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Received August 6, 1998

2-Bromobenzaldehyde reacts with sodium alkanoates in acetonitrile under carbon monoxide pressure in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride to afford the corresponding 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates in moderate to good yields.

*J. Heterocyclic Chem.*, **36**, 289 (1999).

Transition metal-catalyzed heteroannulation provides a useful and convenient tool for the construction of structural core of complex organocyclic molecules, many heterocyclic compounds being synthesized by a remarkable catalytic action of catalysts [1]. The synthesis of phthalides also has been attempted by the aid of transition metals [2-13] since phthalides play an important role as an intermediate for the synthesis of biological active compounds [14,15]. As our series of studies on transition metal-catalyzed synthesis of heterocyclic compounds [16,17], recently, we also developed and reported a synthetic method for the formation of 3-substituted phthalides from 2-bromobenzaldehyde and alcohols [18] as well as 1,3-dicarbonyl compounds [19]. It was suggested that both reactions proceeded *via* an organometallic carbonylative cyclization process in which alcohols and 1,3-dicarbonyl compounds worked as nucleophiles. This finding prompted us to explore a similar palladium-catalyzed cyclization of 2-bromobenzaldehyde with other nucleophiles for the formation of 3-substituted phthalides. We here report another approach for the synthesis of 3-substituted phthalides from 2-bromobenzaldehyde and sodium alkanoates *via* palladium-catalyzed carbonylative cyclization.

The several results of carbonylative cyclization and coupling between 2-bromobenzaldehyde (**1**) and sodium acetate (**2a**) are summarized in Table 1. Treatment of 2-bromobenzaldehyde (**1**) with two equivalents of sodium acetate (**2a**) in acetonitrile under 20 atmospheres of carbon monoxide in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (5 mol% based on **1**) and triphenylphosphine (10 mol% based on **1**) at 80° for 18 hours afforded 3-oxo-1,3-dihydro-1-isobenzofuranyl acetate (**3a**) in 35% yield (Scheme 1). The yield of **3a** was slightly affected by the molar ratio of **2a** to **1**, the molar ratio of 5 being shown to be best for obtaining **3a** (44% yield). When *N,N*-dimethylformamide was used as the solvent in place of acetonitrile, the reaction did not proceed at all toward the formation of **3a**. Potassium acetate could be alternatively used as a coupling counterpart, but the yield of **3a** was lower than when sodium acetate (**2a**) was used.

The reaction system could also be applied to many sodium alkanoate **2b-2f**, several representative results being summarized in Table 1. Table 1 indicates that the structural nature of

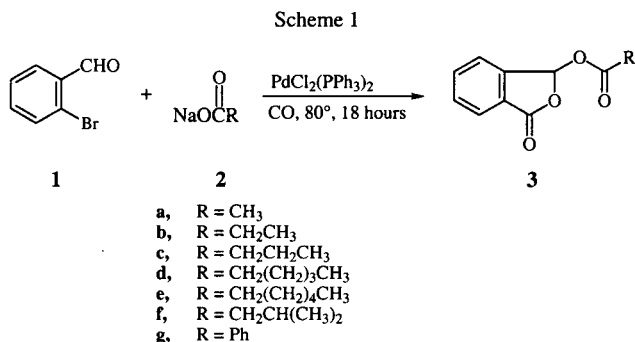


Table 1  
Palladium-Catalyzed Synthesis of 3-Oxo-1,3-dihydro-1-isobenzofuranyl Alkanoates **3** [a]

