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Cu(II) Catalyzed Imine C−H Functionalization Leading to Synthesis of 2,5-Substituted 1,3,4-Oxadiazoles‡

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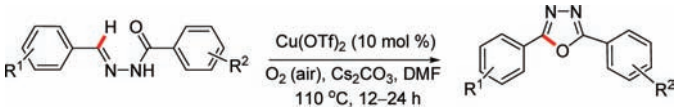
ABSTRACT



A direct access to symmetrical and unsymmetrical 2,5-disubstituted [1,3,4]-oxadiazoles has been accomplished through an imine C−H functionalization of *N*-arylidenearoylhydrazide using a catalytic quantity of $Cu(OTf)_2$. This is the first example of amidic oxygen functioning as a nucleophile in a Cu-catalyzed oxidative coupling of an imine C−H bond. These reactions can be performed in air atmosphere and moisture making it exceptionally practical for application in organic synthesis.

The π-conjugated heterocycles comprise an important structure class as they find applications in the field of material science and pharmaceutical chemistry. Among them, the 2,5-disubstituted-1,3,4-oxadiazole motifs are of considerable importance primarily due to their unique optoelectronic properties that are being exploited in the development of organic light emitting diodes (OLEDS) and utilized in energy efficient, full-color, flat-panel displays.[1] Certain suitably conjugated oxadiazoles are also

‡ Dedicated to Professor Y. D. Vankar on the occasion of his 60th birthday.

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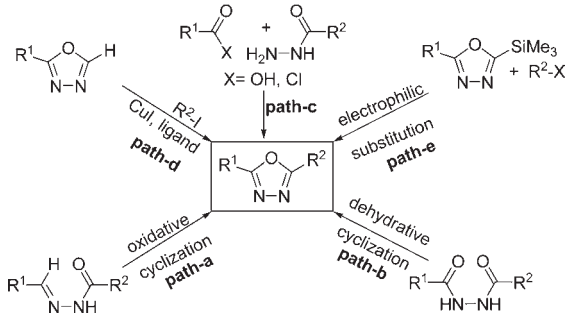
known to perform as multiphoton absorbing systems.[1b] Besides their electronic properties, these scaffolds encompass a wide range of biological properties[2−4] that make them particularly attractive in the field of organic synthesis.

To date, the literature reports the following methods for their preparation (Scheme 1): (a) oxidative cyclization of *N*-acylhydrazones with various oxidizing agents such as hypervalent iodines,[5a−e] chloramine T,[5f] ceric ammonium nitrate,[5g] $FeCl_3$,[5h] tetravalent lead reagents,[5i,j] Br_2,[5k] $KMnO_4$ under microwave condition,[5l] or HgO/I_2;[5m] (b) cyclodehydration of 1,2-diacylhydrazines with reagents such as thionyl chloride, PPA, phosphorus oxychloride, or sulfuric acid;[6] (c) direct reaction of carboxylic acids or acyl chlorides with acid hydrazides or hydrazines;[7] (d) C−H activation/Cu mediated arylation of preformed 2-substituted 1,3,4-oxadiazole;[8] and (e) electrophilic substitution of 2-substituted-5-trimethylsilyl-1,3,4-oxadiazole toward various electrophiles.[9]

Scheme 1. Various Methods of Preparation of 2,5-Substituted 1,3,4-Oxadiazoles



Yet, the disadvantages associated with these methodologies, owing to the use of expensive, hazardous materials or cumbersome multistepped processes, bind them to a limited synthetic scope. Although the Cu mediated direct arylation/C−H activation path (route d)[8] seems advantageous, it uses preformed 2-substituted 1,3,4-oxadiazoles as the precursors which are difficult to prepare.

Of late the transition metal catalyzed direct functionalization of otherwise unreactive C−H has attracted much attention from an atom-economic point of view, for an overall streamlining of sustainable synthesis. To add to it, the great advances made toward the transition metal catalyzed activation have led to the organic C−H bonds as being no longer inert and able to be viewed as dormant synthetic equivalents of many reactive functional groups. Development of various catalytic processes to activate the ubiquitously available bond has emerged as the most effective tool, due to operational simplicity and avoidance of the arduous substrate preactivation steps, thereby improving the overall efficiency of a targeted synthesis.[10] In this context, however, the vast majority of the focus has been directed toward the transition metal catalyzed functionalization of the sp^2 C−H bonds of arenes and heteroarenes.[10] In contrast, analogous addition across an imine C−N through functionalization of a C(sp^2)−H bond is relatively rare. Some examples of imine C(sp^2)−H functionalization are, a Pd catalyzed addition of 2-methyl aza-arenes to imines,[11a] benzyl nitriles with sulfonylimines,[11b,c] rhodium catalyzed oxidative coupling of aromatic imines with alkynes,[11d] and 2-pyridyl.[11e] Moreover, compared to late transition metal catalysts, first row transition metal catalysts, especially with Cu, have been less explored toward C−H functionalization.[12] Barring one example of C−C bond formation involving C(sp^2)−H of imine[13] there is no report on C−O bond formation. Mostly, substrates possessing imine functionality have been observed to undergo skeletal rearrangement[14a−c] or

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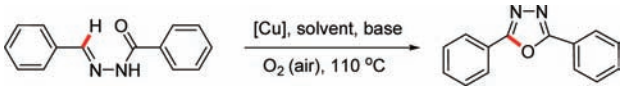
utilize the proximate effect of coordination to the metal center which serves as a directing group toward sp^2 and sp^3 C−H bond activation.[14d−f] There are few examples of amidic oxygen functioning as a nucleophile in catalytic oxidative coupling reactions using Cu catalyst[15] but no precedence of it in catalytic oxidative coupling reactions of imine C−H bonds.

