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Copper-Mediated C–H Activation of 1,3,4-Oxadiazoles with 1,1-Dibromo-1-alkenes Using PEG-400 as a Solvent Medium: Distinct Approach for the Alkynylation of 1,3,4-Oxadiazoles[‡]

Gandolla Chinna Reddy,[a] Penagaluri Balasubramanyam,[a] N. Salvanna,[a] and Biswanath Das*[a]

Keywords: C-H activation / Heterocycles / Alkenes / Copper / Alkynes

The direct C–H alkynylation of 1,3,4-oxadiazoles with 1,1-dibromo-1-alkenes has been accomplished by using a combination of CuBr/LiO*t*Bu in PEG-400 (a green solvent) at 80 °C. The products were formed in high yields (73–86 %) in 2 h. No additional ligand or volatile solvent was required and the conversion was ecofriendly.

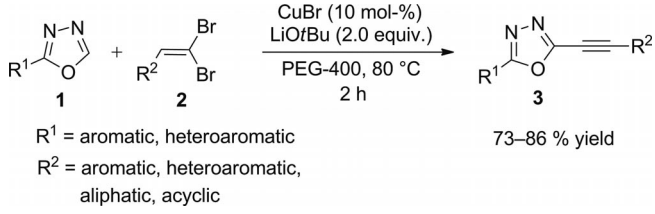
Introduction

Oxadiazole derivatives exhibit various important biological properties including antimicrobial and anticonvulsant activities.[1] They are also known to act as ester and amide bioisosters.[2] Certain oxadiazole derivatives have been applied in the development of organic electronics.[3] Consequently, the preparation of these compounds is of considerable importance in organic synthesis.

The metal-catalyzed direct transformation of C–H bonds into C–C bonds in arenes and heteroarenes has recently been identified as an important method for the preparation of oxadiazole derivatives.[4] Various metal catalysts such as palladium, ruthenium, and rhodium have been employed to carry out these transformations. However, copper catalysts have not been employed so much for this purpose, although their availability is greater and they are less expensive. Their activity is also prominent. Recently, these catalysts have been used for the C–H activation of several arenes and heteroarenes.[5] However, to the best of our knowledge, the copper-mediated C–H activation of 1,3,4-oxadiazoles by using *gem*-dibromoalkenes has not yet been reported, although direct alkynylations with alkynyl bromides[4h] or terminal alkynes[6] are known. Other copper-catalyzed transformations of oxadiazoles have also recently been discovered.[4b,7] The synthetic applications of *gem*-dibromoethenes as an alkynyl donor are also known.[8] Here we disclose an efficient copper-catalyzed conversion of 1,3,4-oxadiazoles by employing *gem*-dibromoalkenes for the preparation of alkynylated 1,3,4-oxadiazoles.

Results and Discussion

In continuation of our work[9] on the development of useful synthetic methodologies, we observed that 1,3,4-oxadiazoles, when treated with 1,1-dibromo-1-alkenes by using CuBr and LiO*t*Bu in polyethylene glycol (PEG-400) at 80 °C, afforded the corresponding 2-alkynyl derivatives in 2 h (Scheme 1).



Scheme 1. Copper-catalyzed C–C cross coupling.

Initially, 2-phenyl-1,3,4-oxadiazole (**1a**) was treated with 1-(2,2-dibromovinyl)-4-methylbenzene (**2a**) for the optimization of the reaction conditions. The reaction was carried out with various copper compounds and different bases and solvents (Table 1).

The conversion was found to be most effective when CuBr (10 mol-%) and LiO*t*Bu (2.0 equiv.) were used in PEG-400 at 80 °C. The yield was 82% after 2 h. When the temperature was raised to 120 °C, the yield remained unchanged, but at room temperature the yield was low (39%). The catalytic activities of $CuBr_2$, CuCl, and CuI were weak. Instead of PEG-400, when CH_2Cl_2 and CH_3CN were used

[‡] Studies on Novel Synthetic Methodologies, 231. Part 230: B. Das, N. Bhunia, M. Lingaiah, *Synthesis*, **2011**, 3471.

