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

Chinnari Lekkala, Varaprasad Bodala, Kumari Yettula, Bharat Kumar Karasala, Rajitha Lakshmi Podugu, and Siddaiah Vidavalur*

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. 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, anti-inflammatory, antiallergic, anticancer, antimalarial, antiviral, antiproliferative, antidepressant, antihypertensive, antibacterial, insecticidal, herbicidal, analgesic, antioxidant, immunosuppressant, monooxime oxidase inhibitory, and urease inhibitory activities (Figure 1). 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. Moreover, some of the conjugated oxadiazoles act as multiphoton absorbing systems.

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. 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, esters, and anhydrides 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, chloramine T, ceric ammonium nitrate, tetravalent lead reagents, Br2, KMnO4 under microwave condition, Fe(III)/TEMPO, Cu(OTf)2, I2/K2CO3 and isobutyl aldehyde/O2/PhI (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). Subsequently, He et al. disclosed a metal- and base-free reaction to obtain 2,5-diallyl 1,3,4-oxadiazoles from aryl tetrazoles by N-acylation with aldehydes followed by thermal rearrangement (Scheme 1c). Recently, Li Liu et al. developed a novel approach to assemble 2,5-disubstituted 1,3,4-oxadiazoles from α-carboxylic acids via a decarboxylative cyclization by photoredox catalysis using hypervalent (III) iodine as a catalyst (Scheme 1d). 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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Recently, transition-metal-catalyzed decarboxylative coupling of carboxylic acids, in particular, C(sp³) arylacetic acids, has been employed as an effective tool in organic synthesis to forge various heterocyclic compounds because arylacetic acids are highly stable compared to aldehydes and release a nontoxic byproduct (CO₂). 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. 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 K₂CO₃ (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...
copper catalysts such as CuCl₂, 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 NaHCO₃, Cs₂CO₃, and Na₂CO₃ were tested, and K₂CO₃ 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-CH₃, 4-CH₃, 3-OCH₃, and 4-OCH₃ 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

Scheme 2. Scope of Hydrazides and Arylacetic Acids

Relevant conditions: 1a (0.7 mmol), 2a (0.7 mmol), CuCl (20 mol%), K₂CO₃ (0.5 equiv), and DMF (2.0 mL), 120 °C, under an oxygen atmosphere, 4 h. *Isolated yields.
### Table 1. Optimization of Reaction Conditions

| s. no | catalyst (mol %) | oxidant | base   | solvent | T (°C) | yield (%) |
|-------|------------------|---------|--------|---------|--------|-----------|
| 1     | CuI (20)         | O₂      | K₂CO₃  | DMF     | 120    | 74        |
| 2     | CuCl₂ (20)       | O₂      | K₂CO₃  | DMF     | 120    | 82        |
| 3     | CuBr (20)        | O₂      | K₂CO₃  | DMF     | 120    | 80        |
| 4     | Cu(OAc)₂ (20)    | O₂      | K₂CO₃  | DMF     | 120    | 84        |
| 5     | CuCl (20)        | O₂      | K₂CO₃  | DMF     | 120    | 92        |
| 6     | O₂               | K₂CO₃  | DMF    | 120     | NR     |           |
| 7     | CuCl (20)        | DTBP    | K₂CO₃  | DMF     | 120    | 23        |
| 8     | CuCl (20)        | PIDA    | K₂CO₃  | DMF     | 120    | 45        |
| 9     | CuCl (20)        | TBHP    | K₂CO₃  | DMF     | 120    | 34        |
| 10    | CuCl (20)        | Air     | K₂CO₃  | DMF     | 120    | 32        |
| 11    | CuCl (20)        | O₂      | NaHCO₃ | DMF     | 120    | 82        |
| 12    | CuCl (20)        | O₂      | Cs₂CO₃ | DMF     | 120    | 36        |
| 13    | CuCl (20)        | O₂      | Na₂CO₃ | DMF     | 120    | 43        |
| 14    | CuCl (20)        | O₂      |        | DMF     | 120    | NR        |
| 15    | CuCl (20)        | O₂      | K₂CO₃  | DMSO    | 120    | 85        |
| 16    | CuCl (20)        | O₂      | K₂CO₃  | Dioxane | 120    | 76        |
| 17    | CuCl (20)        | O₂      |        | Toluene | 120    | 62        |
| 18    | CuCl (30)        | O₂      | K₂CO₃  | DMF     | 120    | 80        |
| 19    | CuCl (10)        | O₂      | K₂CO₃  | DMF     | 120    | 65        |
| 20    | CuCl (20)        | O₂      | K₂CO₃  | DMF     | 80     | 22        |
| 21    | CuCl (20)        | O₂      | K₂CO₃  | 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

**Scheme 3. Scope of Arylacetic Acids**

`\[ R\text{-NH}_2\text{NH}_2 + R'\text{-COOH} \rightarrow \text{CuCl (20 mol %), K}_2\text{CO}_3 (0.5 equiv), \text{DMF, O}_2, 120 \, {\circ}C, 4 \, h \]`
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-CH₃, 4-CH₃, 3-OCH₃, and 4-OCH₃ (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
presence of a copper catalyst under an oxygen atmosphere (Scheme 4, eq 2). As shown in eq 3, when we performed the reaction of benzaldehyde with acyl hydrazide under standard conditions, the desirable product 3 was obtained in a 92% yield. It strongly revealed that benzaldehyde forms an intermediate in the reaction.

Based on the above results and previous studies, 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=C 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.

AUTHOR INFORMATION

Corresponding Author
Siddaiah Vidavalur — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India; orcid.org/0000-0002-7190-7932; Email: sidduchem@gmail.com

Authors
Chinnari Lekkala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Varaprasad Bodala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Kumari Yettula — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Bharat Kumar Karasala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Rajitha Lakshmi Podugu — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acsomega.2c01586

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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AUTHOR INFORMATION

Corresponding Author
Siddaiah Vidavalur — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India; orcid.org/0000-0002-7190-7932; Email: sidduchem@gmail.com

Authors
Chinnari Lekkala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Varaprasad Bodala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Kumari Yettula — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Bharat Kumar Karasala — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India
Rajitha Lakshmi Podugu — Department of Organic Chemistry & FDW, Andhra University, Visakhapatnam 530003, India

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acsomega.2c01586
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