Synthesis of 3-Phenoxy-1,3-dihydro-1-isobenzofuranones by Palladium-Catalyzed Carbonylative Cyclization of 2-Bromobenzaldehyde with Phenols

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2-Bromobenzaldehyde reacts with phenols in acetonitrile under carbon monoxide pressure in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride to afford the corresponding 3-phenoxy-1,3-dihydro-1-isobenzofuranones in high yields.

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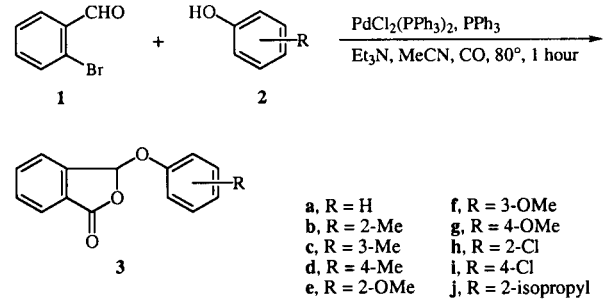
The structural core of heterocyclic compounds play an important role as an intermediate for the design of complex organocyclic molecules containing heteroatoms which exert biological activities, many heterocyclic compounds being synthesized by a remarkable catalytic action of transition metal catalysts [1]. The synthesis of phthalides also has been attempted by the aid of transition metals [2-13]. Recently, we developed and reported a transition metal-catalyzed synthetic method for *N*-heterocyclic compounds such as indoles [14], isoindolinones [15], β-lactams [16], and quinolines [17]. In connection with present report, we also carried out successfully a new palladium-catalyzed approach for the synthesis of 3-substituted phthalides from 2-bromobenzaldehyde and nucleophilic precursors such as aliphatic primary alcohols [18], 1,3-dicarbonyl compounds [19], and sodium alkanoates [20]. The key step of all reactions seemed to be the coordination of the oxygen of the formyl group adjacent to the palladium of the aroylpalladium intermediate followed by nucleophilic attack by nucleophiles. This finding prompted us to explore the similar palladium-catalyzed carbonylative cyclization of 2-bromobenzaldehyde with other nucleophiles for the formation of 3-substituted phthalides. We here report a new approach for the synthesis of 3-phenoxy phthalides (3-phenoxy-1,3-dihydro-1-isobenzofuranones) from 2-bromobenzaldehyde and phenols *via* palladium-catalyzed carbonylative cyclization in which phenols work as nucleophiles.

We employed similar catalytic systems [$PdCl_2(PPh_3)_2$-PPh_3-base-solvent] as has been used in our recent palladium-catalyzed synthesis of 3-substituted phthalides [18-20]. Treatment of equimolar amounts of 2-bromobenzaldehyde (**1**) and phenols **2** in acetonitrile in the presence of bis(triphenylphosphine)palladium(II) chloride (5 mole %) and triphenylphosphine together with triethylamine under carbon monoxide pressure afforded the corresponding carbonylative cyclized and coupling products, 3-phenoxy-1,3-dihydro-1-isobenzofuranones **3** in high yields. The reaction was performed until the starting 2-bromobenzaldehyde (**1**) disappeared on thin layer chromatography, generally, the reaction time being within 1 hour (Scheme 1). In the synthesis of 3-alkoxy phthalides from 2-bromobenzaldehyde (**1**) and aliphatic primary alcohols [18], the alcohols were used as both solvent and nucleophilic counterpart. However, in the present reaction, when the phenols were introduced as both solvent and reaction counterpart, the reaction has a drawback which is wasteful of a large amount of expensive phenols and difficult to separate the product from the reaction mixture. Thus, among solvents examined, acetonitrile revealed to be the most effective for the formation of the phthalides.

Scheme 1



The present carbonylative cyclization could also be applied to many phenols **2b-2j**, several representative results being summarized in Table 1. Table 1 indicates that the structural and electronic natures of the substituents on phenols showed no decisive influence on the formation of the corresponding 3-phenoxy-1,3-dihydro-1-isobenzofuranones **3**. With phenols, having both electron-donating **2b-2g** and electron-withdrawing **2h-2j** characters, the reaction resulted in high yields of 3-phenoxy-1,3-dihydro-1-isobenzofuranones **3** without the formation of detectable side-products. In the case of sterically bulky 2-isopropylphenol (**2j**), the reaction also proceeded well to give the corresponding phthalide **3j** in high yield. All phthalides described above were obtained as cotton candy solids after general chromatography separation and recrystallization except for 3-(2-isopropylphenoxy)-1,3-dihydro-1-isobenzofuranone (**3j**), which was obtained as a colorless crystalline solid.

Table 1

Palladium-Catalyzed Synthesis of 3-Phenoxy-1,3-dihydro-1-isobenzofuranones **3** [a]

Phenol	Product	Isolated yield
2a	**3a**	79
2b	**3b**	82
2c	**3c**	83
2d	**3d**	83
2e	**3e**	79
2f	**3f**	93
2g	**3g**	85
2h	**3h**	78
2i	**3i**	88
2j	**3j**	82

[a] All reactions were carried out with 2-bromobenzaldehyde (2 mmoles), phenol (2 mmoles), bis(triphenylphosphine)palladium(II) chloride (0.1 mmole), triphenylphosphine (0.2 mmole), and triethylamine (5 mmoles) under carbon monoxide (20 atm) in dry acetonitrile (10 ml) at 80° for 1 hour.

