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PALLADIUM-CATALYZED CARBONYLATIVE COUPLING OF HYPERVALENT IODONIUM SALTS WITH AMIDOXIMES: SYNTHESIS OF OXADIAZOLES†

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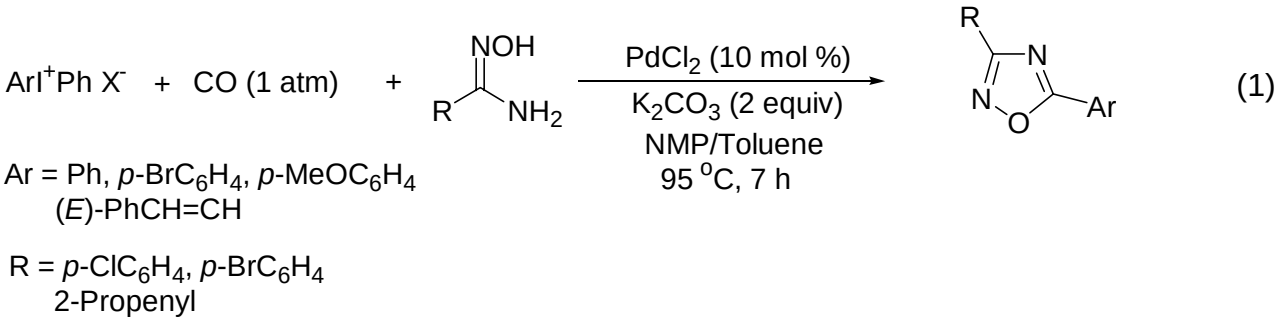
Abstract - Aryl-substituted oxadiazoles have been synthesized in one-pot procedure by the palladium-catalyzed carbonylative coupling of hypervalent iodonium salts with amidoximes under atmospheric pressure of carbon monoxide.

Oxadiazole moiety is an important structure unit in drugs and chemical materials.[1] Several methods are reported in the literature for the preparation of oxadiazoles.[2] In general, amidoxime is reacted with acid derivatives at high temperature, wherein *O*-acylation followed by cyclodehydration.[3] Recently, Young *et al*.[4] reported one-pot palladium-catalyzed coupling of aryl iodides with acetamidoxime at high temperature under carbon monoxide to give methyl-substituted oxadiazoles. With aryl iodides only acetamidoxime could be applied. To extend the scope of this method to aryl- and alkenyl-substituted amidoximes to synthesize a variety of oxadiazoles, we have utilized hypervalent iodonium salts as an electrophile instead of iodides. Here we wish to report one-pot carbonylative coupling of iodonium salts with amidoximes to form the substituted oxadiazoles (Eq. 1).



