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Room Temperature Direct Alkynylation of 1,3,4-Oxadiazoles with Alkynyl Bromides under Copper Catalysis

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The direct alkynylation reaction of 1,3,4-oxadiazoles with alkynyl bromides efficiently proceeds in the presence of a copper catalyst at room temperature to create the corresponding heteroaryl−alkynyl linkage in good yields. This direct coupling provides a rapid and convergent access to oxadiazole core π-conjugated systems.

Metal-mediated direct functionalization of C−H bonds has grown rapidly in modern synthetic chemistry because of its possibility for concise increase of molecular complexity from the ubiquitous C−H bonds.[1] In particular, the catalytic direct transformation of C−H to C−C bonds with organic halides or pseudohalides has had a significant impact on the conventional cross-coupling reactions with organometallic compounds[2] since the inevitable preactivation step, metalation, can be obviated in such methodologies. So far, a variety of catalyst systems have been explored, and the direct arylation,[3] alkenylation,[4] and alkynylation[5] of arenes and heteroarenes has become possible. However, these catalytic reactions generally suffered from the need for drastic conditions such as elevated temperature and longer reaction periods. Although current efforts by Sanford, Chen, Larrosa, and Waser overcome these problems and achieve the room temperature direct arylation[6] and alkynylation[7] under palladium or gold catalysis, the substrates are still limited to the highly electron-rich heterocycles such as indoles, pyrroles, and imidazolines. Moreover, some cases require use of the special hypervalent iodine reagents as aryl or alkynyl sources.[6a,7] Thus, further developments of catalyst systems are quite appealing for milder reaction conditions.

Recently, relatively common and less expensive copper salts and complexes have received much attention in the field of direct arylation[8] and alkenylation.[9] In addition to its economical benign effect, the unique catalytic activity of copper is also observed.[8e] Herein, we report an efficient example of the copper-catalyzed direct alkynylation of a useful heteroarene core having an electron-deficient nature.

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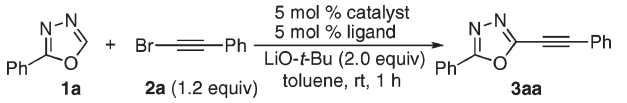
Thus, the copper-based process has been found to allow the direct functionalization of 1,3,4-oxadiazoles with alkynyl bromides even at room temperature.[10,11] As certain oxadiazole derivatives are known to act as ester and amide bioisosteres and π-conjugated systems involving the heterocycle unit may have good electron-transporting and hole-blocking abilities, this transformation also appears to be of interest in pharmaceutical and materials chemistry.[12]

During our recent studies on the nickel-catalyzed direct alkynylation of azoles, we found that a copper cocatalyst such as CuI dramatically accelerated the reaction.[5f] When we applied the cooperative catalyst system of $Ni(cod)_2$, dppbz (1,2-bis(diphenylphosphino)benzene), and CuI to the reaction of 2-phenyl-1,3,4-oxadiazole (**1a**) with (bromoethynyl)-benzene (**2a**) in the presence of LiO-*t*-Bu, the coupling product **3aa** was produced even at room temperature albeit with a low yield (Table 1, entry 1). However, to our surprise, some additional investigation revealed that the use of CuI alone gave the better result in this transformation (entry 2). Therefore, we turned our attention to the optimization studies based on copper catalysts. An increase in the amount of LiO-*t*-Bu to 4.0 equiv gave the positive effect on yield (entry 3). Then, various ligands were surveyed. Among the N-based ligands, 2,2′-bipyridine (bpy) and *N*,*N*′-dimethylethylenediamine (dmeda) did not affect reaction efficiency (entries 5 and 6), while 1,10-phenanthroline (phen) slightly improved the yield to 70% (entry 4). On the other hand, the phosphorus ligand, PPh_3, was detrimental to the direct coupling (entry 7). The choice of copper salts was also crucial for the reaction, as exemplified by entries 8 and 9: CuBr or $Cu(OTf)_2$ instead of CuI resulted in the large drop of the yield. Notably, either use of other bases such as NaO-*t*-Bu, KO-*t*-Bu, and Cs_2CO_3 or that of a polar solvent (e.g., DMF) instead of toluene sluggishly afforded **3aa** (not shown).

With the conditions employed for entry 4 of Table 1, we carried out the room temperature direct alkynylation of an array of oxadiazoles **1** with **2a** (Table 2). The oxadiazoles bearing electron-donating 4-methylphenyl and 4-methoxyphenyl groups as well as the simple phenyl one underwent alkynylation smoothly to furnish **3ba** and **3ca** in 67% and 64% yields, respectively (entries 1−3). Electron-withdrawing trifluoromethyl substituent did not interfere with the reaction (entry 4). Notably, the carbon−chloride moiety on the benzene ring was tolerant under the standard reaction conditions, which could enjoy further manipulation based on the palladium chemistry (entry 5). The bulky naphthalene motif also could be introduced to the oxadiazole−alkyne conjugation without any difficulties (entry 6). On the other hand, phenethyl-substituted oxadiazole **1g** showed moderate reactivity (entry 7).