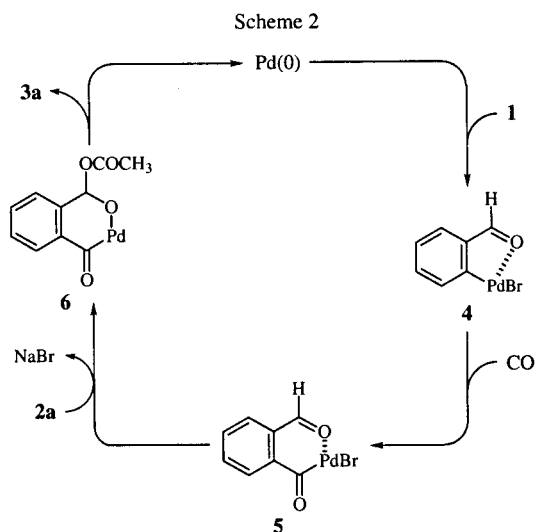
Sodium alkanoate	Product	Isolated yield [b]
<b>2a</b> [c]	<b>3a</b>	35
<b>2a</b>	<b>3a</b>	44
<b>2a</b> [d]	<b>3a</b>	0
[e]	<b>3a</b>	31
<b>2b</b>	<b>3b</b>	55
<b>2c</b>	<b>3c</b>	62
<b>2d</b>	<b>3d</b>	58
<b>2e</b>	<b>3e</b>	67
<b>2f</b>	<b>3f</b>	31
<b>2g</b>	<b>3g</b>	35

[a] All reactions were carried out with 2-bromobenzaldehyde (2 mmoles), sodium alkanoate (10 mmoles), bis(triphenylphosphine)palladium(II) chloride (0.1 mmole), and triphenylphosphine (0.2 mmole) under carbon monoxide (20 atmospheres) in solvent (10 ml) at 80° for 18 hours unless otherwise stated. [b] Based on 2-bromobenzaldehyde. [c] Sodium acetate (4 mmoles) was used. [d] In *N,N*-dimethylformamide. [e] Potassium acetate was used in place of sodium acetate.

alkyl moiety of sodium alkanoates **2b-2f** showed no decisive influence on the formation of the corresponding 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates **3a-3f**. However, the reactions with sodium alkanoates such as sodium propionate (**2b**), sodium butanoate (**2c**), sodium hexanoate (**2d**) and sodium heptanoate (**2e**) generally resulted in higher yields of the corresponding 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates **3b-3e** than when sodium 3-methylbutanoate (**2f**) was used. In the case of sodium benzoate (**2g**), the yield of

the corresponding product **3g** was similar as has been observed in the reaction with sodium 3-methylbutanoate (**2f**). This result indicates that the present cyclization and coupling was not affected by the type of organic moiety of the carboxylic acid sodium salts (**2**) except for sodium cinnamate which resulted in the formation of many unseparatory unidentified compounds.

Although the details of the reaction pathway are not yet fully understood, a plausible pathway is presented in Scheme 2. Oxidative addition of the carbon-bromide bond of 2-bromobenzaldehyde (**1**) to palladium(0) produces an arylpalladium(II) complex **4**, where carbon monoxide coordination to palladium and then aryl migration from palladium to the carbon of carbon monoxide occurs to give an aroylpalladium(II) intermediate **5**. This is followed by the nucleophilic attack of sodium acetate (**2a**) on the carbon of the formyl group and the coincident elimination of sodium bromide to give aroylalkoxypalladium(II) intermediate **6** which can reductively eliminate to afford 3-oxo-1,3-dihydro-1-isobenzofuranyl acetate (**3a**). A similar catalytic process has already been proposed in palladium-catalyzed synthesis of 3-substituted phthalides from 2-bromobenzaldehyde and nucleophiles [18,19].



The  $^1\text{H}$  (300 MHz) and  $^{13}\text{C}$  (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  $\delta$  units downfield from tetramethylsilane. Infrared spectra were recorded on a Galaxy Series FT-IR 7000M spectrophotometer. 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<sub>254</sub>, Merck). Commercially available organic and inorganic compounds were used without further purification.

Typical Procedure for Palladium-Catalyzed Synthesis of 3-Oxo-1,3-dihydro-1-isobenzofuranyl Alkanoates.

A mixture of 2-bromobenzaldehyde (370 mg, 2 mmoles), sodium acetate (820 mg, 10 mmoles), bis(triphenylphosphine)-palladium(II) chloride (70 mg, 0.1 mmole), triphenylphosphine (53 mg, 0.2 mmole), and anhydrous 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 18 hours. 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 an oil which was separated by column chromatography (ethyl acetate/hexane = 1/5) to give 3-oxo-1,3-dihydro-1-isobenzofuranyl acetate (171 mg, 44% yield based on 2-bromobenzaldehyde). The products obtained by the above procedure were fully characterized spectroscopically as shown below.