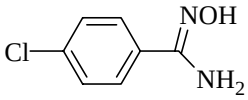
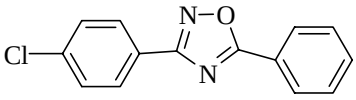
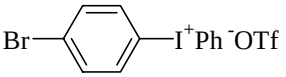
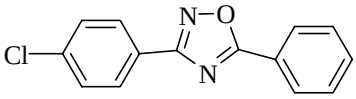
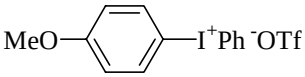
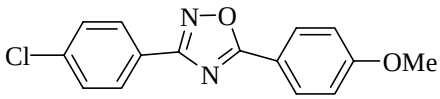
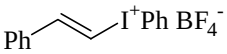
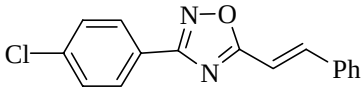
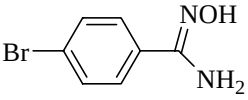
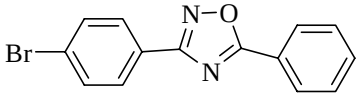
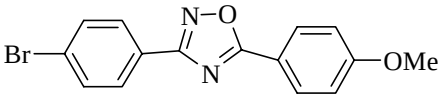
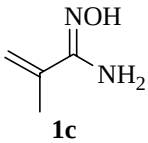
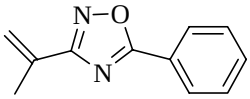
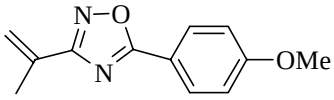
The results of the palladium-catalyzed carbonylative coupling of hypervalent iodonium salts with amidoximes[5] to form oxadiazoles are summarized in Table 1. The amidoxime (**1a**) reacted with diphenyl iodonium tetrafluoroborate (**2a**) in the presence of $PdCl_2$ (10 mol %) and K_2CO_3 (2 equiv.) in 1-methyl-2-pyrrolidone(NMP)/toluene at 95 °C under atmospheric pressure of carbon monoxide to afford the 3-(4-chlorophenyl)-5-phenyl[1,2,4]oxadiazole (**3a)** in 77% yield (Entry 1 in Table). Of the catalyst tested $PdCl_2$, $Pd_2(dba)_3 \cdot CHCl_3$, and $Pd_2(dba)_3$, $PdCl_2$ was the best choice. As a solvent, NMP/toluene (1 : 1) was the most suitable among the solvents, toluene, NMP, NMP/toluene (1 : 1), DMF, DMF/toluene (1 : 1) tested. Under the same conditions, treatment of p-bromophenyl- and p-methoxyphenyl-substituted iodonium salts (2b) and (2c) with 1a gave the oxadiazoles (3a) and (3b) as the sole products in 68 and 79% yields, respectively (Entries 2 and 3). For the alkenyl-substituted iodonium salt (2d), the 3-(4-chlorophenyl)-5-styryl[1,2,4]oxadiazole (3c) was afforded in 56% yield along with 3a (32%) (Entry 4). The p-bromophenyl-substituted amidoxime (1b) was reacted with 2a to provide 3d in 75% yield (Entry 5). The method was applied to alkenyl-substituted amidoxime (1c). The amidoxime (1c) was successfully coupled with diphenyl iodonium tetrafluoroborate (2a) to afford the coupled product (3f) in 73% yield

† Dedicated to Professor Sho Ito in celebration of his 77th birthday.

(Entry 7). Finally the amidoxime (**1c**) was treated with **2c** to give the coupled product (**3g**) in 52% yield (Entry 8).

In summary the aryl- and alkenyl-substituted oxadiazoles were synthesized from hypervalent iodonium salts and amidoximes by the palladium-catalyzed carbonylative coupling under atmospheric pressure of carbon monoxide.

Table 1. Palladium-Catalyzed Carbonylative Coupling of Hypervalent Iodonium Salts with Amidoximes

Entry	Amidoximes	Iodonium Salts	Product	Isolated Yieid(%)
1	 **1a**	$Ph_2I^+ BF_4^-$ **2a**	 **3a**	77
2	**1a**	 **2b**	 **3a**	68
3	**1a**	 **2c**	 **3b**	79
4	**1a**	 **2d**	 **3c** (56%)	**+ 3a** (32%) 56
5	 **1b**	**2a**	 **3d**	75
6	**1b**	**2c**	 **3e**	77
7	 **1c**	**2a**	 **3f**	73
8	**1c**	**2c**	 **3g**	52

EXPERIMENTAL

General: All the reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. IR spectra were recorded on Nicolet 205 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian Unity Inova 500 (500 MHz) spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ and DMSO-d_6 were used as solvents. GC-MS spectra were measured on a Hewlett Packard 5880 GC system and HRMS were measured on a QUATTRO triple quadrupole tandem

micromass autospec mass spectrometer with 70-eV ionization energy (EI). All solvents were distilled from calcium hydride prior to use.