Subsequently, we examined the substitution effect at the alkyne terminus of alkynyl bromide (Table 3). As shown in Table 2, the reactions with electron-rich substrates **2b** and **2c** and sterically demanding **2d** completed at room temperature to afford the corresponding alkynyloxadiazoles **3ab**, **3ac**, and **3ad** in good yields (entries 1−3). In contrast, the

TABLE 1. Optimization for Room Temperature Copper-Catalyzed Direct Alkynylation of 2-Phenyl-1,3,4-oxadiazole (1a) with (Bromoethynyl)-benzene (2a)[a]

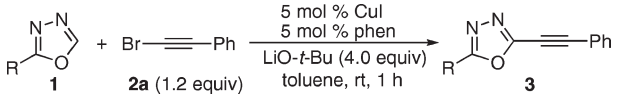


1a 2a (1.2 equiv) 3aa

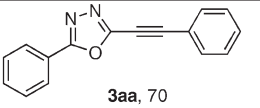
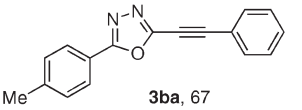
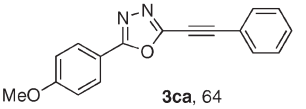
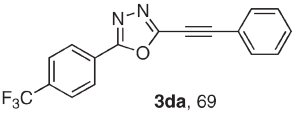
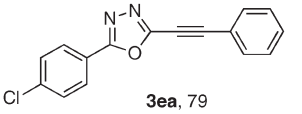
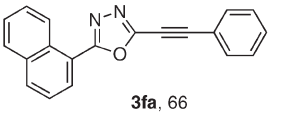
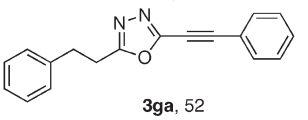
entry	catalyst	ligand	**3aa**, yield (%)[b]
1	$Ni(cod)_2$ and CuI	dppbz	− (19)
2	CuI	none	− (36)
3[c]	CuI	none	− (66)
4[c]	CuI	phen	70 (73)
5[c]	CuI	bpy	− (65)
6[c]	CuI	dmeda	− (67)
7[c]	CuI	PPh_3[d]	− (48)
8[c]	CuBr	phen	− (40)
9[c]	$Cu(OTf)_2$	phen	− (11)

[a]Reaction conditions: [**1a**]:[**2a**]:[LiO-*t*-Bu]:[catalyst]:[lgand] = 0.50:0.60:-1.0:0.025:0.025 (in mmol), in toluene (2.5 mL) under N_2 at room temperature for 1 h. [b]GC yield is in parentheses. [c]With 2.0 mmol of LiO-*t*-Bu. [d]With 0.050 mmol of PPh_3.

TABLE 2. Copper-Catalyzed Room Temperature Direct Alkynylation of Various 1,3,4-Oxadiazoles 1 with (Bromoethynyl)benzene (2a)[a]



1 2a (1.2 equiv) 3

entry	R in **1**	**3**, yield (%)
1	Ph (**1a**)	 **3aa**, 70
2	4-MeC_6H_4 (**1b**)	 **3ba**, 67
3	4-$MeOC_6H_4$ (**1c**)	 **3ca**, 64
4	4-$CF_3C_6H_4$ (**1d**)	 **3da**, 69
5	4-ClC_6H_4 (**1e**)	 **3ea**, 79
6	1-naphthyl (**1f**)	 **3fa**, 66
7	phenethyl (**1g**)	 **3ga**, 52

[a]Reaction conditions: [**1**]:[**2a**]:[LiO-*t*-Bu]:[CuI]:[phen] = 0.50:0.60:2.0:-0.025:0.025 (in mmol), in toluene (2.5 mL) under N_2 at room temperature for 1 h.

(10) Copper-catalyzed direct C−H arylation of 1,3,4-oxadiazoles with aryl iodides: ref 8i.

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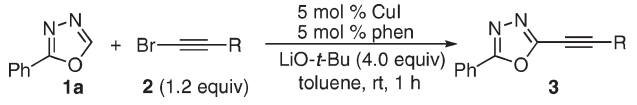
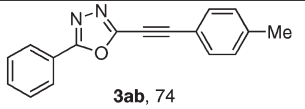
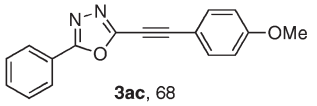
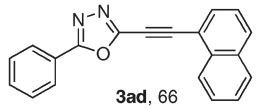
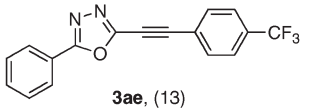
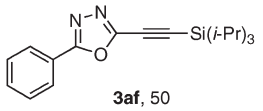
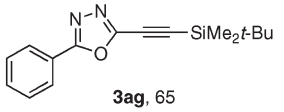
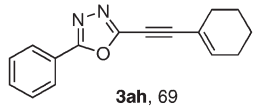
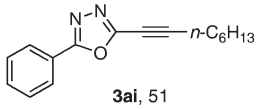
TABLE 3. Copper-Catalyzed Room Temperature Direct Alkynylation of 2-Phenyl-1,3,4-oxadiazole (1a) with Various Alkynyl Bromides 2[a]