Inspired by the recent development of C−H bond functionalization particularly using Cu catalyzed direct arylation of various heterocycles using aryl halides or aryl iodonium(III) salts[16] and intramolecular C−O bond formation via a C−H bond cleavage,[15] we anticipate that a Cu-based strategy could be applied to construct 2,5-disubstituted 1,3,4-oxadiazole from *N*-aryl-*N*-arylidinehydrazines. Thus in an attempt to obliterate the limitations of the earlier methods, herein, we report the development of a straightforward and versatile protocol for the Cu(II) catalyzed oxidative C−H bond functionalization/C−O bond formation of imines from *N*-arylidenearoylhydrazide derivatives to afford various 2,5-disubstituted-1,3,4-oxadiazoles. This method features the use of $Cu(OTf)_2$ that successfully performs the C−H functionalization followed by an intramolecular C−O cross-coupling to afford cyclized products from readily available starting materials.

Table 1. Screening of Reaction Conditions

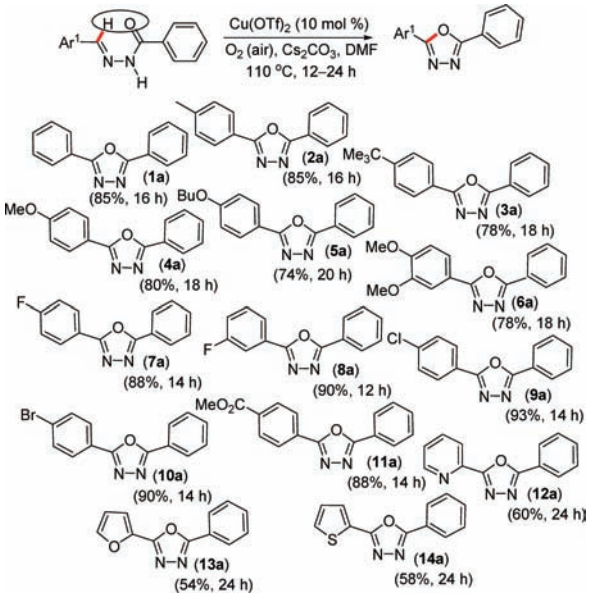


catalyst	solvent	time/h	base	yield (%)[a,b]
10% $Cu(OTf)_2$	DMSO	36	Cs_2CO_3	20
10% $Cu(OTf)_2$	Toluene	36	Cs_2CO_3	12
10% $Cu(OTf)_2$	Dioxane	36	Cs_2CO_3	30
10% $Cu(OTf)_2$	CH_3CN	36	Cs_2CO_3	10
10% $Cu(OTf)_2$	DMF	16	K_2CO_3	63
10% $Cu(OTf)_2$	DMF	16	Cs_2CO_3	85
10% $CuSO_4$	DMF	16	Cs_2CO_3	55
10% $Cu(OAc)_2$	DMF	16	Cs_2CO_3	40
10% CuI	DMF	16	Cs_2CO_3	8
10% CuBr	DMF	16	Cs_2CO_3	25
10% $CuCl_2$	DMF	16	Cs_2CO_3	65

[a] Reactions were carried out in an air atmosphere. [b] Isolated yield.

To develop this idea, substrate *N*-benzylidenebenzohydrazide (**1**) was selected for the cyclization reaction. Variations in the nature of the base, solvents, and reaction temperature were explored to arrive at the best possible yield (Table 1). After a series of experimentation the product (**1a**) could be obtained in 85% isolated yield when performed in the presence of $Cu(OTf)_2$ (10 mol %), Cs_2CO_3 as the base, at 110 °C in DMF under an air atmosphere (O_2 as the terminal oxidant). Under all other conditions substantial decomposition, multitudes of side products, or poor yields were obtained. No product was obtained in the absence of either catalyst or base which suggests that a metal/base combination is required for the reaction to occur.