Although the exact nature of the reaction is still obscure, the reaction seems to be proceeded as has been proposed in the palladium-catalyzed synthesis of 3-substituted phthalides [18-20].

EXPERIMENTAL

The ^1H (300 MHz) and ^{13}C (75.5 MHz) nmr spectra were recorded on a Varian Unity Plus 300 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported in δ units downfield from tetramethylsilane. The ir spectra were recorded on a Galaxy Series FT-IR 7000M spectrophotometer as potassium bromide pellets. Electron impact mass spectra were obtained on a shimadzu QP-1000 spectrometer. Melting points were determined on a Thomas Scientific capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out *via* column chromatography (silica gel 60 HF_{254}, Merck). Commercially available organic and inorganic compounds were used without further purification except for solvents, which was distilled prior to use. Bis(triphenylphosphine)palladium(II) chloride was synthesized as reported previously [21].

General Procedure for Palladium-Catalyzed Synthesis of 3-Phenoxy-1,3-dihydro-1-isobenzofuranones **3**.

A mixture of 2-bromobenzaldehyde (370 mg, 2 mmoles), phenol (2 mmoles), bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmole), triphenylphosphine (53 mg, 0.2 mmole), triethylamine (0.5 ml, 5 mmoles), and dry acetonitrile (10 ml) was placed in a 50 ml stainless steel autoclave. After the system was flushed and then pressurized with carbon monoxide to 20 atmospheres, the mixture was stirred at 80° for 1 hour. The reaction mixture was filtered through a short column (silica gel, chloroform) and poured into brine (50 ml). The organic layer was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a crude mixture which was separated by column chromatography using chloroform-hexane mixture as an eluent to give the corresponding 3-phenoxy-1,3-dihydro-1-isobenzofuranones. The products obtained by the above procedure were fully characterized spectroscopically as shown below.

3-Phenoxy-1,3-dihydro-1-isobenzofuranone (**3a**).

This compound was obtained as white solid, mp 117-118° (from chloroform-hexane); ir (potassium bromide): ν 1775 (C=O), cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.86 (s, 1H, CH), 7.14 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.35-7.40 (m, 2H), 7.64-7.72 (m, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 99.6, 117.1, 123.7, 123.8, 125.6, 126.8, 129.8, 131.2, 134.7, 144.5, 156.6, 168.1; ms: m/z (%) 226 (M^+, 3), 133 (100), 105 (12), 77 (23), 65 (10), 51 (18).
Anal. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.19; H, 4.40.

3-(2-Methylphenoxy)-1,3-dihydro-1-isobenzofuranone (**3b**).

This compound was obtained as white solid, mp 115-116° (from chloroform-hexane); ir (potassium bromide): ν 1796 (C=O), cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 6.80 (s, 1H, CH), 7.05 (t, J = 7.5 Hz, 1H), 7.20-7.27 (m, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.64-7.72 (m, 2H), 7.79 (t, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 16.2, 100.3, 115.6, 123.5, 123.6, 125.5, 126.8, 127.2, 127.8, 131.0, 131.1, 134.7, 144.7, 155.1, 168.2; ms: m/z (%) 240 (M^+, 5), 149 (22), 133 (100), 105 (17), 77 (34).
Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.17; H, 5.11

3-(3-Methylphenoxy)-1,3-dihydro-1-isobenzofuranone (**3c**).

This compound was obtained as white solid, mp 98-99° (from chloroform-hexane); ir (potassium bromide): ν 1784 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 3H, CH_3), 6.81 (s, 1H, CH), 6.94 (d, J = 7.2 Hz, 1H), 7.02-7.06 (m, 2H), 7.22-7.26 (m, 1H), 7.62-7.69 (m, 2H), 7.76 (t, J = 7.2 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 21.5, 99.7, 114.0, 117.7, 123.8, 124.5, 125.6, 126.8, 129.5, 131.2, 134.7, 140.0, 144.6, 156.7, 168.2; ms: m/z (%) 240 (M^+, 6), 133 (100), 132 (85), 104 (8), 77 (14).
Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.15; H, 5.18.

3-(4-Methylphenoxy)-1,3-dihydro-1-isobenzofuranone (**3d**).

This compound was obtained as white solid, mp 118-119° (from chloroform-hexane); ir (potassium bromide): ν 1790 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, CH_3), 6.80 (s, 1H, CH), 7.10-7.17 (m, 4H), 7.61-7.79 (m, 3H), 7.92 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 20.6, 100.0, 117.1, 123.7, 125.5, 126.8, 130.1, 131.1, 133.2, 134.6, 144.5, 154.5, 168.2; ms: m/z (%) 240 (M^+, 4), 133 (100), 105 (9), 77 (15).
Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.26; H, 5.16.

