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Synthesis of phthalides via Pd/CNTs-catalyzed reaction of terminal alkynes and *o*-iodobenzoic acid under copper- and ligand-free conditions

Lei Zhou and Huan-Feng Jiang*

College of Chemistry, South China University of Technology, Guangzhou 510640, PR China

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Abstract—A phosphine- and copper-free protocol for the synthesis of phthalides via Pd/CNTs-catalyzed tandem coupling-cyclization process has been developed. The palladium immobilized on CNTs showed high catalytic activity, and the reactions with a variety of terminal alkynes and *o*-iodobenoic acid proceeded smoothly to give phthalides in moderate to good yields catalyzed by 0.1% mmol Pd/CNTs.

Phthalides represent an important class of naturally occurring lactones,[1] a structural subunit in numerous natural products that exhibit a wide range of biological activities, such as antispasmodic,[2] antifungal,[3] vasodilators, and coronary artery dilators.[2] Among the numerous methods to synthesize phthalides, the use of *o*-halobenzoic acid derivatives and terminal alkynes as starting materials is one of the most attractive routes.[4] Usually, this process was performed in two separate steps: (1) coupling of *o*-halobenzoic acid derivatives with terminal alkynes, typically by the Sonogashira reaction and (2) cyclization mediated by metal complexes,[5–7] bases,[8] and halogen.[4b,9]

The first one pot synthesis of phthalides was reported by Castro et al., but the mixture of phthalides and isocoumarins was obtained.[10] Greater selectivity for phthalides was exhibited in the combination of $PdCl_2(PPh_3)_2$–Et_3N–CuI as a catalyst system for a variety of terminal alkynes.[11] However, the presence of CuI resulted in the formation of some oxidative homocoupling byproducts.[12] In addition, triphenylphosphine was used as a ligand, which makes product isolation more difficult (Fig. 1).

On the other hand, Pal and co-workers have shown that isocoumarins could be obtained as major products when *o*-iodobenzoic acid was reacted with terminal alkynes in the presence of Pd/C–Et_3N–CuI.[13] Though the reasons for the observed regioselectivity for isocoumarins are not yet clear, the use of EtOH as solvent and Pd/C as catalyst has been found to be responsible for the predominant formation of isocoumarins over phthalides.

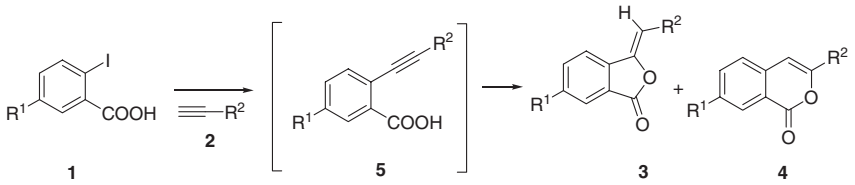

Figure 1. Construction of the phthalide and isocoumarin ring.

Keywords: Phthalide; Palladium; Terminal alkynes; Copper-free; Ligand-free.
* Corresponding author. Tel./fax: +86 20 87112906; e-mail: jianghf@scut.edu.cn

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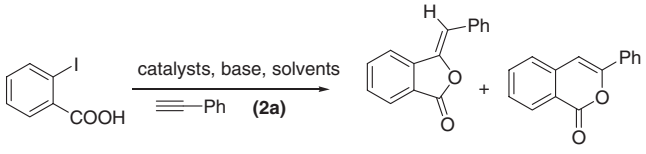
In spite of the numerous studies made in phosphine- and copper-free palladium-catalyzed coupling of aryl halides with terminal alkynes,[14] to the best of our knowledge, the use of phosphine- and copper-free condition for the synthesis of phthalides or isocoumarins has never been reported thus far. Herein, we report the first synthesis of phthalides via Pd/CNTs-catalyzed reaction of terminal alkynes and *o*-iodobenzoic acid under copper- and ligand-free conditions.

Carbon nanotubes (CNTs), which have excellent electronic properties, good chemical stability, and large surface areas, make them promising supports for advanced catalytic systems.[15] Very recently, we have developed the Pd/CNTs-catalyzed Suzuki reaction in $scCO_2$. In order to extend the application scope of this kind of catalysts, we treated *o*-iodobenzoic acid **1a** and phenylacetylene **2a** with catalytic amount of Pd/CNTs (1 mol %) in the presence of a base. Initially, four bases including NEt_3, NaOAc, K_2CO_3, and DABCO were tested (Table 1, entries 1–4), and DABCO was most efficient for this reaction, affording the mixture of phthalide **3a** and isocoumarin **4a** (7:1) in 75% yield. When NaOAc was used as the base, a mixture of **3a** and **4a** was obtained in low yield (20%, 9:1). This observation promoted us to examine the use of the mixture of NaOAc and DABCO as the bases for the reaction. In the presence of Pd/CNTs (1 mol %), DABCO (40 mol %), NaOAc (2 equiv), and DMF (3 mL), phthalide was isolated as the major product in 70% yield (entry 5). A set of solvents such as DMF, EtOH, and H_2O were also examined, and DMF gave the best result (entries 5–7). When EtOH was employed as the solvent, the overall yields of products were improved slightly but the ratio of phthalide **3a** and isocoumarin **4a** was decreased to 2:1. Interestingly, when 5 mol % of water was added to DMF as the solvents, phthalide **3a** was isolated as the sole product in this case (entry 8). Finally, the catalytic efficiency of Pd/CNTs was evaluated. For the coupling of *o*-iodobenzoic acid **1a** with phenylacetylene **2a**, satisfied yields could still be obtained after prolonged reaction time when the catalyst loading was reduced to 0.1 mol % (entry 9). Further decrease of the catalyst loading to 0.01 mol % led to a low yield (25%, TONs = 25,000, entry 10). Comparing to Pd/CNTs, when 5% Pd/C was employed as the catalyst, the overall yields of products were obtained only in 35% yield (entry 11).

