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Palladium-Catalyzed Decarboxylative Cross-Coupling of 1,3,4-Oxadiazoles with Alkynoic Acids: A Simple Route for the Preparation of 2-Alkynylated 1,3,4-Oxadiazoles

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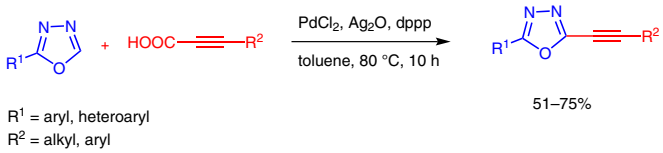

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Abstract For the first time 2-alk-1-ynyl-5-(het)aryl-1,3,4-oxadiazole derivatives have been synthesized by the decarboxylative cross-coupling of alk-2-ynoic acids with 2-(het)aryl-1,3,4-oxadiazoles, employing palladium(II) chloride as the catalyst and silver(I) oxide as an oxidant with 1,3-bis(diphenylphosphanyl)propane as a ligand. Products were formed in high yields with no byproduct.

Keywords alkynoic acids, 1,3,4-oxadiazole, palladium catalyst, alkynylation, cross-coupling, 1,3-bis(diphenylphosphanyl)propane

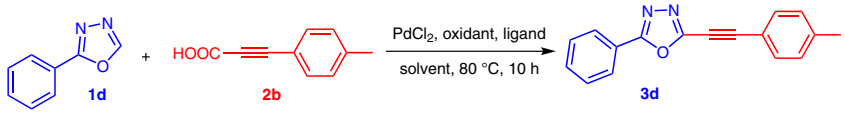
In recent years, a promising strategy of C–H bond activation has been extensively utilized for C–C bond formation, and this is one of the most important topics in organic chemistry.[1] For chemist and biologists, oxadiazole derivatives have become an interesting area of research due to their wide applications in pharmaceuticals, material sciences, and organic electronics.[2] They possess good electron-transporting, hole-blocking abilities,[3] and anticonvulsant and antimicrobial activity.[4] They also act as amide and ester bioisosteres.[5] Oxadiazole derivatives possess multiphoton absorbing capacities and optoelectronic properties.[6] Substituted alkynes are found to be key building blocks in organic chemistry, material science, and bioactive natural products[7] and they are versatile synthetic intermediates.[8] Thus we realized that 2-alk-1-ynyl-1,3,4-oxadiazoles are biologically important compounds.

Carboxylic acid substrates were reported to be successful coupling counterparts, with heterocyclic compounds[9] as one of the reaction partners, and they are commercially available and inexpensive. Decarboxylative direct couplings are of great interest, as they reduce the amount of toxic side products,[10] produce only CO_2, and favor purification of the product.

The common methods for formation of 2-alkynyl-1,3,4-oxadiazoles[11] include the use of alkynyl halides, terminal alkynes, *gem*-dihaloalkenes, and copper acetylides. In the present study we have demonstrated a benign alternative method, decarboxylative cross-coupling of alkynoic acids with 1,3,4-oxadiazoles in the presence of palladium chloride, Ag_2O, and a ligand.

Initially we optimized the reaction (Scheme 1,Table 1), with 2-phenyl-1,3,4-oxadiazole (**1d**)[11c] and 3-(4-tolyl)propynoic acid (**2b**)[12] using a palladium catalyst. Various oxidants, ligands, and solvents (Table 1) were examined, considering the yield of the product, the best result was obtained with $PdCl_2$ (10 mol%), dppp (20 mol%), and Ag_2O (2 equiv) in toluene at 80 °C for 10 h (Table 1, entry 4).

