Synthesis of 2-Alkynyl 1,3,4-Oxadiazoles by Palladium-Catalyzed Cross-Coupling Reaction[1]

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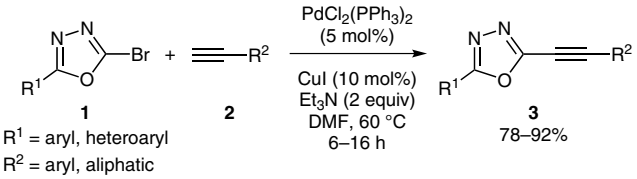
Abstract: Several 2-alkynyl 1,3,4-oxadiazoles have been synthesized efficiently by employing palladium-catalyzed cross-coupling under Sonogashira reaction conditions. This reaction has been applied for the first time for the preparation of oxadiazole derivatives. The products were formed in high yields and no side products were detected.

Key words: 1,3,4-oxadiazole, Sonogashira coupling, palladium-catalyzed reaction, copper(I) iodide, alkynylation



Scheme 1 Palladium-catalyzed C–C cross-coupling

Oxadiazole derivatives are highly important in pharmaceutical and material sciences. They are used as antimicrobial and anticonvulsant agents.[2] They also act as amide and ester bioisosteres.[3] In addition, substituted oxadiazoles possess multiphoton-absorbing capacities and optoelectronic properties.[4] They are also known to exhibit good electron-transporting and hole-blocking abilities[5] and consequently find application in the development of organic electronics.[6] Herein we report the first application of the Sonogashira reaction[7] for the efficient synthesis of 2-alkynyl 1,3,4-oxadiazoles.

Substituted alkynes are a common unit in natural products and bioactive compounds and are found to be an important feature in various bioactive substances, such as endyne antibiotics.[8] The alkyne moiety can also extend the conjugation of aryl and heteroaryl rings with which it is attached. Thus we realized that 2-alkynyl 1,3,4-oxadiazoles may have bioactivity as well as potential for use in organic materials chemistry.

In continuation of our work[9] on the synthesis of substituted oxadiazoles we discovered that 2-bromo-1,3,4-oxadiazoles (**1**; readily be prepared from 1,3,4-oxadiazoles[10]) can be subjected to palladium-catalyzed cross-coupling with terminal alkynes under Sonogashira reaction conditions[7] to prepare 2-alkynyl 1,3,4-oxadiazoles (Scheme 1).

Alkynylation of heterocyclic-based halides using Sonogashira reaction conditions has been frequently employed for the preparation of various novel systems.[11] However, to our knowledge, this reaction has not yet been applied for the generation of oxadiazolyl alkynes (Scheme 1).

Initially we optimized the reaction conditions with 2-bromo-5-phenyl-1,3,4-oxadiazole (**1a**) and 2-(4-methylphenyl)acetylene (**2a**) using various amounts of different palladium catalysts and CuI (Table 1). Different bases and solvents were also used. In addition, the temperature and the time of the reaction were varied. Considering the yield of the reaction the best result was obtained when $PdCl_2(PPh_3)_2$ (5mol%), CuI (10 mol%), and Et_3N (2 equiv) were used in DMF at 60 °C for six hours (Table 1, entry 1). In the absence of CuI the yield was low (Table 1, entry 6). When the reaction was conducted with other bases (such as Cs_2CO_3, *i*-PrNH; Table 1, entries 7 and 8) and other solvents (such as THF, DMSO, dioxane; Table 1, entries 2, 4, and 5) the yield was also low. On increasing the amount of base (Et_3N) no significant change in yield was observed (Table 1, entry 9). The reaction was also carried out at room temperature but the reaction time increased and the yield was lower (Table 1, entry 10).

It was also observed that – with other terminal acetylenes other than 2-(4-methylphenyl)acetylene – longer times were required (Table 2). The conversion also did not proceed smoothly with 2-chloro-1,3,4-oxadiazoles, requiring longer reaction times and resulting in lower yields.

After optimization of the reaction conditions (Table 1) several 2-alkynyl-1,3,4-oxadiazoles (**3**) were prepared successfully from various 2-bromo-1,3,4-oxadiazoles **1** and terminal alkynes **2** (Table 2). The bromooxadiazoles contained different aromatic moieties at C-5 possessing electron-donating as well as electron-withdrawing groups as well as oxygen and nitrogen heterocycles. The terminal alkynes also contained aromatic and heteroaromatic rings at C-2 and even an alkyne with a long aliphatic chain underwent the transformation smoothly (Table 2, entry 6). The products were formed in high yields within 6–16 hours. All the products were characterized from their spectroscopic data and were compared to known compounds.[9] No side reaction including alkyne homocoupling could be observed.