entry	R in **2**	**3**, yield (%)[b]
1	4-MeC$_6$H$_4$ (**2b**)	 **3ab**, 74
2	4-MeOC$_6$H$_4$ (**2c**)	 **3ac**, 68
3[c,d]	1-naphthyl (**2d**)	 **3ad**, 66
4	4-CF$_3$C$_6$H$_4$ (**2e**)	 **3ae**, (13)
5[c,e]	*i*-Pr$_3$Si (**2f**)	 **3af**, 50
6[c,f]	*t*-BuMe$_2$Si (**2g**)	 **3ag**, 65
7[f]	1-cyclohexenyl (**2h**)	 **3ah**, 69
8[c,g]	*n*-C$_6$H$_{13}$ (**2i**)	 **3ai**, 51

[a]Reaction conditions: [**1a**]:[**2**]:[LiO-*t*-Bu]:[CuI]:[phen] = 0.50:0.60:2.0:-0.025:0.025 (in mmol), in toluene (2.5 mL) under N_2 at room temperature for 1 h. [b]GC yield is in parentheses. [c]With 1.0 mmol of **2**. [d]8 h. [e]24 h. [f]6 h. [g]2 h.

electron-deficient nature of trifluoromethyl group caused the rapid decomposition of alkynyl bromide under the reaction conditions, and the desired product was detected in only 13% GC yield (entry 4). However, the silyl-protected **2f** and **2g** coupled with **1a** in acceptable yields so as to complement the lack of generality with electron-poor substrates through the subsequent desilylation/Pd-catalyzed Sonogashira coupling sequence (entries 5 and 6). It is noteworthy that the conjugate enyne **2h** and aliphatic alkyne **2i** were also available for use (entries 7 and 8).[13]

Although the exact reaction mechanism for the copper catalysis is not clear at this stage, the most plausible course based on the literature information[8,9] may involve the sequential cupration of oxadiazole with the aid of LiO-*t*-Bu/σ-bond metathesis with alkynyl bromide. Nevertheless, the pathway including addition/elimination[14] or formation of Cu(III) species[15] at the step of the reaction with alkynyl bromide could not be completely excluded.

In summary, we have demonstrated that 2-aryl- and 2-alkyl-1,3,4-oxadiazoles efficiently undergo direct alkynylation upon treatment with readily accessible alkynyl bromides[16] in the presence of a copper catalyst. The reaction proceeds very smoothly even at room temperature.[17] Thus, the copper catalysis can compensate for the conventional Sonogashira coupling and provide a facile approach to the substituted oxadiazoles of interest in both biological and physical properties.

Experimental Section

Typical Procedure for Copper-Catalyzed Room Temperature Direct Alkynylation of 1,3,4-Oxadiazoles 1 with Alkynyl Bromides 2. The reaction of 2-phenyl-1,3,4-oxadiazole (**1a**) with (bromoethynyl)benzene (**2a**) is representative (Table 2, entry 1). CuI (4.8 mg, 0.025 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol), LiO-*t*-Bu (160 mg, 2.0 mmol), 2-phenyl-1,3,4-oxadiazole (**1a**, 73 mg, 0.50 mmol), (bromoethynyl)benzene (**2a**, 109 mg, 0.60 mmol), toluene (2.5 mL), and 1-methylnaphthalene (ca. 50 mg, internal standard) were placed in a 20 mL two-necked reaction flask. After the mixture was stirred at room temperature for 1 h, the consumption of **1a** was checked by GC analysis. The resulting mixture was then poured into water. The mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification (hexane:ethyl acetate = 95:5) gave 2-phenyl-5-(phenylethynyl)-1,3,4-oxadiazole (**3aa**, 86 mg, 0.35 mmol) in 70% yield. **3aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.44 (m, 2H), 7.46−7.59 (m, 4H), 7.65 (dd, J = 8.1, 1.4 Hz, 2H), 8.10 (dd, J = 8.1, 1.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 97.2, 119.8, 123.3, 127.1, 128.7, 129.1, 130.6, 132.1, 132.3, 150.7, 164.8; HRMS m/z (M^+) calcd for $C_{16}H_{10}N_2O$ 246.0793, found 246.0792 .

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Supporting Information Available: Characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Relatively difficult in the precedent direct sp^{2}C−H alkynylation. See ref 5.

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