With the optimized reaction conditions in hand, several 2-alk-1-ynyl-1,3,4-oxadiazoles **3** were prepared successfully from various 1,3,4-oxadiazoles **1** and α,β-ynoic acids **2** (Scheme 2). Oxadiazoles with different aromatic, heteroaromatic, and with electron-donating or -withdrawing substituted aromatic compounds at the C-2 position underwent the reaction smoothly. The scope of the reaction was also examined with various α,β-ynoic acids containing aro-



Scheme 1 Optimization for Pd-catalyzed C–C cross-coupling of 1,3,4-oxadiazoles with alkynoic acids

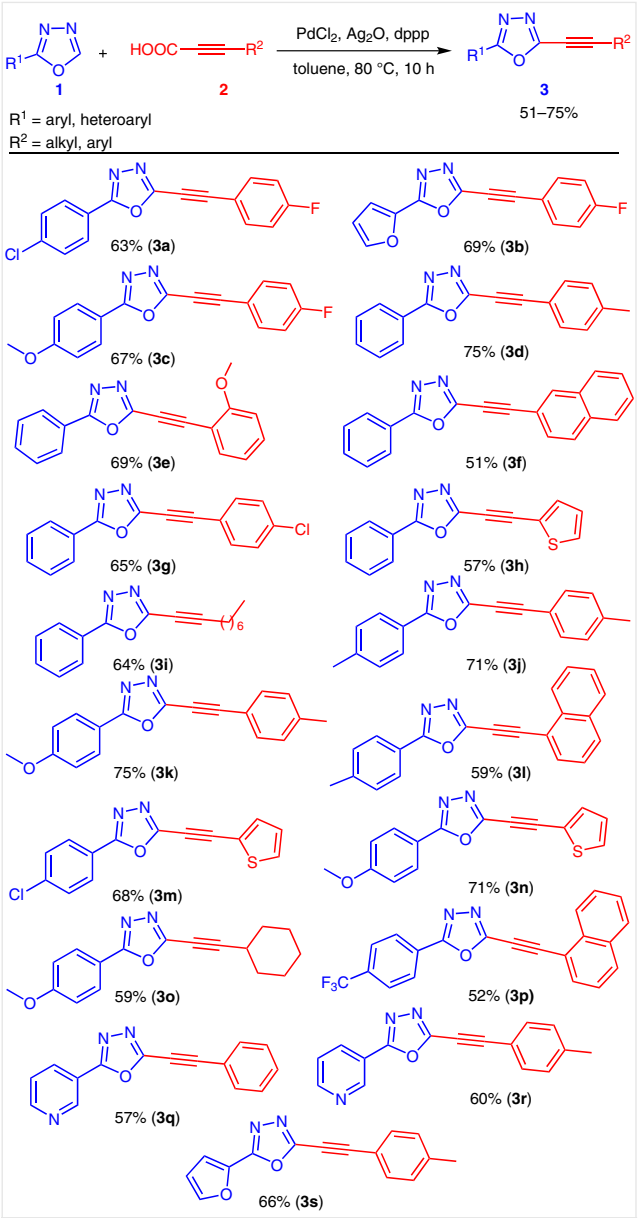
Table 1 Optimization for Palladium-Catalyzed Cross-Coupling of 2-Phenyl-1,3,4-oxadiazole (**1d**) and 3-(4-Tolyl)propynoic Acid (**2b**) Using Various Oxidants, Ligands, and Solvents[a]

Entry	Ligand	Oxidant	Solvent	Yield[b] (%)
1	PPh_3	Ag_2O	toluene	31
2	dppe	Ag_2O	toluene	71
3	Johnphos	Ag_2O	toluene	trace
4	**dppp**	**Ag_2O**	**toluene**	**75**
5	dppf	Ag_2O	toluene	43
6	dppp	Ag_2O	xylene	35
7	dppp	Ag_2O	benzene	52
8	dppp	Ag_2O	1,4-dioxane	trace
9	dppp	$Cu(OTf)_2$	toluene	trace
10	dppp	AgOAc	toluene	trace
11	dppp	$Cu(OAc)_2$	toluene	trace

[a] Reaction conditions: 2-phenyl-1,3,4-oxadiazole (**1d**, 0.5 mmol), 3-(4-tolyl)propynoic acid (**2b**, 0.45 mmol), $PdCl_2$ (10 mol%), oxidant (0.9 mmol), ligand (20 mol%), solvent (3 mL).
[b] Isolated yield of **3d** after column chromatography.

matic, heteroaromatic, and aliphatic substitution at C-3 position and products were formed in high yields and unreacted starting material (1,3,4-oxadiazole) was recovered. All the products were characterized from the spectral (^{1}H and ^{13}C NMR and MS) data.

