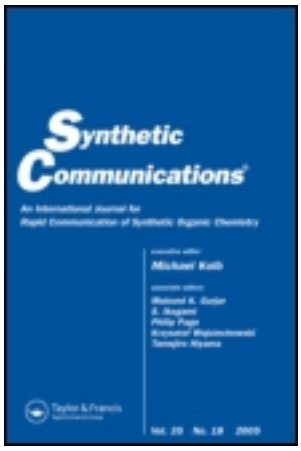

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HYPERVALENT IODINE IN SYNTHESIS. 75. A CONVENIENT SYNTHESIS OF OXADIAZOLES BY PALLADIUM-CATALYZED CARBONYLATION AND CYCLIZATION OF DIARYLIODONIUM SALTS AND AMIDOXIMES

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ABSTRACT

3,5-Disubstituted-1,2,4-oxadiazoles were prepared in one-pot procedure in moderate yields via the palladium-catalyzed carbonylation of diaryliodonium salts with amidoximes under one atmosphere of carbon monoxide followed by intramolecular dehydrative cyclization.

As part of our research interest in palladium-catalyzed reaction of diaryliodonium salts,[1] here we wish to report a convenient synthetic method for 3,5-disubstituted-1,2,4-oxadiazoles by palladium-catalyzed carbonylation and cyclyzation of diaryliodonium salts and amidoximes (Scheme 1).

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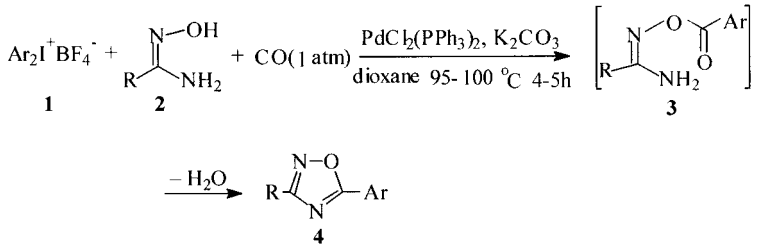

Scheme 1.

We examined the reaction of diphenyliodonium tetrafluoroborate and benzamidoxime under one atmosphere of carbon monoxide in the presence of palladium catalyst at 95–100°C in several alternative solvents including DMF, DME, dioxane and diglyme and found that dioxane was the most suitable solvent for this reaction. Diaryliodonium salt reacts with amidoxime under one atmosphere of carbon monoxide in the presence of palladium catalyst to form *O*-acylation product **3** which is subjected to a rapid intramolecular cyclo-dehydration at about 100°C in dioxane to give oxadiazole **4** in moderate yields. Several diaryliodonium salts having electron-donating or -withdrawing group (such as methyl, methoxy, chloro, nitro and bromo) and amidoximes were tested, the reaction is applicable for these substrates. The results are summarized in Table 1. All products were characterized by satisfactory ^{1}H NMR, IR and m.p. data.

In summary, we have described a convenient one-pot synthesis of 3,5-disubstituted-1,2,4-oxadiazoles by palladium-catalyzed carbonylation and cyclization of diaryliodonium salts and amidoximes. With the simple procedure and the mild reaction conditions, our method nicely complements existing ones.[2–9] Furthermore, the range of useful applications of palladium-catalyzed reaction of diaryliodonium salts in organic synthesis has been extended.

EXPERIMENTAL

Melting points were uncorrected. ^{1}H NMR data were recorded on PMK-60 spectrometer using $CC1_4$ as the solvent or on Avance 400 spectrometer using $CDC1_3$ as the solvent with TMS as an internal standard. IR spectra were determined on Vector 22 infrared spectrometer with KBr pallet. MS spectrum was recorded on HP5859B mass spectrometer. Elemental analysis was determined on EA1110.

Table 1. Preparation of 3,5-Disubstituted-1,2,4-oxadiazoles

Entry	Ar	R	Product	Yield (%)*
1	Ph	Ph	**4a**	72
2	*p*-Tol	Ph	**4b**	71
3	*p*-ClC_6H_4	Ph	**4c**	64
4	*p*-$CH_3OC_6H_4$	Ph	**4d**	62
5	*p*-BrC_6H_4	Ph	**4e**	56
6	*m*-$NO_2C_6H_4$	Ph	**4f**	78
7	Ph	*p*-$CH_3OC_6H_4$	**4g**	52
8	*p*-Tol	*p*-$CH_3OC_6H_4$	**4h**	61
9	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	**4i**	70
10	*p*-ClC_6H_4	*p*-$CH_3OC_6H_4$	**4j**	65
11	Ph	*p*-ClC_6H_4	**4k**	53
12	*p*-Tol	*p*-ClC_6H_4	**4l**	58
13	Ph	$PhCH_2$	**4m**	42

*Isolated yield based on diaryliodonium salt.

General procedure for preparation of 3,5-disubstituted oxadiazoles. A mixture of diaryliodonium salt **1** (1 mmol), amidoxime **2** (2 mmol), K_2CO_3 (2.5 mmol), $PdCl_2(PPh_3)_2$ (5 mol%) and dioxane (8 ml) was stirred under CO atmosphere (1 atm) at 95–100°C for 4–5 h. After cooling, the reaction mixture was diluted with saturated NH_4Cl aqueous (20 ml), and extracted with diethyl ether (3 × 15 ml). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate. After the removal of solvent under vacuum, the residue was chromatographed on silica gel plate using c-hexane/ethyl acetate (8:1) as a developer to give pure product **4**.

