A Facile Synthesis of 3-Alkoxy Phthalides by the Palladium Catalyzed Carbonylative Cyclization of *o*-Bromobenzaldehyde

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The palladium catalyzed carbonylative cyclization of *o*-bromobenzaldehyde **1** in alcoholic solution gave 3-alkoxyphthalides **3a-e** in 61-85% isolated yields *via* intramolecular cyclization induced by the coordinated formyl group on the palladium.

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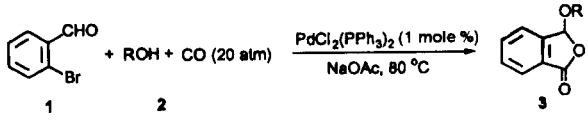
Compounds containing the phthalide moiety are known to be the constituents of various naturally occuring substanes [1-3]. Phthalides have also played an important role as intermediates for the synthesis of several natural products of complex structure [4]. Various methods [5], respectively palladium catalyzed carboannulations [6] and heteroannulation reactions [7], are known for the synthesis of phthalide-containing structures. Recently, Uozumi *et. al.* reported a palladium-catalyzed formation of 3-alkylidenephthalides from *o*-bromoacetophenone derivatives and CO [8]. This route was an intramolecular reaction involving an enol intermediate to form the product.

In this note we report a very convenient and general method for the carbonylative cyclization of *o*-bromobenzaldehyde (**1**) through palladium-catalyzed reactions which lead to the 3-alkoxyphthalides (**3**). This synthesis of a phthalide-containing structure from carbonylative cyclization of *o*-bromobenzaldehyde (**1**) mediated through a palladium catalyst in alcoholic solution has not yet been reported [9].

The reactions were usually carried out by heating a mixture of *o*-bromobenzaldehyde (**1**) with a base, alcohol (**2**), and triphenylphosphine in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ under pressure of CO for 8 hours led to the formation of 3-alkoxyphthalides (**3**) in good yields (Scheme 1).

Scheme 1



2, 3	R
a	CH_3
b	CH_2CH_3
c	$CH_2CH_2CH_3$
d	$CH_2CH_2CH_2CH_3$
e	$CH(CH_3)_2$
f	$C(CH_3)_3$

To optimize reaction conditions the effects of the CO pressure, base, and catalyst type were examined. The model system used in this study was the formation of 3-ethoxyphthalide (**3b**) from *o*-bromobenzaldehyde (**1**) and ethanol (**2b**). The results are listed in Table 1. As shown in Table 1, the yields of products depended significantly on the pressure of carbon monoxide and showed the highest at 20 atmospheres. The yield was not varied when the reaction time was prolonged in run 3. Among bases employed in the reaction, sodium acetate and triethylamine gave the same yields and in the case of potassium carbonate the yield was greatly decreased by its low solubility in ethanol. The nature of the catalyst precursor also greatly effects the reaction; $PdCl_2(PPh_3)_2$ + PPh_3 was found to be the most effective precursor. Other palladium complexes such as $PdCl_2(PPh_3)_2$, $PdCl_2$ + PPh_3 and $Pd(OAc)_2$ + PPh_3 as well as $Pd(PPh_3)_4$ showed only low catalytic activity.

Various aliphatic alcohols **2a**, **2c-e** were successfully utilized for carbonylative cyclization (see Table 2) and in the case of primary alcohols such as ethanol, 1-propanol, and *n*-butanol the yields of the products **3b-d** were fair to excellent. Methanol (**2a**) gave a lower yield of product **3a** because of its low nucleophilicity. Steric bulkiness of alcohol also influences the yield of the product; the sec-

Table 1

Reaction Conditions on the Palladium Catalyzed Synthesis of 3-Ethoxy-1-phthalides **2b** [a]

Run	Base	P_{CO} (atm) [a]	Yield (%) [b]
1	NaOAc	20	84
2	NEt_3	20	84
3	K_2CO_3	20	22
4	NaOAc	14	73
5	NaOAc	27	67
6 [c]	NaOAc	20	73
7 [d]	NaOAc	20	28
8 [e]	NaOAc	20	67
9 [f]	NaOAc	20	28

