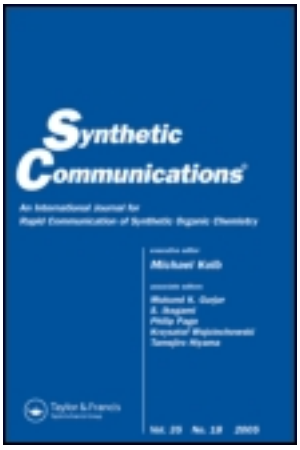

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Palladium-Catalyzed Synthesis of 3-Alkylphthalides via Carbonylative Cyclization of o-Bromobenzaldehyde with 1,3-Dicarbonyl Compounds

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PALLADIUM-CATALYZED SYNTHESIS OF 3-ALKYLPHTHALIDES VIA CARBONYLATIVE CYCLIZATION OF *o*-BROMOBENZALDEHYDE WITH 1,3-DICARBONYL COMPOUNDS

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Abstract: *o*-Bromobenzaldehyde reacts with 1,3-dicarbonyl compounds under carbon monoxide in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ to give the corresponding 3-alkylphthalides in moderate to good yields.

Transition metal-catalyzed cyclization process has been widely introduced for the formation of skeletons of heterocyclic compounds.[1] Thus, the construction of structural core of phthalides also has been applied by the aid of transition metals since phthalides play an important role as an intermediate for the synthesis of several complex natural products and exhibit biological activities.[2] Among them, it is worth while to note the palladium-catalyzed synthesis of 3-alkylidenephthalides from *o*-iodoaryl alkenyl ketones[3] and *o*-functionalized (Br, OTf) acetophenones[4] and carbon monoxide *via* carbonylative cyclization. We also have recently reported that *o*-bromobenzaldehyde reacted with alcohols under carbon monoxide

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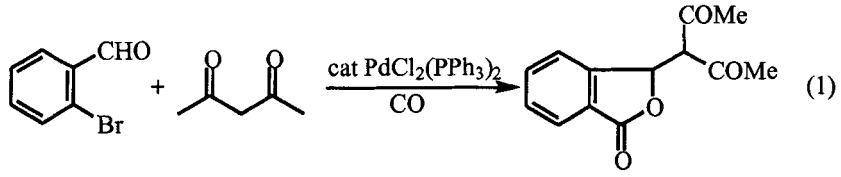
in the presence of a palladium catalyst to give 3-alkoxyphthalides due to organometallic carbonylative cyclization sequence.[5] This finding prompted us to explore the similar carbonylative cyclization of *o*-bromobenzaldehyde with other nucleophiles, which provide a useful route to the formation of various 3-substituted phthalides. Herein, we disclose and report the development of a method for the synthesis of 3-alkylphthalides from readily available *o*-bromobenzaldehyde and 1,3-dicarbonyl compounds.

We examined the carbonylative cyclization between 2-bromobenzaldehyde (**1**) and 2,4-pentanedione (**2**) to optimize reaction conditions under the similar catalytic systems we introduced for the synthesis of 3-alkoxyphthalides (eq 1).[5]

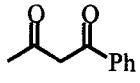
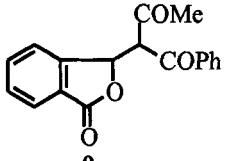
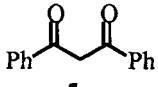
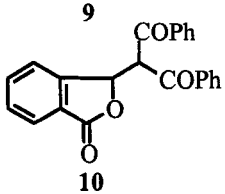
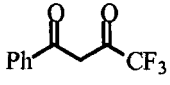
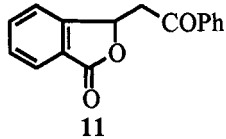
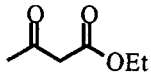
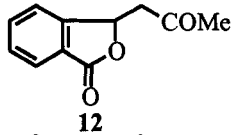
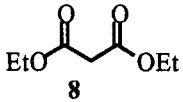
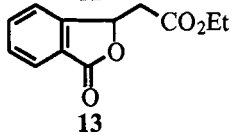


(1)

1 **2** **3**

Treatment of equimolar amounts of **1** and **2** under carbon monoxide (20 atm) in *N*,*N*-dimethylformamide in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (1 mol%) and sodium acetate (2 mol equiv to **1**) at 80 °C for 8 h afforded 3-(1,1-diacetylmethyl)phthalide (**3**) in 75% isolated yield. This reaction condition was eventually revealed to be best for obtaining **3**. The yield of **3** was not improved by a longer reaction time. Although the reaction proceeded even by use of other solvents and bases, Table shows that the choice of solvent and base was crucial for the effective formation of **3**. Moreover, the yield of **3** was considerably affected by the molar ratio of **2** to **1** and increasing the ratio (**2**/**1** = 2) resulted in lower yield of **3** (18%).

Table

dicarbonyl compound	base	solvent	product	yield (%)[a]
2	NaOAc	DMF	**3**	(75)
	NaOAc	hexane		17
	NaOAc	THF		trace
	NaOAc	benzene		20
	NaOAc	MeCN		36
	K_2CO_3	DMF		10
	KOH	DMF		25
	Et_3N	DMF		22
	pyridine	DMF		13
 **4**	NaOAc	DMF	 **9**	(65)
 **5**	NaOAc	DMF	 **10**	(65)
 **6**	NaOAc	DMF	 **11**	(68)
 **7**	NaOAc	DMF	 **12**	(39)
 **8**	NaOAc	DMF	 **13**	(37)

[a] GLC yield. Isolated yield is shown in parentheses.

