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FACILE PALLADIUM-CATALYZED SYNTHESIS OF 3-OXO-1,3-DIHYDRO-1-ISOBENZOFURANYL ALKANOATES FROM 2-BROMOBENZALDEHYDE AND CARBOXYLIC ACIDS

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Abstract: 2-Bromobenzaldehyde reacts with carboxylic acids in acetonitrile under carbon monoxide pressure in the presence of a catalytic amount of a palladium catalyst to give the corresponding 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates in high yields.

Transition metal-catalyzed heteroannulation provides a useful and convenient tool for the construction of complex heteroatom-containing organic molecules. The synthesis of the structural core of phthalides also has been attempted by the aid of transition metal catalysts[1-8] since phthalides play an important role as an intermediate for the synthesis of anticancer agents such as daunomycin, adriamycin, nogalamycin and 7-con-*O*-methylnogarol.[9] Recently, we also developed and reported a synthetic method for the formation of 3-substituted phthalides from 2-bromobenzaldehyde and nucleophiles such as aliphatic alcohols,[10] phenols,[11] 1,3-dicarbonyl compounds[12] and sodium alkanoates[13] through a mechanistic palladium-catalyzed carbonylative

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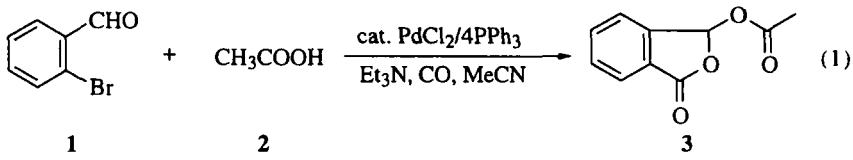
cyclization. In conjunction with this report, it is worth while to note the synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates from 2-bromobenzaldehyde and sodium alkanoates.[13] However, the replacement of sodium alkanoates by more readily available carboxylic acids and a base under the similar catalytic system led to the effective formation of products. We here report an improved approach for the synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates from 2-bromobenzaldehyde and various carboxylic acids *via* palladium-catalyzed carbonylative cyclization.

We examined the cyclization between 2-bromobenzaldehyde (**1**) and acetic acid (**2**) to optimize the reaction conditions under a similar catalytic system which we introduced for the synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates from **1** and sodium alkanoates.[13] Thus, treatment of **1** and **2** in anhydrous solvent under carbon monoxide pressure (20 atm) in the presence of a catalytic amount of a palladium (5 mol%) together with a base at 100 °C afforded 3-oxo-1,3-dihydro-1-isobenzofuranyl acetate (**3**) (eq 1).



1 **2** **3** (1)

Among reaction variants such as palladium catalyst, base and solvent examined, $PdCl_2/4PPh_3$-Et_3N-MeCN or $Pd(OAc)_2/4PPh_3$-Et_3N-MeCN system was revealed to be the best for obtaining **3** (97% GLC yield based on **1**; 83% isolated yield). The reaction was performed until the starting **1** disappeared on thin layer chromatography or GLC, generally, the reaction time being within 1 h. The yield of **3** was affected

by the molar ratio of **2** to **1** as has been observed in the synthesis of **3** from **1** and sodium acetate, the highest yield being optimized at the molar ratio of 2.

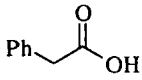
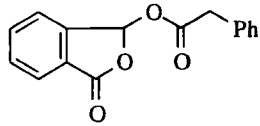
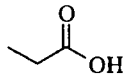
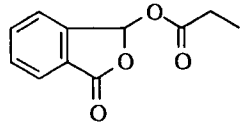
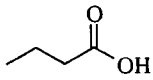
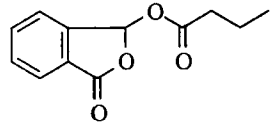
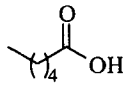
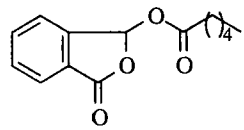
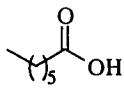
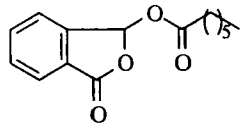
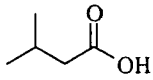
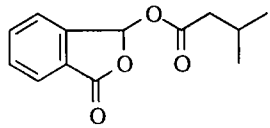
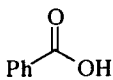
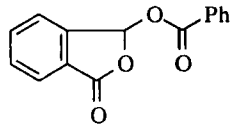
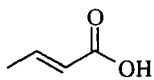
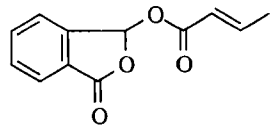
The present cyclization could be applied to many carboxylic acids, several representative results being summarized in Table 1. From easily available aliphatic and aromatic carboxylic acids the corresponding 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates **4-10** were also formed in high yields (runs 1-7). In the reaction with α,β–unsaturated carboxylic acid, crotonic acid, the yield of product **11** was slightly lower than that when aliphatic and aromatic carboxylic acids were used (run 8). The result indicates that the structural and electronic nature of carboxylic acids showed no decisive influence on the formation of products.