In conclusion, we have developed a simple synthesis of 2-alk-1-ynyl-5-(het)aryl-1,3,4-oxadiazoles from alkynoic acids and 1,3,4-oxadiazoles using $PdCl_2$ as a catalyst.



Scheme 2 Pd-Catalyzed cross-coupling of 1,3,4-oxadiazoles with alkynoic acids to prepare 2-alk-1-ynyl-1,3,4-oxadiazoles

Column chromatography was performed using silica gel 60–120 mesh (Qingdao Marine Chemical, China) and thin-layer chromatography (TLC) on Merck Silica Gel 60 F254 plates. NMR spectra: Gemini 200 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are expressed as δ values in ppm and coupling constants (*J*) are given in Hz. ESI-MS: VG-Autospec micromass instrument. The solvents used were all of AR grade.

Abbreviations: 1,2-bis(diphenylphosphanyl)ethane (dppe); 1,3-Bis(diphenylphosphanyl)propane(dppp); 1,1-bis(diphenylphosphanyl)ferrocene (dppf).

2-Alk-1-ynyl-5-(het)aryl-1,3,4-oxadiazoles 3a–s; General Procedure

To a 10-mL round-bottom flask $PdCl_2$ (6.7 mg, 10 mol%), dppp (24.7 mg, 20 mol%), Ag_2O (208.6 mg, 0.9 mmol), and α,β-ynoic acid **2** (0.45 mmol) and toluene (3 mL) were added under air. To this mixture 1,3,4-oxadiazole **1** (0.5 mmol) was added and the entire mixture was refluxed at 80 °C for 10 h (TLC monitoring). After completion of the reaction, the mixture was allowed to cool, quenched by the addition of H_2O, and subsequently extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried (anhyd Na_2SO_4). Concentration of the organic layer in vacuo followed by column chromatography (silica gel) afforded oxadiazole derivatives **3** (Scheme 2).

2-(4-Chlorophenyl)-5-[(4-fluorophenyl)ethynyl]-1,3,4-oxadiazole (3a)

Yellow solid; yield: 94 mg (0.31 mmol, 63%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2225, 1662, 1597, 1536, 1470, 1226 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.0 Hz, 2 H), 7.70–7.61 (m, 2 H), 7.51 (d, *J* = 8.0 Hz, 2 H), 7.10 (t, *J* = 8.0 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.5, 163.0 (d, *J* = 280.0 Hz), 150.6, 138.5, 134.2 (d, *J* = 4.0 Hz), 129.9, 128.2, 121.7, 116.2 (d, *J* = 10.0 Hz), 115.9, 96.1, 72.6.

MS (ESI): *m*/*z* = 299, 301 [M + H]$^+$.

Anal. Calcd for $C_{16}H_8ClFN_2O$: C, 64.34; H, 2.70. Found: C, 64.46; H, 2.73.

2-[(4-Fluorophenyl)ethynyl]-5-(2-furyl)-1,3,4-oxadiazole (3b)

Yellow solid; yield: 87 mg (0.34 mmol, 69%); R_f = 0.35 (hexane/EtOAc 80:20).

IR: 2220, 1606, 1458, 1374, 1228 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.61 (m, 3 H), 7.22 (m, 1 H), 7.11 (t, J = 8.0 Hz, 2 H), 6.62 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 163.8 (d, J = 280.0 Hz), 152.8, 146.1, 139.2, 134.8 (d, J = 4.0 Hz), 116.4 (d, J = 10.0 Hz), 116.0, 115.9, 112.2, 96.4, 72.9.

MS (ESI): m/z = 255 $[M + H]^+$.