The reaction could also be applied to many dicarbonyl compounds (**4-8**) under the optimized reaction conditions described above. In cases of 1-phenyl-1,3-butanedione (**4**) and 1,3-diphenyl-1,3-propanedione (**5**), the products were 3-(dicarbonylmethyl)phthalides (**9-10**) as has been observed in the reaction with 2,4-pentanedione (**2**). Furthermore, the reaction with **4** proceeded with high diastereoselectivity (99%<), which was determined by ^{1}H NMR spectroscopy. However, the reaction with 4,4,4-trifluoro-1-phenyl-1,3-butanedione (**6**) did not proceed in a similar way as **2**, **4** and **5** and involved deacetylation to give phthalide **11**. Similar reaction was also observed in the reaction with ethyl acetoacetate (**7**) and diethyl malonate (**8**), but the yield of phthalides (**12-13**) was generally lower than that by the use of dicarbonyl compounds mentioned above. On the other hand, the use of 3-methyl-2,4-pentanedione was not successful for the present reaction for the formation of 3-substituted phthalide and resulted in the formation of many unidentified compounds.

Although a clear understanding of the present reaction is yet to be realized, a plausible catalytic pathway has already been proposed in the transition metal-catalyzed carbonylative cyclization reactions.[5-10]

EXPERIMENTAL

General procedure for palladium-catalyzed synthesis of 3-alkylphthalides: A mixture of *o*-bromobenzaldehyde (**1**) (0.370 g, 2 mmol), 1,3-dicarbonyl compound (2 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol), PPh_3 (0.021 g, 0.08 mmol), and sodium acetate (0.164 g, 2 mmol) in DMF was placed in a pressure vessel. After the system was flushed and then pressurized with carbon monoxide (20 atm), the mixture was stirred at 80 °C for 8 h. The reaction mixture was filtered through a

short column (silica gel) and evaporated under reduced pressure. The preparative thin layer chromatography separation using ethyl acetate/hexane (10/3) as an eluent gives 3-alkylphthalides. The products prepared by the above procedure were characterized spectroscopically as shown below.

3-(1,1-Diacetylmethyl)phthalide (3): 75% yield; IR (KBr) 1767, 1729, 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.34 (s, 3H), 3.98 (d, J = 9.6 Hz, 1H), 6.10 (d, J = 9.6 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.48-7.63 (m, 2H), 7.83 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.7, 30.9, 71.9, 78.5, 123.1, 125.5, 125.9, 129.9, 134.5, 147.2, 169.2, 199.4, 200.6; MS *m/z* (relative intensity) 189 (M^+-COMe, 57), 147 (83), 146 (M^+-2COMe, 61), 133 (33), 105 (17), 77 (25), 43 (100).

3-(1-Acetyl-1-benzoylmethyl)phthalide (9): 65% yield; IR (KBr) 1760, 1718, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.84 (d, J = 9.6 Hz, 1H), 6.45 (d, J = 9.6 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.46-7.65 (m, 5H), 7.87 (d, J = 6.9 Hz, 1H), 7.96-7.99 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.8, 67.3, 79.3, 123.3, 125,5, 125.8, 129.0 (x 2), 129.7, 134.4, 134.5, 135.7, 147.4, 169.2, 192.8, 199.1; MS *m/z* (relative intensity) 251 (M^+-COMe, 23), 147 (35), 105 (100), 77 (84).

3-(1,1-Dibenzoylmethyl)phthalide (10): 65% yield; IR (KBr) 1769, 1692, 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 7.35-7.61 (m, 9H), 7.81-7.84 (m, 3H), 7.92-7.95 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 60.3, 80.0, 124.1, 125.4, 125.7, 128.6, 128.7, 128.9, 129.6, 133.9, 134.1, 134.2, 135.6, 135.7, 147.4, 169.2, 192.4, 192.8; MS *m/z* (relative intensity) 251 (M^+-COPh, 15), 105 (100), 77 (65).

3-(1-Benzoylmethyl)phthalide (11): 68% yield; IR (KBr) 1763, 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (dd, J = 17.9 and 7.4 Hz, 1H), 3.79 (dd, J = 17.9 and 5.9 Hz, 1H), 6.19 (t, J = 6.5 Hz, 1H), 7.47-7.70 (m, 6H), 7.91-7.98 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.7, 77.2, 122.8, 125.7, 125.9, 128.1, 128.8, 129.4, 133.8, 134. 3, 136.2, 149.7, 170.1, 196.0; MS *m/z* (relative intensity) 252 (M^+, 5), 147 (15), 105 (55), 77 (93), 76 (100).

3-(1-Acetylmethyl)phthalide (12): 39% yield; IR (KBr) 1764, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.85-3.08 (m, 2H), 5.84 (t, J = 6.5 Hz, 1H), 7.41-7.48 (m, 2H), 7.57-7.62 (m, 1H), 7.78 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.4, 47.8, 76.5, 122.2, 125.4, 125.5, 129.2, 134.1, 149.2, 169.8, 204.3; MS *m/z* (relative intensity) 190 (M^+, 7), 175 (6), 147 (100), 105 (76), 77 (22).

3-(1-Carbethoxymethyl)phthalide (13): 37% yield; IR (KBr) 1763, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3H), 2.80-2.83 (m, 2H), 4.10 (q, J = 7.2 Hz, 2H), 5.79 (t, J = 6.6 Hz, 1H), 7.41-7.83 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 61.0, 69.6, 76.6, 122.0, 125.4, 125.4, 129.3, 133.8, 148.5, 169.7, 170.9; MS *m/z* (relative intensity). 220 (M^+, 15), 146 (100), 132 (67), 105 (67), 77 (28).

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