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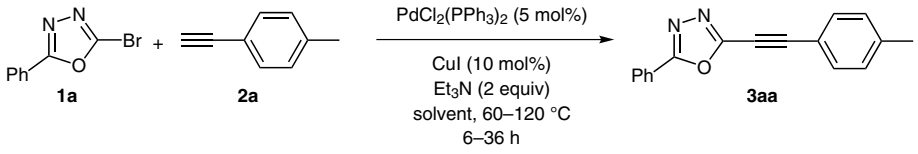
Table 1 Optimization of Reaction Conditions for the Cross-Coupling of 2-Bromo-5-phenyl-1,3,4-oxadiazole (**1a**) with 2-(4-Methylphenyl)acetylene (**2a**) Using Different Metal Catalysts and Various Bases[a]



Entry	Catalyst	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$, CuI	Et_3N	DMF	60	6	92
2	$PdCl_2(PPh_3)_2$, CuI	Et_3N	THF	60	10	58
3	$PdCl_2(PPh_3)_2$, CuI	*i*-Pr_2NH	DMF	120	24	68
4	$PdCl_2(PPh_3)_2$, CuI	Et_3N	DMSO	60	16	62
5	$PdCl_2(PPh_3)_2$, CuI	Et_3N	dioxane	60	12	55
6	$PdCl_2(PPh_3)_2$	Et_3N	DMF	60	36	15
7	$PdCl_2(PPh_3)_2$, CuI	Cs_2CO_3	DMF	120	24	54
8	$PdCl_2(PPh_3)_2$, CuI	*i*-Pr_2NH	DMF	120	24	66
9	$PdCl_2(PPh_3)_2$, CuI	Et_3N	DMF	60	6	92[d]
10	$PdCl_2(PPh_3)_2$, CuI	Et_3N	DMF	27	24	40[c]

[a] Reaction conditions: 2-bromo-5-phenyl-1,3,4-oxadiazole **1a** (0.7 mmol), 2 (4-methylphenyl) acetylene **2** (1.0 mmol), ($PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), base (2.0 equiv), 60–120 °C, 6–36 h, solvent (3 mL).
[b] Isolated yield of **3** after column chromatography.
[c] Reaction was carried out at r.t. (27 °C).
[d] Base (4.0 equiv).

In conclusion, we have successfully applied the Sonogashira reaction for the first time for the synthesis of a series of 2-alkynyl 1,3,4-oxadiazoles. The products were formed under mild reaction conditions and in high yield.

General Experimental Procedure for the Alkynylation of 2-Bromo 1,3,4-Oxadiazoles with Terminal Alkynes

In a 10 mL round-bottom flask under N_2 atmosphere, 2-bromo-1,3,4-oxadiazole (0.7 mmol), alkyne (1.0 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), and Et_3N (2.0 equiv) in anhydrous DMF (2.0 mL) were combined. The reaction mixture was stirred at 60 °C for 6–16 h, and progress of reaction was monitored by TLC. After the consumption of the starting materials, the reaction mixture was allowed to cool, and subsequently extracted with Et_2O (2 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo followed by flash chromatography on silica to afford the corresponding 2-alkynyl-1,3,4-oxadiazole in good yield.

Selected Spectroscopic Data

2-Phenyl-5-(*p*-tolylethynyl)-1,3,4-oxadiazole (3ab)

IR (neat): 2215, 1601, 1533, 1476, 1279 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09 (2 H, d, *J* = 8.0 Hz), 7.56–7.48 (5 H, m), 7.22 (2 H, d, *J* = 8.0 Hz), 2.41 (3 H, s). ^{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. ESI-MS: *m/z* = 283 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{12}N_2ONa$ $[M + Na]^+$: 283.0847; found: 283.0849.

2-Phenyl-5-(thiophen-2-ylethynyl)-1,3,4-oxadiazole (3af)

IR (neat): 2211, 1544, 1478, 1411, 1211 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.13–8.09 (2 H, m), 7.59–7.46 (5 H, m), 7.10 (1 H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 150.9, 135.5, 132.2, 131.0, 129.1, 127.3, 127.1, 126.9, 123.5, 91.0, 77.1; ESI-MS: *m/z* 253 $[M + H]^+$, 275 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{14}H_8N_2OSNa$ $[M + Na]^+$: 275.0255; found: 275.0250.