3-Oxo-1,3-dihydro-1-isobenzofuranyl Acetate.

This compound was obtained as colorless solid, mp 61-62°; ir (potassium bromide):  $\nu$  3067, 2986, 1782, 1053, 754  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  2.20 (s, 3H), 7.43 (s, 1H), 7.60-7.69 (m, 2H), 7.77 (t,  $J = 7.8$  Hz, 1H), 7.93 (d,  $J = 7.5$  Hz, 1H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  20.8, 92.6, 123.6, 125.8, 126.5, 131.3, 134.9, 144.3, 167.9, 169.5; ms:  $m/z$  (%) 192 ( $\text{M}^+$ , 0.7), 149 (22), 132 (100), 104 (43), 76 (30).

Anal. Calcd. for  $\text{C}_{10}\text{H}_8\text{O}_4$ : C, 62.50; H, 4.20. Found: C, 62.58; H, 3.92.

3-Oxo-1,3-dihydro-1-isobenzofuranyl Propionate.

This compound was obtained as colorless solid, mp 74-75°; ir (potassium bromide):  $\nu$  3001, 2944, 1765, 1057, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  1.21 (t,  $J = 6.9$  Hz, 3H), 2.47 (q,  $J = 6.9$  Hz, 2H), 7.46 (s, 1H), 7.61-7.69 (m, 2H), 7.78 (t,  $J = 7.8$  Hz, 1H), 7.93 (d,  $J = 7.8$  Hz, 1H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  8.5, 27.2, 92.5, 123.4, 125.5, 126.3, 131.1, 134.7, 144.2, 167.8, 172.8; ms:  $m/z$  (%) 149 ( $\text{M}^+ - 57$ , 20), 133 (100), 104 (23), 76 (21), 57 (19).

Anal. Calcd. for  $\text{C}_{11}\text{H}_{10}\text{O}_4$ : C, 64.07; H, 4.89. Found: C, 63.78; H, 5.16.

3-Oxo-1,3-dihydro-1-isobenzofuranyl Butyrate.

This compound was obtained as colorless solid, mp 53-54°; ir (potassium bromide):  $\nu$  2971, 1777, 1053, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  0.92 (t,  $J = 6.9$  Hz, 3H), 1.59-1.71 (m, 2H), 2.36 (t,  $J = 6.9$  Hz, 2H), 7.39 (s, 1H), 7.54-7.63 (m, 2H), 7.71 (dd,  $J = 6.0$  and 7.8 Hz, 1H), 7.86 (d,  $J = 6.6$  Hz, 1H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  13.3, 17.9, 35.6, 92.4, 123.4, 125.5, 126.2, 131.1, 134.7, 144.2, 167.8, 171.9; ms:  $m/z$  (%) 220 ( $\text{M}^+$ , 0.2), 148 (25), 132 (100), 104 (20), 76 (17).

Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{O}_4$ : C, 65.45; H, 5.49. Found: C, 65.11; H, 5.65.

3-Oxo-1,3-dihydro-1-isobenzofuranyl Hexanoate.

This compound was obtained as colorless solid, mp 49-51°; ir (potassium bromide):  $\nu$  2969, 2909, 1771, 1049, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  0.89 (t,  $J = 6.9$  Hz, 3H), 1.31-1.34 (m, 4H), 1.64-1.71 (m, 2H), 2.44 (t,  $J = 7.5$  Hz, 2H), 7.46 (s, 1H), 7.62-7.70 (m, 2H), 7.79 (t,  $J = 7.5$  Hz, 1H), 7.92 (d,  $J = 7.2$  Hz, 1H);  $^{13}\text{C}$  nmr (deuteriochloroform):  $\delta$  13.7, 22.1, 24.0, 30.9, 33.7, 92.4, 123.4, 125.5, 126.2, 131.1, 134.7, 144.2, 167.7, 172.1; ms:  $m/z$  (%) 149 ( $\text{M}^+ - 99$ , 0.4), 134 (27), 105 (100), 77 (45).