Anal. Calcd for $C_{14}H_7FN_2O_2$: C, 66.14; H, 2.78. Found: C, 66.30; H, 2.75.

2-[(4-Fluorophenyl)ethynyl]-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3c)

White solid; yield: 98 mg (0.33 mmol, 67%); R_f = 0.30 (hexane/EtOAc 80:20).

IR: 2223, 1609, 1537, 1494, 1262 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 2 H), 7.70–7.61 (m, 2 H), 7.11 (t, J = 8.0 Hz, 2 H), 6.99 (d, J = 8.0 Hz, 2 H), 3.90 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.1 (d, J = 280.0 Hz), 162.9, 162.2, 150.2, 134.9 (d, J = 4.0 Hz), 131.8, 129.0, 116.3 (d, J = 10.0 Hz), 116.1, 114.9, 96.1, 73.1, 55.6.

MS (ESI): m/z = 295 $[M + H]^+$, 317 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{11}FN_2O_2$: C, 69.38; H, 3.77. Found: C, 69.50; H, 3.75.

2-Phenyl-5-(4-tolylethynyl)-1,3,4-oxadiazole (3d)

Light yellow solid; yield: 97 mg (0.37 mmol, 75%); R_f = 0.45 (85:15 Hexane/EtOAc).

IR: 2215, 1601, 1533, 1476, 1279 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.0 Hz, 2 H), 7.56–7.48 (m, 5 H), 7.22 (d, J = 8.0 Hz, 2 H), 2.41 (s, 3 H).

^{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.

MS (ESI): m/z = 283 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65. Found: C, 78.55; H, 4.61.

2-[(2-Methoxyphenyl)ethynyl]-5-phenyl-1,3,4-oxadiazole (3e)

Yellow solid; yield: 95 mg (0.34 mmol, 69%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2219, 1537, 1480, 1275 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.0 Hz, 2 H), 7.60–7.46 (m, 4 H), 7.39 (t, J = 8.0 Hz, 1 H), 6.99–6.89 (m, 2 H), 3.92 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.8, 161.0, 150.9, 134.2, 132.1, 131.9, 129.0, 126.9, 123.2, 120.5, 110.9, 109.1, 94.2, 76.9, 55.8.

MS (ESI): m/z = 277 $[M + H]^+$, 299 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38. Found: C, 73.78; H, 4.41.

2-(2-Naphthylethynyl)-5-phenyl-1,3,4-oxadiazole (3f)

Light yellow solid; yield: 75 mg (0.28 mmol, 51%); R_f = 0.45 (hexane/EtOAc 80:20).

IR: 2218, 1635, 1602, 1520, 1453, 1253 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.27–8.08 (m, 2 H), 7.91–7.80 (m, 3 H), 7.63 (d, J = 8.0 Hz, 1 H), 7.60–7.49 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 150.9, 144.1, 133.9, 133.6, 132.3, 129.9, 129.5, 129.0, 128.4, 128.3, 128.2, 127.1, 123.5, 117.2, 116.0, 97.9, 73.5.

MS (ESI): m/z = 319 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{12}N_2O$: C, 81.07; H, 4.08. Found: C, 81.20; H, 4.10.

2-[(4-Chlorophenyl)ethynyl]-5-phenyl-1,3,4-oxadiazole (3g)

Yellow solid; yield: 91 mg (0.33 mmol, 65%); R_f = 0.35 (hexane/EtOAc 80:20).

IR: 2224, 1594, 1456, 1282 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.0 Hz, 2 H), 7.63–7.50 (m, 5 H), 7.42 (d, J = 8.0 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 150.6, 137.1, 133.3, 132.0, 129.1, 127.0, 123.1, 118.7, 114.1, 96.0, 74.2.

MS (ESI): m/z = 281, 283 $[M + H]^+$.

Anal. Calcd for $C_{16}H_9ClN_2O$: C, 68.46; H, 3.23. Found: C, 68.60; H, 3.25.