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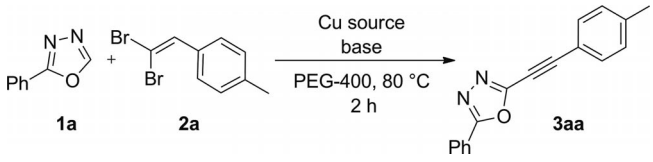
Table 1. Optimization of the C–H activation of 2-phenyl-1,3,4-oxadiazole with 1-(2,2-dibromovinyl)-4-methylbenzene by using PEG-400 as the solvent.[a]



Entry	Cu source	Base	*T* [°C]	Yield [%][b]
1	CuI	K_2CO_3	80	45
2	CuI	K_3PO_4	80	54
3	CuI	LiO*t*Bu	80	69
4	CuI	Cs_2CO_3	80	47
5	CuI	LiO*t*Bu	120	69
6	CuBr	LiO*t*Bu	80	82
7	CuBr	K_3PO_4	80	59
8	CuBr	LiO*t*Bu	120	82
9	CuBr	Cs_2CO_3	80	51
10	Cu(PPh$_3$)Br	LiO*t*Bu	80	35
11	Cu(PPh$_3$)Br	K_3PO_4	80	26
12	$CuBr_2$	LiO*t*Bu	80	48
13	CuCl	LiO*t*Bu	80	51
14	Cu_2O	LiO*t*Bu	80	57
15	CuBr	LiO*t*Bu	r.t.	39[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Cu source (10 mol-%), base (1.0 equiv.), PEG-400 at 80 °C over 2 h. [b] Isolated yield of **3aa** after column chromatography. [c] Room temperature = 27 °C.

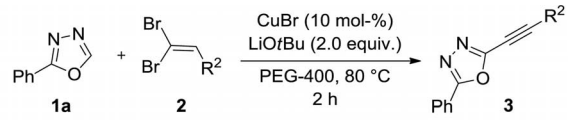
as the solvent the reaction did not proceed. Among the bases, LiO*t*Bu was found to be the most efficient, and with other bases the yields were low.

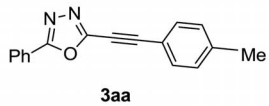
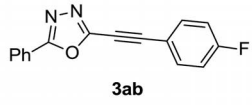
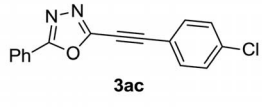
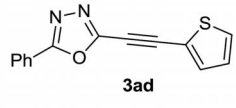
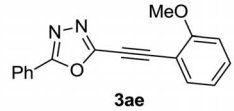
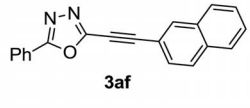
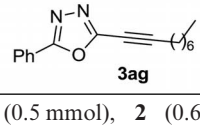
Following the standardization of the above reaction, a series of alkynylated derivatives of 2-phenyl-1,3,4-oxadiazoles were prepared by using different 1,1-dibromo-1-alkenes (Table 2). Aromatic, heteroaromatic, and aliphatic alkenes underwent the conversion smoothly. The products were formed in high yields (73–86%). 1,1-Dibromo-2-naphthylethylene also afforded desired alkyne **3af** (Table 2, Entry 6) in an impressive yield of 81%.

The present copper-mediated direct cross-coupling reaction was carried out by using various 2-aryl-1,3,4-oxadiazoles and different 1,1-dibromo-1-alkenes (Table 3). The aryl group of the oxadiazoles contained both aromatic and heteroaromatic moieties. The aromatic moiety possessed electron-donating as well as electron-withdrawing groups, whereas the heteroaromatic moiety comprised oxygen and nitrogen heterocycles. The 1,1-dibromo-1-alkenes also contained both aromatic and aliphatic groups. Thus, the present conversion has versatile scope for the preparation of various alkynylated oxadiazole derivatives.

PEG-400 was used here as a reaction medium.[10] In recent years, chemists have tended to avoid volatile organic solvents, especially chlorinated solvents, which create environmental problems. Polyethylene glycol has now been introduced as a green solvent system.[11] It is less expensive, recyclable, and miscible with different organic solvents. This solvent medium has successfully been utilized here for alkynylation of oxadiazoles.

Table 2. Copper-mediated direct cross-coupling of 2-phenyl-1,3,4-oxadiazole with different 1,1-dibromo-1-alkenes by using PEG-400 as the solvent.[a]



Entry	2	R^2	Product 3	Yield [%][b]
1	**2a**	4-MeC$_6$H$_4$	 **3aa**	82
2	**2b**	4-FC$_6$H$_4$	 **3ab**	78
3	**2c**	4-ClC$_6$H$_4$	 **3ac**	73
4	**2d**	2-thienyl	 **3ad**	76
5	**2e**	2-OMe	 **3ae**	86
6	**2f**	2-naphthyl	 **3af**	81
7	**2g**	C_7H_{15}	 **3ag**	73

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), CuBr (10 mol-%), LiO*t*Bu (2.0 equiv.), PEG-400(2 mL) at 80 °C over 2 h. [b] Isolated yield of **3** after column chromatography.