*Anal.* Calcd. for  $C_{14}H_{16}O_4$ : C, 67.73; H, 6.50. Found: C, 67.54; H, 6.68.

### 3-Oxo-1,3-dihydro-1-isobenzofuranyl Heptanoate.

This compound was obtained as colorless oil; ir (neat):  $\nu$  2930, 2861, 1790, 1710, 1053, 754  $cm^{-1}$ ;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.88 (t,  $J = 6.6$  Hz, 3H), 1.26-1.40 (m, 6H), 1.58-1.72 (m, 2H), 2.43 (t,  $J = 7.5$  Hz, 2H), 7.45 (s, 1H), 7.59-7.68 (m, 2H), 7.77 (t,  $J = 7.8$  Hz, 1H), 7.93 (d,  $J = 7.5$  Hz, 1H);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  13.9, 22.3, 24.4, 28.5, 31.2, 33.9, 92.5, 123.4, 125.7, 126.4, 131.1, 134.7, 144.3, 167.8, 172.2; ms:  $m/z$  (%) 149 ( $M^+$ -113, 131), 133 (100), 104 (13), 77 (12), 61 (17).

*Anal.* Calcd. for  $C_{15}H_{18}O_4$ : C, 68.69; H, 6.92. Found: C, 68.34; H, 7.17.

### 3-Oxo-1,3-dihydro-1-isobenzofuranyl 3-Methylbutanoate.

This compound was obtained as colorless oil; ir (neat):  $\nu$  2963, 2876, 1765, 1711, 1053, 754  $cm^{-1}$ ;  $^1H$  nmr (deuteriochloroform):  $\delta$  0.91 (d,  $J = 6.0$  Hz, 3H), 1.00 (d,  $J = 6.0$  Hz, 3H), 2.05-2.24 (m, 1H), 2.23 (d,  $J = 6.6$  Hz, 1H), 2.32 (d,  $J = 6.6$  Hz, 1H), 7.47 (s, 1H), 7.60-7.69 (m, 2H), 7.77 (t,  $J = 6.9$  Hz, 1H), 7.93 (d,  $J = 7.8$  Hz, 1H);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  22.1, 22.2, 25.5, 42.8, 92.5, 123.4, 125.6, 126.4, 131.1, 134.8, 144.4, 167.9, 171.4; ms:  $m/z$  (%) 149 ( $M^+$ -85, 15), 133 (100), 104 (18), 76 (21), 42 (21).

*Anal.* Calcd. for  $C_{13}H_{14}O_4$ : C, 66.66; H, 6.02. Found: C, 66.79; H, 6.24.

### 3-Oxo-1,3-dihydro-1-isobenzofuranyl Benzoate.

This compound was obtained as colorless solid, mp 128-129°; ir (potassium bromide):  $\nu$  3009, 1778, 1744, 1055, 754  $cm^{-1}$ ;  $^1H$  nmr (deuteriochloroform):  $\delta$  7.45 (t,  $J = 7.8$  Hz, 2H), 7.61 (t,  $J = 7.5$  Hz, 1H), 7.66-7.70 (m, 3H), 7.76-7.81 (m, 1H), 7.97 (d,  $J = 8.1$  Hz, 1H), 8.05 (d,  $J = 7.5$  Hz, 2H);  $^{13}C$  nmr (deuteriochloroform):  $\delta$  93.2, 123.7, 125.7, 126.5, 128.3, 128.5, 130.1, 131.3, 134.0, 134.9, 144.4, 165.0, 167.9; ms:  $m/z$  (%) 254 ( $M^+$ , 0.3), 149 (29), 133 (100), 105 (34), 77 (37).

*Anal.* Calcd. for  $C_{15}H_{10}O_4$ : C, 70.86; H, 3.96. Found: C, 70.86; H, 3.67.

### Acknowledgment.

This work was supported by Korea Science & Engineering Foundation (98-05-01-05-01-3) and Ministry of Education (BSRI-97-3408) and by grant of Post-Doc. (C.S.C.) Program from Kyungpook National University (1998).

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