol % (Table 1, entries 17−19). In addition, the parallel reaction conducted at 80 °C gave a lower yield of **3a**, and increasing the reaction temperature could not enhance the yield either (Table 1, entries 20 and 21).

With the optimal reaction conditions in hand, we then explored the scope of various substituted hydrazides and arylacetic acids to generate the desired products. In general, substituted aryl hydrazides reacted with arylacetic acid **2a** and delivered the respective products in moderate to good yields (Scheme 2). Simple hydrazide **1a** reacted with arylacetic acid **2a** and gave the desired product **3a** in a 92% yield. Hydrazides with electron-donating groups such as 3-CH_3, 4-CH_3, 3-OCH_3, and 4-OCH_3 groups on the aromatic ring could convert efficiently and give good yields (Scheme 2). Hydrazides having electron-withdrawing groups such as 2-Cl, 4-Cl, 2-Br, and 4-F on the aromatic ring also took part in the

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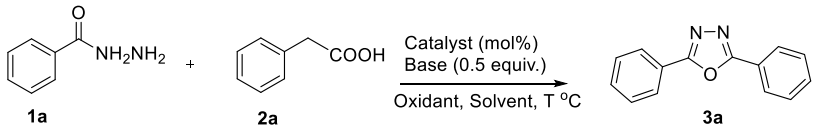
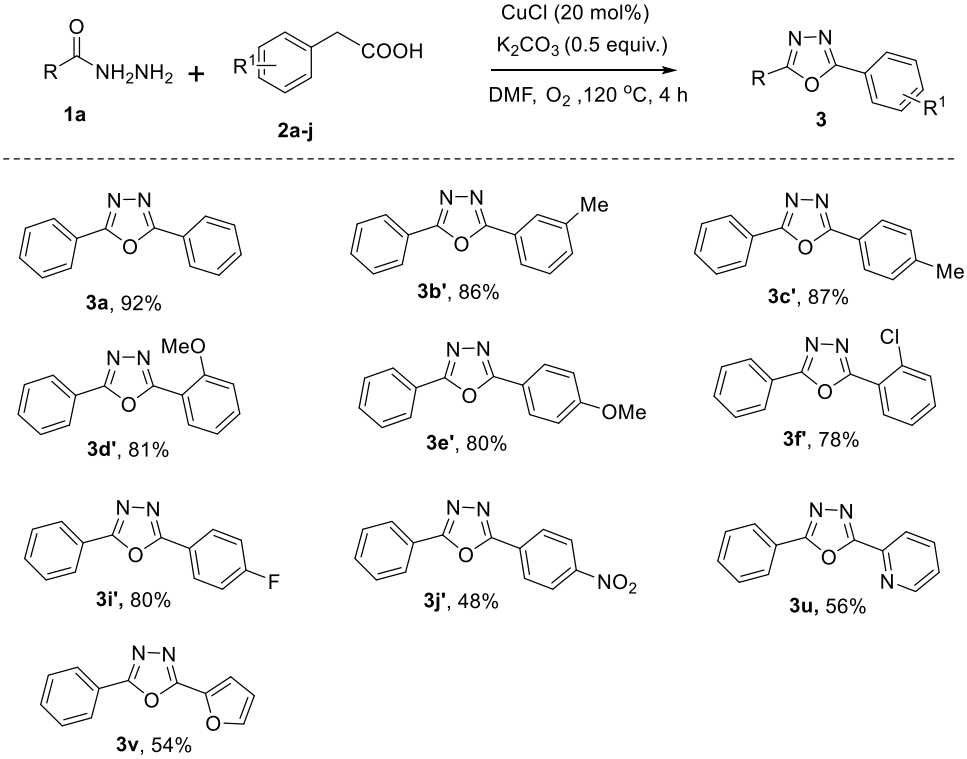
Table 1. Optimization of Reaction Conditions[a]