[a] The procedure is: into an autoclave, *o*-bromobenzaldehyde (2 mmoles), $PdCl_2(PPh_3)_2$ (0.02 mmole) + PPh_3(0.08 mmole), anhydrous base (2 mmoles), and ethanol (15 ml) were charged and pressured with CO at 80° for 8 hours at room temperature. [b] Isolated yields. [c] $PdCl_2(PPh_3)_2$ (0.02 mmole), no PPh_3. [d] $PdCl_2$ (0.02 mmole) + PPh_3 (0.04 mmole). [e] $Pd(OAc)_2$ (0.02 mmole) + PPh_3 (0.08 mmole). [f] $Pd(PPh_3)_4$ (0.02 mmole).

ondary and tertiary alcohols **2e**, **2f** give lower yields than a primary alcohol.

Table 2

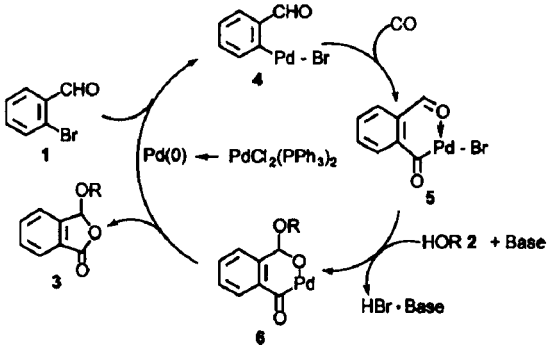
Carbonylative Cyclizations of *o*-Bromobenzaldehyde with Alcohols

Run	Alcohol	Product	Yield (%) [a]
1	**2a**	**3a**	61
2	**2b**	**3b**	84
3	**2c**	**3c**	83
4	**2d**	**3d**	85
5	**2e**	**3e**	60
6	**2f**	**3f**	trace

[a] Isolated yields.

We believe that this carbonylative cyclization process as shown in Scheme 2: (1) reduction of $PdCl_2(PPh_3)_2$ to the actual catalyst Pd(0); (2) oxidative addition of the aryl halide to Pd(0) [10]; (3) arylpalladium coordination to the CO and then insertion of the CO to form an acylpalladium complex **5**; (4) addition to alcohol into the formyl group to form a palladium intermediate **6** and then elimination of hydrogen bromide by base; and (5) regeneration of the Pd(0) catalyst by reductive elimination to the 3-alkoxy phthalide **3** (Scheme 2).

Scheme 2



The formyl group seemed to play a significant role in the formation of 3-alkoxyphthalides **3**. In the acylpalladium complex **5**, the fifth coordination site [11] may be blocked by the oxygen of the formyl group. Dissociation of triphenylphosphine could free a coordinaton site. This may make the nucleophilic attack of alcohol more facile on the carbon of the formyl group. Although a formyl group is not a good ligand for palladium, the close proximity in which it is held to palladium could greatly enhance its coordinative ability. This is supported by the palladium-catalyzed carbonylation of *o*-iodobenzyl alcohol [12] and the reaction of an iridium complex with alkyl halides [13].

We have described the first successful palladium-catalyzed reaction for the synthesis of phthalides from readily available starting materials. The method is easy to carry out under relatively mild conditions, with catalytic amounts of palladium reagents, and does not involve any toxic reagents. The process is thus amenable to the synthesis of various phthalide-containing naturally occuring substances and compounds of biological interest.

EXPERIMENTAL

Melting points were determined on a Yamato Model MP-21 and are uncorrected. Infrared (ir) spectra were recorded on a Mattson Galaxy 6030 E FT-IR spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz for ^1H nmr and 75.5 MHz for ^{13}C nmr. Electron impact mass spectra (ms) were obtained on a Shimadzu-QP 1000 spectrometer. Elemental analyses were performed by the Korea Organic Chemical Research Center, Seoul and a Carlo Erba 1108 Elemental analyzer.

General Procedure for the Preparation of **3**.

Into an autoclave, *o*-bromobenzaldehyde **1** (2 mmoles), $PdCl_2(PPh_3)_2$ (0.02 mmole), alcohol **2** (15 ml), anhydrous sodium acetate (2 mmoles) and triphenylphosphine (0.02 g) were charged and pressured with carbon monoxide to 20 atmospheres. The contents were heated to 80° for 8 hours. After the usual workup, the product was isolated by preparative thin layer chromatography (silica gel, *n*-hexane:ethyl acetate = 10:1 v/v) and purified by recrystalization (ether-*n*-hexane).