With an understanding of copper-catalyzed cross-coupling reactions,[12] a plausible mechanism for the present conversion is given in Scheme 2. The reaction medium, polyethylene glycol, acts as a ligand[13] to form species **A**. The mechanism involves (heteroaryl) Cu^I intermediate **I** and Cu^{III} complex **II** to form alkynylated product **3**.

In an alternative mechanism, the alkynyl bromides derived from the 1,1-dibromo-1-alkenes interact with **I** to form complex **III**, which produces alkynylated derivative **3** (Scheme 3).

The present conversion took place spontaneously and no intermediate could be isolated. However, when we treated a 1,3,4-oxadiazole with a bromoacetylene under similar reaction conditions; the alkynylated product was produced in high yield (Scheme 4). Thus, we feel that the second mechanism (Scheme 3) is more favorable for the present conversion.

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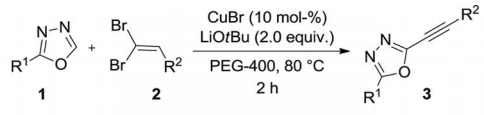
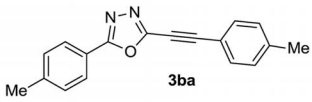
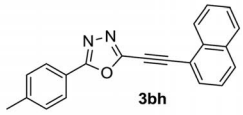
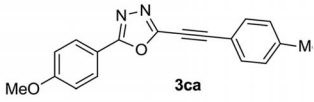
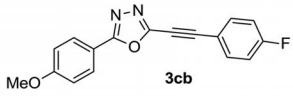
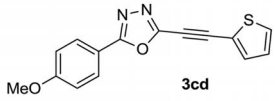
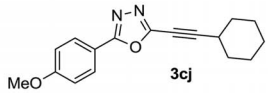
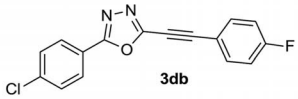
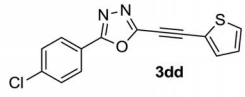
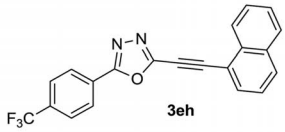
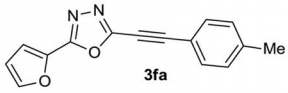
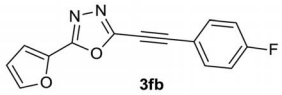
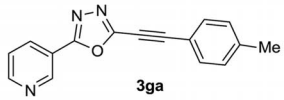
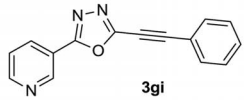
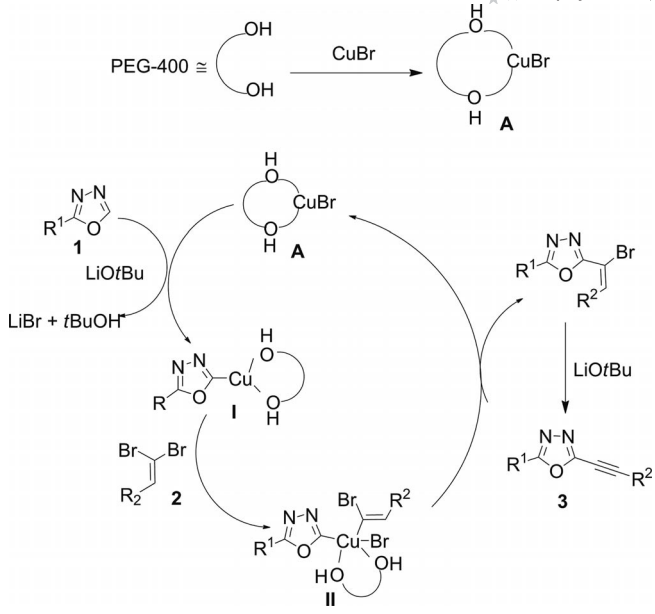
Table 3. Copper-mediated direct cross-coupling of various 1,3,4-oxadiazole with different 1,1-dibromo-1-alkenes by using PEG-400 as the solvent.[a]