s. no	catalyst (mol %)	oxidant	base	solvent	T (°C)	yield[b] (%)
1	CuI (20)	O_2	K_2CO_3	DMF	120	74
2	$CuCl_2$(20)	O_2	K_2CO_3	DMF	120	82
3	CuBr (20)	O_2	K_2CO_3	DMF	120	80
4	$Cu(OAc)_2$ (20)	O_2	K_2CO_3	DMF	120	84
5	CuCl (20)	O_2	K_2CO_3	DMF	120	92
6		O_2	K_2CO_3	DMF	120	NR
7	CuCl (20)	DTBP	K_2CO_3	DMF	120	23
8	CuCl (20)	PIDA	K_2CO_3	DMF	120	45
9	CuCl (20)	TBHP	K_2CO_3	DMF	120	34
10	CuCl (20)	Air	K_2CO_3	DMF	120	22
11	CuCl (20)	O_2	$NaHCO_3$	DMF	120	82
12	CuCl (20)	O_2	Cs_2CO_3	DMF	120	36
13	CuCl (20)	O_2	Na_2CO_3	DMF	120	43
14	CuCl (20)	O_2		DMF	120	NR
15	CuCl (20)	O_2	K_2CO_3	DMSO	120	85
16	CuCl (20)	O_2	K_2CO_3	Dioxane	120	76
17	CuCl (20)	O_2	K_2CO_3	Toluene	120	62
18	CuCl (30)	O_2	K_2CO_3	DMF	120	80
19	CuCl (10)	O_2	K_2CO_3	DMF	120	65
20	CuCl (20)	O_2	K_2CO_3	DMF	80	22
21	CuCl (20)	O_2	K_2CO_3	DMF	150	44

[a]Reaction conditions: **1a** (0.7 mmol), **2a** (0.7 mmol), catalyst (20 mol%), base (0.5 equiv), and solvent (2.0 mL), 120 °C, under an oxygen atmosphere, 4 h. [b]Isolated yields.

Scheme 3. Scope of Arylacetic Acids[a,b]



[a]Reaction conditions: **1a** (0.7 mmol), **2a** (0.7 mmol), CuCl (20 mol %), K_2CO_3 (0.5 equiv), and DMF (2.0 mL), 120 °C, under an oxygen atmosphere, 4 h. [b]Isolated yields.

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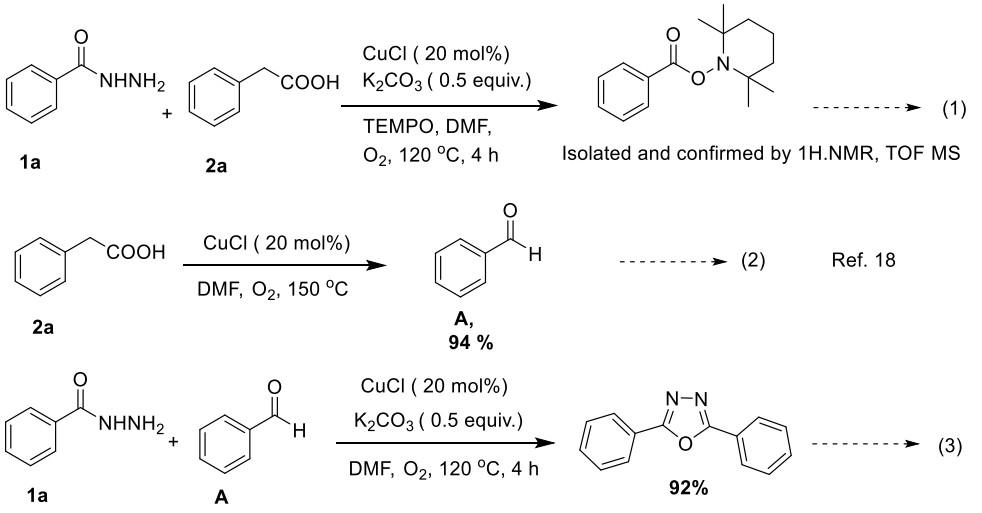
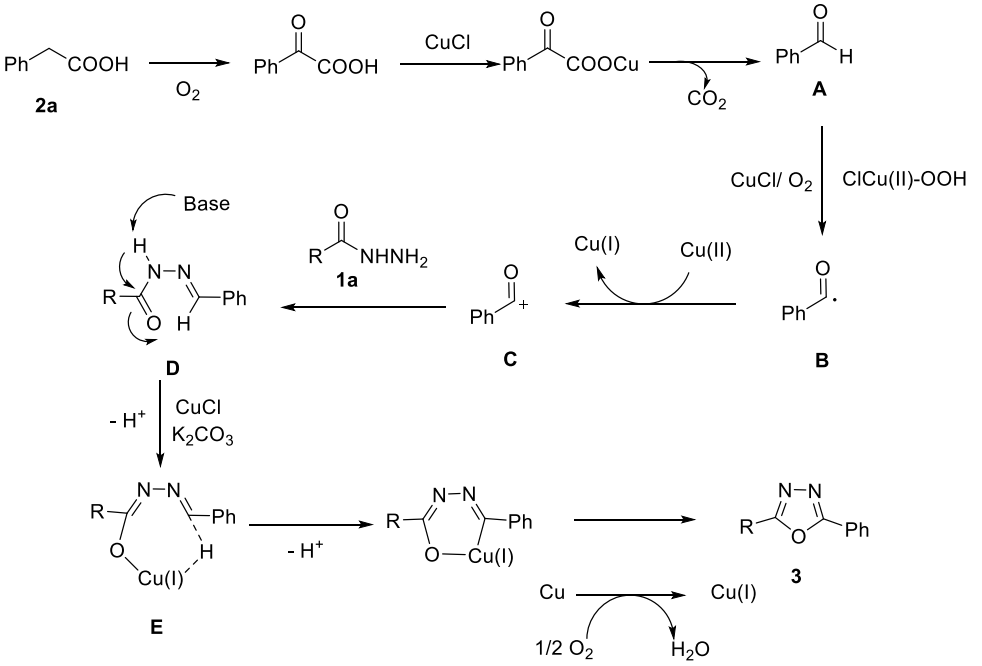
Scheme 4. Control Experiments