Scheme 2. One-Pot Synthesis of 2,5-Substituted [1,3,4]-Oxadiazoles[a]



[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

With these results in hand, we sought to examine the scope and generality of the method. As the results shown in Scheme 1 attest, this methodology is compatible with a variety of electron-donating and -withdrawing groups. *N*-Arylidenearoylhydrazides derived from arylaldehydes possessing electron-donating groups such as −Me, −CMe_3, −OMe, −OBu, *di*-OMe all gave substituted 1,3,4-oxa ziazoles **2a**, **3a**, **4a**, **5a**, and **6a** in good yields (Scheme 2). Similarly substrates possessing electron-withdrawing groups such as −F, −Cl, −Br, $-CO_2Me$ underwent C−H functionalization to give 1,3,4-oxaziazoles **7a**, **8a**, **9a**, **10a**, and **11a** in excellent yields. As can be seen from Scheme 2, compared to substrates bearing electron-donating groups, electron-withdrawing substrates gave better yields. Benzohydrazide substrates originating from heterocyclic aldehydes such as pyridine, furan, and thiophene gave poorer yields of the products **12a**, **13a**, and **14a**. Benzohydrazide derived from aliphatic aldehydes are inert, and no C−H

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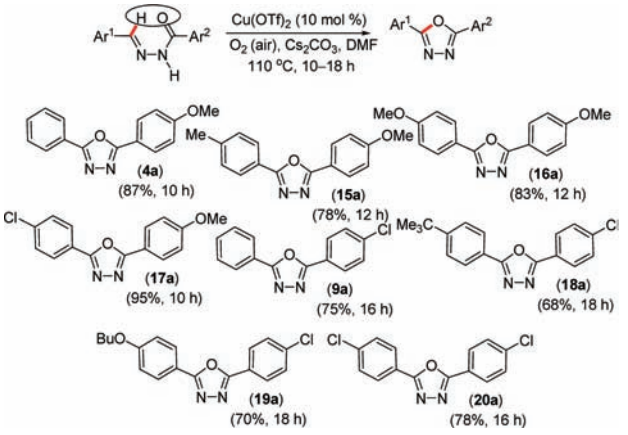
activation was observed. The substrate decomposed to aldehyde along with several other inseparable products. This is possibly because of the lesser acidic character of the imine C−H bonds, consistent with the reactivity trend observed for substituted aromatics.

Scheme 3. One-Pot Synthesis of 2,5-Substituted [1,3,4]-Oxadiazoles[a]



[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Besides *N*-arylidenearoylhydrazides, other hydrazides such as *N*′-arylidine-4-methoxybenzohydrazides reacted equally efficiently giving substituted oxadiazoles **4a**, **15a**, **16a**, and **17a** in good to excellent yields (Scheme 3). Similarly *N*′-arylidines-4-chlorobenzohydrazides underwent reaction smoothly to afford the corresponding unsymmetrical oxadiazoles **9a**, **18a**, **19a**, and **20a** (Scheme 3) but in a slightly moderate yields compared to the methoxy analogue. It may be worth mentioning here that a comparative study of the unsubstituted 4-OMe and 4-Cl substrates on the aroylhydrazide part suggest the reaction to be superior for the methoxy substrate (**4a**) (Scheme 3) followed by unsubstituted (**1a**) (Scheme 2) and chloro (**9a**) (Scheme 3) analogues in terms of yields and enhanced reaction rates. Also it was observed that electron-withdrawing substituents on the arylaldehydes improved the yields as in the case of **7a**−**11a** (Scheme 2) probably through an increment of the acidity of the imine proton thereby facilitating the metalation step.

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It is interesting to mention here that both *N*′-(4-methoxybenzylidene) benzylhydrazides (Scheme 2) and *N*′-benzylidene-4-methoxybenzohydrazide (Scheme 3) gave 2-(4-methoxyphenyl)-5-phenyl-1,3,5-oxadiazole (**4**). The yield was superior by the latter approach. Similarly, product **9a** (Schemes 2 and 3) can be obtained from either *N*′-4-chlorobenzylidene)benzohydrazide (Scheme 2) or *N*′-benzylidene-4-chlorobenzohydrazide (Scheme 3), but for this the former approach is better.

An insight into the mechanism through kinetic isotope studies suggests that the hydrogen abstraction step is not involved in the rate-limiting step (observed $K_H/K_D = 1$). Thus a plausible mechanism of this reaction keeping in view the above observations and related literature reports[10f,12l,13,16a] suggests the possible occurrence of agostic interaction (see Supporting Information (SI)) in which the first step involves concurrent deprotonation/metalation at the imine sp^2 C−H bond followed by the reductive elimination and C−O bond formation leading to the 2,5-disubstituted 1,3,4-oxadiazoles. However, in view of the earlier works[17] where analogous substrates had undergone heterocyclization, an alternative pathway cannot be ruled out. The resultant Schiff base forms a five-coordinated species with Cu(II) (see SI) which then undergoes oxidative dehydrogenation to afford a C−O bond leading to corresponding oxadiazoles. The catalytic cycle is retained by the oxidation of Cu(I) to Cu(II) under atmospheric oxygen. Further, a radical pathway cannot be overlooked for this transformation.[18]

In summary, we have for the first time developed a catalytic method for the synthesis of 2,5-disubstituted [1,3,4]-oxadiazoles via imine C−H functionalization of *N*-benzylidenebenzohydrazide. Low catalyst loading under ligand-free conditions, an inexpensive metal catalyst, performance under ordinary atmospheric conditions, and compatibility with a wide range of substrates make this method superior to all methods reported so far, which is of potential industrial significance. A detailed mechanistic study and further substrate scope are underway.

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Supporting Information Available. General information, experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.