3-Methoxyphthalide (**3a**).

This compound had mp 40-42°; ir (potassium bromide): ν 1775 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.51 (s, 3H, OCH_3), 6.20 (s, 1H, CH), 7.46-7.75 (m, 4H, Ar-H); ^{13}C nmr (deuteriochloroform): ppm 56.4, 102.9, 123.2, 125.0, 126.8, 130.6, 134.2, 144.4, 166.3; ms: m/z (%) 164 (3, M^+), 163 (12), 162 (10), 149 (4), 148 (3), 133 (100), 132 (91), 120 (29), 119 (29), 118 (15), 106 (5), 105 (51), 104 (38), 103 (13).

Anal. Calcd. for $C_9H_8O_3$: C, 65.87; H, 4.88. Found: C, 65.96; H, 4.92.

3-Ethoxyphthalide (**3b**).

This compound had mp 68°; ir (potassium bromide): ν 1784 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 7.1, 3H, CH_3), 3.84 (m, J = 10.6, J = 7.06, decoupled, 1H), 3.96 (m, J = 10.6, J = 7.06, decoupled, 1H), 6.33 (s, 1H, CH), 7.50-7.80 (m, 4H, Ar-H); ^{13}C nmr (deuteriochloroform): ppm 15.0, 65.8, 102.3, 123.4, 125.3, 127.1, 130.7, 134.3, 144.9, 166.7; ms: m/z (%) 177 (M^+-1, 3), 176 (M^+-2, 3), 150 (5), 149 (16), 148 (17), 134 (31), 133 (94), 132 (100), 106 (7), 105 (50), 104 (49), 103 (10).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.42; H. 5.69. Found: C, 67.56; H. 5.79.

3-Propylphthalide (**3c**).

This compound had ir (potassium bromide): ν 1774 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.96 (t, 3H, CH_3), 1.68 (m, 2H, CH_2), 3.75 (m, 1H), 3.84 (m, 1H), 6.31 (s, 1H, CH), 7.57-7.89 (m, 4H, Ar-H); ^{13}C nmr (deuteriochloroform): ppm 10.4, 22.9, 71.9, 102.6, 123.4, 125.4, 127.4, 130.8, 134.3, 145.2,

168.7; ms: m/z (%) 149 (13), 148 (17), 147 (12), 146 (15), 135 (2), 134 (10), 133 (100), 132 (89), 105 (38), 104 (32), 103 (6).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.77; H, 6.25. Found: C, 68.83; H, 6.21.

3-Butylphthalide (**3d**).

This compound had ir (potassium bromide): ν 1773 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.89 (t, J = 10.1, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 3.75 (dt, J = 14.0, J = 9.7, 1H), 3.86 (dt, J = 14.0, J = 9.7, 1H), 6.33 (s, 1H, CH), 7.50-7.80 (m, 4H, Ar-H); ^{13}C nmr (deuteriochloroform): ppm 13.6, 19.0, 31.4, 69.9, 102.4, 123.3, 125.2, 127.1, 130.6, 134.2, 145.0, 168.6; ms: m/z (%) 206 (1, M^+), 205 (1), 149 (6), 148 (5), 134 (10), 133 (100), 132 (94), 105 (34), 104 (32).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.87; H, 6.86. Found: C, 69.94; H, 6.74.

3-Propylphthalide (**3e**).

This compound had mp 58-60°; ir (potassium bromide): ν 1772 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.28 (d, 6H, $2CH_3$), 4.18 (m, 1H, OCH), 6.38 (s, 1H, CH), 7.49-7.80 (m, 4H, Ar-H); ^{13}C nmr (deuteriochloroform): ppm 22.0, 23.1, 73.6, 101.3, 123.2, 125.1, 127.0, 130.6, 134.2, 145.4, 168.8; ms: m/z (%) 194 (2, M^++2), 193 (6, M^++1), 192 (1, M^+), 151 (6), 150 (3), 149 (37), 148 (41), 147 (19), 134 (17), 133 (100), 132 (26), 107 (8), 106 (12), 105 (88), 104 (15), 103 (3).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.77; H, 6.25. Found: C, 68.88; H, 6.36.

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