In summary, in comparision with the palladium-catalyzed carbonylative heteroannulation of **1** with sodium alkanoates leading to 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates, the present palladium-catalyzed carbonylative cyclization of **1** with carboxylic acids has several advantages such as more readily available carboxylic acids, shorter reaction time, lower molar ratio of nucleophilic counterpart to **1** and higher yield of products.

EXPERIMENTAL

Typical procedure for palladium-catalyzed synthesis of 3-oxo-1,3-dihydro-1-isobenzofuranyl alkanoates from 2-bromobenzaldehyde (1) and carboxylic acids: A mixture of 2-bromobenzaldehyed (0.370 g, 2 mmol), phenylacetic acid (0.545 g, 4 mmol), palladium(II) chloride (0.018 g, 0.1 mmol), triphenylphosphine (0.105 g, 0.4 mmol), and triethylamine (0.7 mL, 5 mmol) in dry acetonitrile (10 mL) was placed in a 50 mL stainless steel autoclave. After the system was flushed

Table 1. Palladium-Catalyzed Synthesis of 3-Oxo-1,3-dihydro-1-isobenzofuranyl Alkanoates

entry	carboxylic acids	products		isolated yield (%)
1			**4**	81
2			**5**	81
3			**6**	82
4			**7**	84
5			**8**	84
6			**9**	81
7			**10**	80
8			**11**	71

and then pressurized with carbon monoxide to 20 atm, the mixture was stirred at 100 °C for 1 h. The reaction mixture was filtered through a short column (silica gel, chloroform/ethyl acetate = 1/1) 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 ethyl acetate-hexane mixture as an eluent to give 3-oxo-1,3-dihydro-1-isobenzofuranyl phenylacetate (**4**) (0.435 g, 81%). The products prepared by the above procedure were characterized spectroscopically. The spectroscopic data of compounds **5-10** are noted in our recent report. Compounds **4** and **11** are new.

3-Oxo-1,3-dihydro-1-isobenzofuranyl phenylacetate (4): colorless solid; mp 115-117 °C; IR (KBr) 1790 (C=O), 1761 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 2H, $-CH_2-$), 7.27-7.92 (m, 5H), 7.42-7.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.9, 92.9, 123.6, 125.8, 126.5, 127.5, 128.7, 129.3, 131.3, 132.6, 134.8, 144.2, 167.8 (C=O), 170.1 (C=O); MS *m/z* (relative intensity) 268 (M^+, 0.8), 133 (M^+-$OCOCH_2Ph$, 100), 105 (9), 91 (15), 77 (11). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.6; H, 4.5. Found: C, 71.3; H, 4.5.

3-Oxo-1,3-dihydro-1-isobenzofuranyl crotonate (11): colorless solid; mp 51-52 °C; IR (KBr) 1769 (C=O), 1744 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.91 (dd, J = 6.9 and 1.5 Hz, 2H, $-CH_3$), 5.90 (dq, J = 15.5 and 1.5 Hz, 1H, -COC<u>H</u>=CH-), 7.07-7.19 (m, 1H, =C<u>H</u>-CH_3), 7.50 (s, 1H, C<u>H</u>), 7.65-7.70 (m, 2H), 7.76-7.81 (m, 1H), 7.91 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.0, 92.4, 120.7, 123.4, 125.3, 126.1, 130.9, 134.6, 144.2, 148.2, 164.2 (C=O), 167.7 (C=O); MS *m/z* (relative intensity) 133 (M^+-$OCOCH=CHCH_3$, 100), 105 (14), 77 (20). Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.6. Found: C, 65.9; H, 4.9.

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