General Procedure for Carbonylative Coupling of Amidoximes. To a mixture of diphenyliodonium tetrafluoroborate (**2a**) (500 mg, 1.36 mmol), $PdCl_2$ (12 mg, 0.0680 mmol, 5 mol %), and K_2CO_3 (376 mg, 2.72 mmol) was added 4-chloro-*N*-hydroxybenzamidine (**1a**) (231 mg 1.36 mmol) under atmospheric pressure of CO at 95 °C in NMP (20 mL). The reaction mixture was stirred at 95 °C for 7 h, extracted with ether (20 mL × 3), and the extract was washed with water (20 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc/hexanes = 1 : 10, R_f = 0.51) to afford 3-(4-chlorophenyl)-5-phenyl[1,2,4]-oxadiazole (**3a**) (269 mg, 77%). mp 106~108 °C, TLC, SiO_2, EtOAc/hexanes 1 : 10, R_f = 0.51. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 1 H), 7.56 (m, 2 H), 7.63 (m, 2 H), 8.12 (m, 2 H), 8.21 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.8, 168.7, 137.6, 135.3, 134.6, 130.7, 130.1, 129.1, 126.2, 124.4; IR(KBr) 1712, 1606, 1559, 1413, 1359, 1093 cm^{-1}; MS (EI): m/z (relative intensity) = 258 (16), 256 (46), 135 (38), 153 (100), 105 (11), 103 (10), 77 (35); HRMS calcd for $C_{14}H_9N_2OCl$: 256.0403. found: 256.0412.

4-Chloro-*N*-hydroxybenzamidine (1a) mp 128~130 °C, ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.86 (s, 2 H), 7.41 (m, 2 H), 7.67 (m, 2 H), 9.71 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 151.1, 135.2, 133.3, 129.4, 128.3; IR(KBr) 3592, 3406, 3055, 2987, 1712, 1603, 1550, 1423, 1157, 896 cm^{-1}; MS (EI): m/z (relative intensity) = 172 (23), 170 (78), 156 (15), 154 (47), 153 (91), 138 (100), 137 (97), 114 (42), 102 (37), 75 (32); HRMS calcd for $C_7H_7N_2OCl$: 170.0246. found: 170.0252.

4-Bromo-*N*-hydroxybenzamidine (1b) mp 139~140 °C, ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.87 (s, 2 H), 7.54 (m, 2 H), 7.61 (m, 2 H), 9.76 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 151.1, 133.7, 132.3, 128.6, 123.4; IR(KBr) 3572, 3406, 3055, 2899, 1668, 1587, 1070 cm^{-1}; MS (EI): m/z (relative intensity) = 214 (54), 200 (44), 199 (66), 198 (48), 197 (63), 184 (75), 183 (50), 182 (78), 102 (100), 90 (64); HRMS calcd for $C_7H_7N_2OBr$: 213.9741. found: 213.9744.

***N*-Hydroxy-2-methylacrylamidine (1c)** dark brown oil, ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.79 (s, 3 H), 5.08 (s, 1 H), 5.34 (s, 2H), 5.42 (s, 1 H), 9.61 (s, 1 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 171.5, 137.9, 115.0, 19.8; IR(KBr) 3572, 3406, 3055, 2987, 1659, 1618, 1424, 897 cm^{-1}; MS (EI): m/z (relative intensity) = 100 (100), 99 (77), 84 (27), 83 (33), 70 (45), 68 (46), 53 (16); HRMS calcd for $C_4H_8N_2O$: 100.0636. found: 100.0633.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)[1,2,4]oxadiazole (3b) mp 110 °C, TLC, SiO_2, EtOAc/ hexanes 1 : 10, R_f = 0.21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3. 79 (s, 3 H), 7.38 (m, 2 H), 7.47 (m, 2 H), 8.10 (m, 2 H), 8.16 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.7, 168.7, 163.0, 137.9, 130.8, 129.7, 128.2, 126.8, 125.2, 115.1, 56.2; IR(KBr) 1712, 1608, 1553, 1422, 1362, 1265, 1093 cm^{-1}; MS (EI): m/z (relative intensity) = 288 (25), 286 (70), 135 (69), 133 (100), 90 (24); HRMS calcd for $C_{15}H_{11}N_2O_2Cl$: 286.0509. found: 286.0505.