Scheme 5. Plausible Mechanism



reaction with arylacetic acid and afforded good yields. It is noteworthy that nitro-substituted hydrazide also survived and gave the respective 1,3,4-oxadiazole (**3j**) in a 52% yield.

Moreover, hydrazide with a heterocyclic substituent was compatible with this conversion and gave a 63% yield (**3r**). To our delight, hydrazides with alkyl substituents were also well tolerated and afforded good yields (**3s** and **3t**). To prove the practicability of this protocol, the reaction was scaled up to the gram scale. The coupling of **1a** (1.0 g, 7.3 mmol) with **2a** (1.0 g, 7.3 mmol) on the gram scale proceeded smoothly under the optimized conditions to obtain the desired product **3a** in an 82% yield.

Next, various arylacetic acids under the optimized reaction conditions were examined and the results are shown in Scheme 3. Arylacetic acids bearing either electron-donating 3-CH_3, 4-CH_3, 3-OCH_3, and 4-OCH_3 (**2b**, **2c**, **2d**, **2e**) or electron-withdrawing groups 2-Cl and 4-F (**2f** and **2i**) on the aromatic ring were able to undergo this transformation smoothly to get the intended 2,5-disubstituted 1,3,4-oxadiazoles in moderate to good yields (Scheme 3). To our delight, 4-nitroarylacetic acid was also tolerated for this reaction and gave a 48% yield of the corresponding 1,3,4-oxadiazole (**3j′**). Notably, heteroarylacetic acids were also compatible in this reaction and gave the desired products in good yields (**3v, 3w**).

To gain insight into the mechanism of this protocol, several control experiments have been performed (Scheme 4). Since the reaction involves oxygen, radical trapping experiments were conducted with arylacetic acid under optimized conditions. During these experiments, we observed that the reaction was obviously inhibited in the presence of butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). The results showed that the reaction presumably underwent a radical pathway (Scheme 4, eq 1). In our previous work, we identified that arylacetic acids can be converted into aldehydes via oxidative decarboxylation in the

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presence of a copper catalyst under an oxygen atmosphere (Scheme 4, eq 2).[18] As shown in eq 3, when we performed the reaction of benzaldehyde with aryl hydrazide under standard conditions, the desirable product **3** was obtained in a 92% yield. It strongly revealed that benzaldehyde is formed as an intermediate in the reaction.

Based on the above results and previous studies,[18−20] the plausible mechanism of the present reaction is illustrated in Scheme 5. In the first step, arylacetic acid gives araldehyde (**A**) *via* oxidative decarboxylation in the presence of a copper catalyst under an oxygen atmosphere. The araldehyde (**A**) further converts into acyl radical (**B**) followed by acyl cation (**C**) in the presence of copper and oxygen. Then, a nucleophilic reaction of hydrazide (**1**) to **C** forms **D**. Coordination of **D** with Cu(I) ion provides **E** in the presence of a base. Finally, product **3** affords by the intramolecular nucleophilic attack of an oxygen atom to the double bond followed by oxidation.

In conclusion, we have developed a simple and efficient protocol for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from hydrazides and arylacetic acids *via* copper-catalyzed dual oxidation in DMF at 120 °C for 4 h under an oxygen atmosphere. This protocol involves the oxidative decarboxylation of arylacetic acids followed by oxidative functionalization of the imine C−H bond. In this reaction, various hydrazides and arylacetic acids are well tolerated and provided the 2,5-disubstituted 1,3,4-oxadiazoles in good yields. Usage of the easily available starting substrates, operational simplicity, and avoiding the use of expensive ligands are the advantages of this methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01586.

General experimental procedure; ^{1}H NMR and ^{13}C NMR spectral data; and copies of ^{1}H NMR, ^{13}C NMR, and TOF MS spectra for all of the products (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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