2-(Non-1-ynyl)-5-phenyl-1,3,4-oxadiazole (3ag)

IR (neat): 2223, 1584, 1451, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.08–7.98 (2 H, m), 7.58–7.44 (3 H, m), 2.59 (2 H, t, *J* = 8.0 Hz), 1.79–1.70 (2 H, m), 1.59–1.51 (2 H, m), 1.48–1.32 (6 H, m), 0.96 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.5, 151.9, 131.9, 129.1, 127.9, 126.8, 98.0, 62.9, 33.2, 30.1, 30.0, 29.9, 22.9, 18.0, 13.2. ESI-MS: *m/z* 291 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{20}N_2ONa$ $[M + Na]^+$: 291.0689; found: 291.0685.

2-(Naphthalen-1-ylethynyl)-5-*p*-tolyl-1,3,4-oxadiazole (3be)

IR (neat): 2215, 1612, 1532, 1491, 1195 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.40 (1 H, d, *J* = 8.0 Hz), 8.04 (2 H, d, *J* = 8.0 Hz), 7.98–7.85 (3 H, m), 7.70–7.48 (3 H, m), 7.31 (2 H, d, *J* = 8.0 Hz), 2.43 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 150.6, 143.0, 133.0, 132.9, 132.2, 131.4, 130.0, 128.8, 127.9, 127.1, 127.0, 125.9, 125.2, 120.8, 117.6, 95.5, 77.8, 21.4. ESI-MS: *m/z* = 311 $[M + H]^+$. ESI-HRMS: *m/z* calcd for $C_{21}H_{15}N_2O$ $[M + H]^+$ 311.1184; found: 311.1178.

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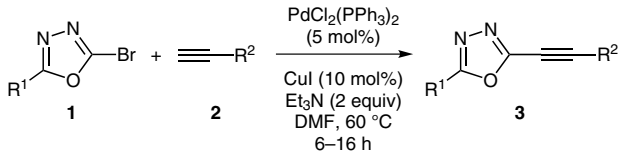
Table 2 Palladium-Catalyzed Cross-Coupling of Various Terminal Alkynes with 2-Bromo-5-aryl-1,3,4-oxadiazole[a]



Entry	R^1	R^2	Time (h)	Yield (%)[b]
1	**1a** Ph	**2b** 4-MeC_6H_4	6	**3ab** 92
2	**1a** Ph	**2c** 4-ClC_6H_4	10	**3ac** 80
3	**1a** Ph	**2d** 4-FC_6H_4	12	**3ad** 82
4	**1a** Ph	**2e** 2-naphthyl	14	**3ae** 78
5	**1a** Ph	**2f** 2-thienyl	8	**3af** 84
6	**1a** Ph	**2g** heptyl	16	**3ag** 80
7	**1a** Ph	**2ai** 2-$MeOC_6H_4$	8	**3ai** 84
8	**1b** 4-MeC_6H_4	**2b** 4-MeC_6H_4	7	**3bb** 87
9	**1b** 4-MeC_6H_4	**2e** 2-naphthyl	10	**3be** 90
10	**1c** 4-$MeOC_6H_4$	**2b** 4-MeC_6H_4	8	**3cb** 90
11	**1c** 4-$MeOC_6H_4$	**2d** 4-FC_6H_4	14	**3cd** 82
12	**1c** 4-$OMeC_6H_4$	**2f** 2-thienyl	12	**3cf** 84
13	**1c** 4-$MeOC_6H_4$	**2h** cyclohexyl	16	**3ch** 78
14	**1d** 4-ClC_6H_4	**2d** 4-FC_6H_4	12	**3dd** 85
15	**1d** 4-ClC_6H_4	**2f** 2-thienyl	14	**3df** 86
16	**1e** 4-$F_3CC_6H_4$	**2e** 2-naphthyl	10	**3ee** 80
17	**1f** 2-furyl	**2b** 4-MeC_6H_4	8	**3fb** 88
18	**1f** 2-furyl	**2d** 4-FC_6H_4	10	**3fd** 84
19	**1g** 2-nicotyl	**2a** Ph	10	**3ga** 80
20	**1g** 2-nicotyl	**2b** 4-MeC_6H_4	8	**3gb** 78

[a] Reaction conditions: 2-bromo-5-aryl 1,3,4-oxadiazole **1** (0.7 mmol), alkyne **2** (1.0 mmol), $(PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), base (2.0 equiv), 60 °C, 6–16 h, DMF (3 mL).
[b] Isolated yield of **3** after column chromatography.

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