Physical and Spectroscopic Data

3,5-Diphenyl-1,2,4-oxadiazole 4a. M.p. 105–107°C (lit[10] 107–108°C). ^{1}H NMR (60 MHz, CCl_4) δ_H 7.3–7.65 (m, 6H), 7.95–8.30 (m, 4H). IR 1609, 1563, 1493, 1446, 1365, 1272, 1181, 1133, 1070, 1024, 972, 720, 795, 727, 688 cm^{-1}.

5-(4-Methylphenyl)-3-phenyl-1,2,4-oxadiazole 4b. M.p. 114–116°C (lit[10] 117–118°C). ^{1}H NMR (60 MHz, CCl_4) δ_H 2.67 (s, 3H), 7.0–7.4 (m, 5H), 7.85–8.3 (m, 4H). IR 1611, 1561, 1495, 1452, 1371, 1262, 1177, 1032, 905, 839, 748, 716, 687 cm^{-1}.

5-(4-Chlorophenyl)-3-phenyl-1,2,4-oxadiazole 4c. M.p. 122–124°C (lit[10] 126°C). ^{1}H NMR (60 MHz, CCl_4) δ_H 7.1–7.55 (m, 5H), 7.8–8.4 (m, 4H).

IR 1630, 1598, 1553, 1506, 1467, 1440, 1332, 1125, 1088, 1012, 895, 780, 695 cm^{-1}.

5-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazole 4d. M.p. 95–97°C (lit[11] 97–98°C). ^1H NMR (60 MHz, CCl_4) δ_H 3.8 (s, 3H), 6.87–7.10 (m), 7.3–7.6 (m, total 5H), 8.0–8.3 (m, 4H). IR 1614, 1503, 1472, 1442, 1421, 1370, 1262, 1180, 1137, 1024, 906, 832, 749, 711, 688 cm^{-1}.

5-(4-Bromophenyl)-3-phenyl-1,2,4-oxadiazole 4e. M.p. 112–114°C (lit[11] 113–114°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (m, 3H), 7.71 (d, 2H), 8.09 (d, 2H), 8.16 (m, 2H). IR 1605, 1554, 1484, 1445, 1362, 1272, 1134, 1011, 970, 913, 834, 743, 708, 690 cm^{-1}.

5-(3-Nitrophenyl)-phenyl-1,2,4-oxadiazole 4f. M.p. 150–152°C (lit[12] 152–153°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (m, 3H), 7.80 (m, 1H), 8.19 (m, 2H), 8.48 (m, 1H), 8.55 (m, 1H), 9.09 (m, 1H). IR 1620, 1525, 1443, 1352, 1270, 1145, 1072, 918, 818, 720, 686 cm^{-1}.

3-(4-Methoxyphenyl)-5-phenyl-1,2,4-oxadiazole 4g. M.p. 96–98°C (lit[8] 97–98°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.89 (s, 3H), 7.02 (m, 2H), 7.54–7.61 (m, 3H), 8.11 (m, 2H), 8.21 (m, 2H). IR 1599, 1555, 1469, 1331, 1294, 1178, 1149, 1125, 760, 693 cm^{-1}.

3-(4-Methoxyphenyl)-5-(4-methylphenyl)-1,2,4-oxadiazole 4h. M.p. 108–110°C (lit[13] 111.5–112°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.45 (m, 3H), 3.88 (s, 3H), 7.01 (d, 2H), 7.35 (d, 2H), 8.10 (m, 4H). IR 1612, 1561, 1504, 1423, 1358, 1254, 1171, 1033, 839, 760 cm^{-1}.

3,5-*bis*(4-Methoxyphenyl)-1,2,4-oxadiazole 4i. M.p. 130–132°C (lit[14] 132°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.86 (s, 6H), 6.95 (d, 4H), 7.59 (d, 4H). IR 1601, 1558, 1482, 1415, 1355, 1272, 1171, 1025, 825 cm^{-1}.

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole 4j. M.p. 138–139°C. ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.88 (s, 3H), 7.02 (d, 2H), 7.53 (d, 2H), 8.10 (d, 2H), 8.15 (d, 2H). IR 1609, 1558, 1490, 1420, 1369, 1253, 1174, 1094, 1032, 837, 759 cm^{-1}. MS *m*/*z* 288 ($M^+ + 2$, 33.23), 286 (M^+, 100), 149 (93.50), 139 (25.55), 111 (15.75), 106 (39.61). Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; N, 9.77. Found: C, 62.72; H, 3.87; N, 9.84.

3-(4-Chlorophenyl)-5-phenyl-1,2,4-oxadiazole 4k. M.p. 108–110°C) (lit[15] 108–109°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.50 (m, 2H), 7.56 (m, 2H), 7.61 (m, 1H), 8.13 (m, 2H), 8.21 (m, 2H). IR 1604, 1557, 1490, 1410, 1362, 1275, 1136, 1090, 1014, 966, 836, 741 cm^{-1}.

3-(4-Chlorophenyl)-5-(4-methylphenyl)-1,2,4-oxadiazole 4l. M.p. 126–128°C (lit[16] 129.5–130°C). ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.46 (s, 3H), 7.35 (m, 2H), 7.49 (m, 2H), 8.10 (m, 4H). IR 1592, 1562, 1501, 1411, 1363, 1274, 1136, 1091, 1014, 839, 754 cm^{-1}.

5-Phenyl-3-phenylmethyl-1,2,4-oxadiazole 4m. M.p. 82–84°C (lit[17] 81–82°C). ^1H NMR (60 MHz, CCl_4) δ_H 4.0 (s, 2H), 7.0–7.6 (m, 8H), 7.9–8.25 (m, 2H). IR 1608, 1561, 1451, 1363, 730, 712, 692 cm^{-1}.

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