2-Phenyl-5-(2-thienylethynyl)-1,3,4-oxadiazole (3h)

Black solid; yield: 71 mg (0.28 mmol, 57%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2211, 1544, 1478, 1411, 1211 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.13–8.09 (m, 2 H), 7.59–7.46 (m, 5 H), 7.10 (m, 1 H).

^{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.

MS (ESI): m/z = 253 $[M + H]^+$, 275 $[M + Na]^+$.

Anal. Calcd for $C_{14}H_8N_2OS$: C, 66.65; H, 3.20. Found: C, 66.52; H, 3.18.

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

Black solid; yield: 85 mg (0.32 mmol, 64%); R_f = 0.5 (hexane/EtOAc 82:18).

IR: 2223, 1584, 1451, 1250 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.08–7.98 (m, 2 H), 7.58–7.44 (m, 3 H), 2.59 (t, J = 8.0 Hz, 2 H), 1.79–1.70 (m, 2 H), 1.59–1.51 (m, 2 H), 1.48–1.32 (m, 6 H), 0.96 (t, J = 7.0 Hz, 3 H).

^{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.

MS (ESI): m/z = 291 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51. Found: C, 76.21; H, 7.48.

2-(4-Tolyl)-5-(4-tolylethynyl)-1,3,4-oxadiazole (3j)

Yellow solid; yield: 97 mg (0.35 mmol, 71%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2221, 1607, 1538, 1489, 1266 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.0 Hz, 2 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 2.44 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.1, 150.5, 143.0, 141.1, 132.1, 129.9, 129.2, 127.0, 120.9, 116.8, 97.3, 72.5, 21.3.

MS (ESI): m/z = 297 $[M + Na]^+$.

Anal. Calcd For $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14. Found: C, 78.95; H, 5.16.

2-(4-Methoxyphenyl)-5-(4-tolylethynyl)-1,3,4-oxadiazole (3k)

White solid; yield: 108 mg (0.37 mmol, 75%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2220, 1609, 1537, 1492, 1255 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.20 (t, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 3.88 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 162.4, 150.8, 141.2, 132.2, 129.6, 129.1, 117.1, 116.0, 114.8, 97.5, 73.0, 55.5, 21.9.

MS (ESI): *m*/*z* = 291 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86. Found: C, 74.62; H, 4.90.

2-(1-Naphthylethynyl)-5-(4-tolyl)-1,3,4-oxadiazole (3l)

Yellow solid; yield: 91 mg (0.29 mmol, 59%); R_f = 0.45 (hexane/EtOAc 80:20).

IR: 2215, 1612, 1532, 1491, 1195 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 2 H), 7.98–7.85 (m, 3 H), 7.70–7.48 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 2.43 (s, 3 H).

^{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.

MS (ESI): *m*/*z* = 311 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.27; H, 4.55. Found: C, 81.44; H, 4.53.

2-(4-Chlorophenyl)-5-(2-thienylethynyl)-1,3,4-oxadiazole (3m)

Black solid; yield: 97 mg (0.34 mmol, 68%); R_f = 0.4 (hexane/EtOAc 80:20).

IR: 2211, 1650, 1599, 1477, 1407, 1211 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.0 Hz, 2 H), 7.58–7.47 (m, 3 H), 7.01 (dd, *J* = 2.0, 1.5 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.2, 150.9, 138.3, 135.4, 130.8, 129.5, 128.2, 127.1, 121.2, 119.0, 91.0, 77.2.

MS (ESI): *m*/*z* = 287, 289 $[M + H]^+$.

Anal. Calcd for $C_{14}H_7ClN_2OS$: C, 58.64; H, 2.46. Found: C, 58.80; H, 2.44.

2-(4-Methoxyphenyl)-5-(2-thienylethynyl)-1,3,4-oxadiazole (3n)

Black solid; yield: 100 mg (0.35 mmol, 71%); R_f = 0.35 (hexane/EtOAc 80:20).