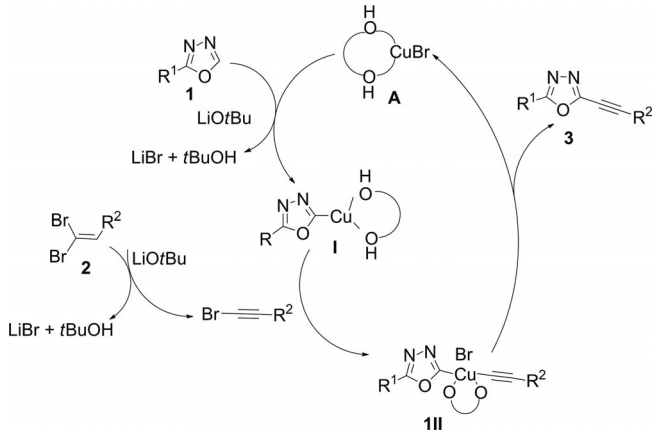
1 2 3

Entry	R^1 (1)	R^2 (2)	Product 3	Yield [%][b]
1	4-MeC_6H_4 (**1b**)	4-MeC_6H_4 (**2a**)	 **3ba**	79
2	4-MeC_6H_4 (**1b**)	1-naphthyl (**2h**)	 **3bh**	82
3	4-$OMeC_6H_4$ (**1c**)	4-MeC_6H_4 (**2a**)	 **3ca**	86
4	4-$OMeC_6H_4$ (**1c**)	4-FC_6H_4 (**2b**)	 **3cb**	75
5	4-$OMeC_6H_4$ (**1c**)	2-thienyl (**2d**)	 **3cd**	77
6	4-$OMeC_6H_4$ (**1c**)	cyclohexyl (**2j**)	 **3cj**	73
7	4-ClC_6H_4 (**1d**)	4-FC_6H_4 (**2b**)	 **3db**	76
8	4-ClC_6H_4 (**1d**)	2-thienyl (**2d**)	 **3dd**	78
9	4-CF_3 (**1e**)	1-naphthyl (**2h**)	 **3eh**	74
10	2-furyl (**1f**)	4-MeC_6H_4 (**2a**)	 **3fa**	81
11	2-furyl (**1f**)	4-FC_6H_4 (**2b**)	 **3fb**	77
12	3-nicotinyl (**1g**)	4-MeC_6H_4 (**2a**)	 **3ga**	82
13	3-nicotinyl (**1g**)	Ph (**2i**)	 **3gi**	78

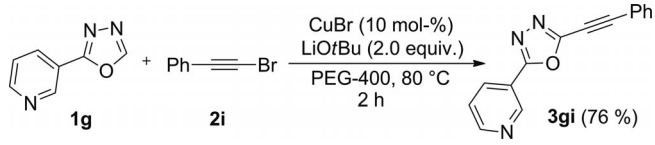
[a] Reaction conditions: **1** (0.5 mmol), 1,1-dibromo-1-alkene **2** (0.6 mmol), CuBr (10 mol-%), LiO*t*Bu (2.0 equiv.), PEG-400 at 80 °C over 2 h. [b] Isolated yield of **3** after column chromatography.



Scheme 2.



Scheme 3.



Scheme 4.

Conclusions

In conclusion we have developed an efficient copper-mediated, green method for the alkynylation of 1,3,4-oxadiazoles by using PEG-400 as the solvent medium. Costly Pd-based catalysts have been avoided. The mild reaction conditions, operational simplicity, ligand- and volatile-solvent-free conversion, application of a nontoxic and recyclable medium, high yields, and rapid formation of the products are the notable advantages of this method.

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Experimental Section

General Experimental Procedure for the Alkynylation of 1,3,4-Oxadiazoles with 1,1-Dibromo-1-alkenes: A 10-mL round-bottomed flask was loaded with CuBr (7 mg, 0.05 mmol), LiO*t*Bu (80 mg, 1.0 mmol), 1,1-dibromo-1-alkene (0.60 mmol), and the 1,3,4-oxadiazole (0.50 mmol) in PEG-400 (2.0 mL). The reaction mixture was stirred at 80 °C for 2 h. The progress of the reaction was monitored by TLC. After the consumption of the starting materials, the reaction mixture was allowed to cool and subsequently extracted with diethyl ether (4 × 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. Concentration of the material in vacuo followed by flash chromatography on silica gel column afforded the 2-alkynyl-1,3,4-oxadiazole in good yield.

2-Phenyl-5-(*p*-tolylethynyl)-1,3,4-oxadiazole (3aa): IR: $\tilde{\nu}$ = 2215, 1601, 1533, 1476, 1279 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, 2 H, J = 8.0 Hz), 7.56–7.48 (m, 5 H), 7.22 (d, J = 8.0 Hz, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.9, 150.9, 141.2, 132.8, 132.7, 129.3, 129.0, 127.1, 123.4, 116.8, 97.6, 72.8, 21.8 ppm. MS (ESI): m/z = 283 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{12}N_2ONa$ $[M + Na]^+$ 283.0847; found 283.0849.

Supporting Information (see footnote on the first page of this article): Experimental details, spectral data, and copies of the ^1H NMR and ^{13}C NMR spectra of all compounds.

Acknowledgments

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