3-(4-Chlorophenyl)-5-styryl[1,2,4]oxadiazole (3c) mp 125~126 °C, TLC, SiO_2, EtOAc/hexanes 1 : 10, R_f = 0.48. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, 1 H, *J* = 16 Hz), 7.46~7.70 (m, 7 H), 8.06 (d, 1 H, *J* = 16 Hz), 8.11 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.1, 168.6, 137.9, 134.9, 133.8, 131.4, 130.3, 129.6, 128.9, 128.1, 126.2; IR(KBr) 1712, 1643, 1090, 972 cm^{-1}; MS (EI): m/z (relative intensity) = 284 (13), 293 (25), 282 (39), 281 (63), 153 (30), 137 (65), 129 (80), 128 (100), 102 (64); HRMS calcd for $C_{16}H_{11}N_2OCl$: 282.0559. found: 282.0557.

3-(4-Bromophenyl)-5-phenyl[1,2,4]oxadiazole (3d) mp 98 °C, TLC, SiO_2, EtOAc/hexanes 1 : 10, R_f = 0.54. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26~7.65 (m, 5 H), 8.05 (m, 2 H), 8.21 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.7, 169.0, 133.6, 132.9, 129.9, 129.7, 128.9, 128.2, 126.6, 124.9; IR(KBr) 1712, 1604, 1558, 1423, 1073 cm^{-1}; MS (EI): m/z (relative intensity) = 303 (16), 302 (100), 300 (99), 199 (75), 197 (80), 105 (40), 90 (86), 77 (52); HRMS calcd for $C_{14}H_9N_2OBr$: 299.9898. found: 299.9889.

3-(4-Bromophenyl)-5-(4-methoxyphenyl)[1,2,4]oxadiazole (3e) mp 148~150 °C, TLC, SiO_2, EtOAc/ hexanes 1 : 10, R_f = 0.23. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 7.03 (m, 2 H), 7.64 (m, 2 H), 8.02 (m, 2 H), 8.14 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 176.5, 168.8, 164.0, 132.8, 130.8, 129.7, 126.9,

126.3, 117.4, 115.3, 56.2; IR(KBr) 1712, 1609, 1553, 1421, 1361, 1265, 1078 cm^{-1}; MS (EI): m/z (relative intensity) = 329, 197, 181, 135, 133 (100), 102, 90, 77; HRMS calcd for $C_{15}H_{11}N_2O_2Br$: 330.0003. found: 330.0018.

3-Isopropenyl-5-phenyl[1,2,4]oxadiazole (3f) mp 50 °C, TLC, SiO_2, EtOAc/hexanes 1 : 10, R_f = 0.58. ^1H NMR (500 MHz, $CDCl_3$) δ 2.23 (t, 3 H, *J* = 1.2 Hz), 5.53 (m, 1 H), 6.27 (m, 1 H), 7.52 (m, 2 H), 7.58 (m, 1 H), 8. 17 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.7, 170.5, 132.2, 130.6, 129.6, 128.7, 126.7, 118.9, 19.5; IR(KBr) 1712, 1659, 1612, 1564, 1423, 897 cm^{-1}; MS (EI): m/z (relative intensity) = 187, 186, 185, 106, 105 (100), 83, 77, 53; HRMS calcd for $C_{11}H_{10}N_2O$: 186.0793. found: 186.0788.

3-Isopropenyl-5-(4-methoxyphenyl)[1,2,4]oxadiazole (3g) mp 77~78 °C, TLC, SiO_2, EtOAc/hexanes 1 : 10, R_f = 0.31. ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 3.90 (s, 3 H), 5.51 (m, 1 H), 6.24 (m, 1 H), 7.01 (m, 2 H), 8.10 (m, 2 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.6, 170.4, 163.8, 132.6, 130.7, 121.8, 117.6, 115.1, 56.2, 19.5; IR(KBr) 1712, 1659, 1613, 1565, 1424, 1265, 897 cm^{-1}; MS (EI): m/z (relative intensity) 217 (3), 216 (25), 135 (99), 133 (100), 103 (12), 77 (13); HRMS calcd for $C_{12}H_{12}N_2O_2$: 216.0898. found: 216.0893.

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