IR: 2208, 1607, 1490, 1417, 1256 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 1.5 Hz, 1 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 7.10 (dd, *J* = 2.0, 1.5 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.0, 162.9, 150.1, 135.4, 130.9, 129.3, 127.9, 119.8, 116.0, 114.4, 90.7, 77.0, 55.2.

MS (ESI): *m*/*z* = 283 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{10}N_2O_2S$: C, 63.82; H, 3.57. Found: C, 63.97; H, 3.54.

2-(Cyclohexylethynyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3o)

Dark green solid; yield: 83 mg (0.29 mmol, 59%); R_f = 0.4 (hexane/EtOAc 75:25).

IR: 1610, 1497, 1456, 1258 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): 7.94 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 3.85 (s, 3 H), 2.52 (s, 1 H), 2.01–1.63 (m, 4 H), 1.50–1.18 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.6, 162.5, 151.8, 129.0, 114.5, 114.2, 89.0, 68.1, 55.2, 29.9, 28.1, 25.2, 25.0.

MS (ESI): *m*/*z* = 283 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43. Found: C, 72.20; H, 6.45.

2-(1-Naphthylethynyl)-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazole (3p)

Yellow solid; yield: 94 mg (0.26 mmol, 52%); R_f = 0.45 (hexane/EtOAc 65:35).

IR: 2220, 1534, 1497, 1322, 1292 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 2 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.98–7.85 (m, 2 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.71–7.50 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.0, 152.2, 133.2, 132.8, 132.0, 128.4, 127.9, 127.4, 127.1, 126.1, 125.3, 125.0, 124.1 (q, *J* = 265.0 Hz), 121.0, 96.2, 75.6.

MS (ESI): *m*/*z* = 365 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{11}F_3N_2O$: C, 69.23; H, 3.04. Found: C, 69.35; H, 3.06.

2-(Phenylethynyl)-5-(3-pyridyl)-1,3,4-oxadiazole (3q)

IR: Brown solid; yield: 70 mg (0.28 mmol, 57%); R_f = 0.35 (hexane/EtOAc 70:30).

IR: 2218, 1657, 1534, 1277 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.30 (br s, 1 H), 8.79 (m, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 2 H), 7.52–7.40 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.9, 152.9, 151.1, 148.0, 134.3, 132.8, 131.2, 129.0, 124.0, 119.9, 119.7, 98.0, 72.8.

MS (ESI): *m*/*z* = 248 $[M + H]^+$.

Anal. Calcd for $C_{15}H_9N_3O$: C, 72.87; H, 3.67. Found: C, 72.67; H, 3.69.

2-(3-Pyridyl)-5-(4-tolylethynyl)-1,3,4-oxadiazole (3r)

Yellow solid; yield: 78 mg (0.30 mmol, 60%); R_f = 0.3 (hexane/EtOAc 65:35).

IR: 2221, 1586, 1529, 1460, 1273 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 9.32 (br s, 1 H), 8.80 (m, 1 H), 8.40 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.50 (m, 1 H), 7.24 (d, *J* = 8.0 Hz, 2 H), 2.41 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.5, 152.8, 151.1, 148.2, 141.1, 134.0, 132.2, 129.7, 124.0, 116.9, 98.2, 72.1, 21.9.

MS (ESI): *m*/*z* = 262 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{12}N_3O$: C, 73.55; H, 4.24. Found: C, 73.67; H, 4.21.

2-(2-Furyl)-5-(4-tolylethynyl)-1,3,4-oxadiazole (3s)

Red solid; yield: 82 mg (0.33 mmol, 66%); R_f = 0.45 (hexane/EtOAc 75:25).

IR: 2214, 1612, 1528, 1338, 1226 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.68 (m, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.26–7.18 (m, 3 H), 6.60 (m, 1 H), 2.42 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.8, 150.0, 146.1, 141.1, 139.4, 132.6, 129.7, 117.0, 114.9, 112.8, 108.1, 72.5, 21.9.

MS (ESI): *m*/*z* = 251 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03. Found: C, 71.80; H, 4.05.

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