3-(2-Methoxyphenoxy)-1,3-dihydro-1-isobenzofuranone (**3e**).

This compound was obtained as white solid, mp 130-131° (from chloroform-hexane); ir (potassium bromide): ν 1782 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.91 (s, 3H, OCH_3), 6.80 (s, 1H, CH), 6.93-6.99 (m, 2H), 7.11-7.17 (m, 1H), 7.32-7.35 (m, 1H), 7.61-7.66 (m, 1H), 7.73-7.83 (m, 2H), 7.91 (d, J = 7.8 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 55.8, 101.3, 112.3, 120.3, 121.0, 124.0, 125.2, 125.4, 126.9, 131.1, 134.6, 144.6, 145.5, 150.4, 168.3; ms: m/z (%) 256 (M^+, 9), 133 (100), 105 (8), 77 (10).

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.45; H, 4.78.

3-(3-Methoxyphenoxy)-1,3-dihydro-1-isobenzofuranone (**3f**).

This compound was obtained as white solid, mp 80-81° (from chloroform-hexane); ir (potassium bromide): ν 1794 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.81 (s, 3H, OCH_3), 6.99 (dd, J = 2.4 and 8.4 Hz, 1H), 6.77 (t, J = 2.4 Hz, 1H), 6.82-6.86 (m, 1H), 6.84 (s, 1H, CH), 7.26 (t, J = 8.1 Hz, 1H), 7.63-7.71 (m, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 55.4, 99.5, 103.3, 108.9, 109.4, 123.7, 125.5, 126.7, 130.2, 131.1, 134.7, 144.4, 157.7, 160.8, 168.1; ms: m/z (%) 256 (M^+, 9), 133 (100), 105 (9), 77 (13).
Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.34; H, 4.82.

3-(4-Methoxyphenoxy)-1,3-dihydro-1-isobenzofuranone (**3g**).

This compound was obtained as white solid, mp 110-111° (from chloroform-hexane); ir (potassium bromide): ν 1790 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.79 (s, 3H, OCH_3), 6.74 (s, 1H, CH), 6.87 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.61-7.79 (m, 3H), 7.91 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 55.6, 100.7, 114.6, 118.8, 123.7, 125.5, 126.8, 131.1, 134.6, 144.5, 150.4, 156.0, 168.2; ms: m/z (%) 256 (M^+, 10), 133 (100), 105 (6), 7 (3).
Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.31; H, 4.72. Found: C, 70.11; H, 4.94.

3-(2-Chlorophenoxy)-1,3-dihydro-1-isobenzofuranone (**3h**).

This compound was obtained as white solid, mp 155-156° (from chloroform-hexane); ir (potassium bromide): ν 1798 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.75 (s, 1H, CH), 7.12 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.42-7.50 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.77-7.84 (m, 2H), 7.94 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 100.8, 119.7, 124.1, 124.8, 125.2, 125.6, 126.7, 128.1, 130.5, 131.3, 134.8, 144.2, 152.4, 168.0; ms: m/z (%) 262 (M^++2, 0.8), 260 (M^+, 2), 215 (1), 133 (100), 105 (7), 77 (5).
Anal. Calcd. for $C_{14}H_9O_3Cl$: C, 64.51; H, 3.48. Found: C, 64.61; H, 3.61.

3-(4-Chlorophenoxy)-1,3-dihydro-1-isobenzofuranone (**3i**).

This compound was obtained as white solid, mp 160-161° (from chloroform-hexane); ir (potassium bromide): ν 1796 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.79 (s, 1H, CH), 7.14-7.19 (m, 2H), 7.29-7.34 (m, 2H), 7.64-7.71 (m, 2H), 7.76-7.81 (m, 1H), 7.94 (d, J = 7.5 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 99.5, 118.5, 123.7, 125.7, 126.7, 128.9, 129.7, 131.3, 134.8, 144.1, 155.1, 167.9; ms: m/z (%) 262 (M^++2, 1), 260 (M^+, 3), 215 (2), 133 (100), 105 (7), 77 (4).
Anal. Calcd. for $C_{14}H_9O_3Cl$: C, 64.51; H, 3.48. Found: C, 64.47; H, 3.51.

3-(2-Isopropylphenoxy)-1,3-dihydro-1-isobenzofuranone (**3j**).

This compound was obtained as colorless solid, mp 98-99° (from chloroform-hexane); ir (potassium bromide): ν 1780 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20 (d, J = 6.8 Hz, 3H, CH_3), 1.26 (d, J = 7.2 Hz, 3H, CH_3), 3.34 (hep, J = 6.8 Hz, 1H, CH), 6.82 (s, 1H, CH), 7.12 (t, J = 7.6 Hz, 1H), 7.22-7.30 (m, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.65-7.70 (m, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 22.7, 23.0, 26.9, 100.3, 115.6, 123.6, 123.9, 125.7, 126.6, 126.9, 127.0, 131.2, 134.8, 138.1, 144.1, 154.2, 168.2; ms: m/z (%) 268 (M^+, 5), 133 (100), 105 (5), 77 (9).
Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.09; H, 6.08

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