With the optimal conditions in hand, we next explored the scope and limitation of the present Pd/CNTs-catalyzed tandem coupling-cyclization method with a variety of terminal alkynes and *o*-iodobenzoic acid (Table 2).[16] Various functional groups including alkyl, hydroxyl and phenyl, present in alkynes **2** were well tolerated during the course of the reaction. Substrates bearing functional groups at the *para*-position of the aromatic ring as well as the carbonmethoxy and hexyl substituent gave the corresponding phthalides (**3b–e**) in good yields (Table 2, entries 2–5). We were pleased to find that the alkyne bearing a hydroxyl group reacted with *o*-iodobenzoic acid under the given conditions to afford the corresponding phthalides in moderate to good yields (entries 6–10); both primary and secondary alcohols present in the terminal alkynes were readily accommodated. In another case an alkyne bearing a $SiMe_3$ group afforded the five-membered ring product **3k** exclusively after subsequent desilylation of the resulting phthalide in one pot (entry 11). 2-(Trimethylsilanyl ethynyl)benzoic acid was isolated as a major byproduct in this case. Further examination of *o*-iodobenzoic acid bearing a nitro group showed that the electron-withdrawing group on the aromatic ring hindered the formation of phthalides. When 2-iodo-5-nitro-benzoic acid was employed, the reaction

Table 1. Optimizaiton of conditions for palladium-catalyzed coupling reaction of *o*-iodobenzoic acid with phenylacetylene[a]

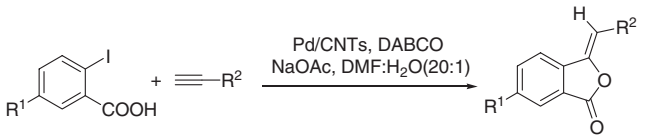


1a 3a 4a

Entry	Pd catalyst (mol %)	Bases (equiv)	Solvent	Time (h)	Yield[b] (%) **3a**:**4a**[c]
1	Pd/CNTs 1%	NEt_3 (5)	DMF	3	55 (3:1)
2	Pd/CNTs 1%	NaOAc (2)	DMF	3	20 (9:1)
3[b]	Pd/CNTs 1%	K_2CO_3 (2)	DMF	3	Trace
4	Pd/CNTs 1%	DABCO (2 equiv)	DMF	3	75 (7:1)
5	Pd/CNTs 1%	NaOAc (2) + DABCO (0.4 equiv)	DMF	3	70 (9:1)
6	Pd/CNTs 1%	NaOAc (2) + DABCO (0.4 equiv)	EtOH	3	82 (2:1)
7	Pd/CNTs 1%	NaOAc (2) + DABCO (0.4 equiv)	H_2O	3	Trace
8	Pd/CNTs 1%	NaOAc (2) + DABCO (0.4 equiv)	DMF/H_2O (20:1)	3	72 (only **3a**)
9	Pd/CNTs 0.1%	NaOAc (2) + DABCO (0.4 equiv)	DMF/H_2O (20:1)	8	68 (only **3a**)
10	Pd/CNTs 0.01%	NaOAc (2) + DABCO (0.4 equiv)	DMF/H_2O (20:1)	15	25 (only **3a**)
11	Pd/C 5%	NaOAc (2) + DABCO (0.4 equiv)	DMF/H_2O (20:1)	15	35 (9:1)

[a] Reaction conditions: *o*-Iodobenzoic acid (**1a**, 1 mmol), **2a** (2.0 equiv), Pd catalyst and bases in the indicated solvent (5 mL) at 100 °C for 3–15 h under N_2.
[b] Isolated yield of **3a** + **4a**.
[c] The ratio was determined by ^1H NMR analysis.

Table 2. Pd/CNTs-catalyzed synthesis of substituted phthalides[a]



1 2 3

Entry	1	2	Time (h)	3	Yield[b] (%)
1	**1a** ($R^1 = H$)	**2a** ($R^2 = C_6H_5$)	8	**3a**	72
2	**1a**	**2b** ($R^2 = CO_2Me$)	6	**3b**	81
3	**1a**	**2c** ($R^2 = p$-F–C_6H_4)	12	**3c**	85
4	**1a**	**2d** ($R^2 = p$-CH_3-C_6H_4)	10	**3d**	69
5	**1a**	**2e** ($R^2 = CH_2(CH_2)_4CH_3$)	4	**3e**	70
6	**1a**	**2f** ($R^2 = CH_2OH$)	12	**3f**	62
7	**1a**	**2g** ($R^2 = CH_2CH_2OH$)	12	**3g**	53
8	**1a**	**2h** ($R^2 = CH_2(CH_2)_3OH$)	12	**3h**	59
9	**1a**	**2i** ($R^2 = CH(OH)(CH_2)_2CH_3$)	8	**3i**	74
10	**1a**	**2j** ($R^2 = C(CH_3)_2OH$)	12	**3j**	75
11	**1a**	**2k** ($R^2 = SiMe_3$)	10	**3k**	20[c]
12	**1b** ($R^1 = NO_2$)	**2e** ($R^2 = CH_2(CH_2)_4CH_3$)	24	**3l**	47

[a] All the reactions were carried out by using **1** (0.5 mmol), **2** (2.0 equiv), 1.1 mg (0.1 mol %) Pd/CNTs, NaOAc (2 equiv) and DABCO (0.4 equiv) in DMF/H_2O (20:1) at 100 °C for the indicated time.
[b] Isolated yield.
[c] 2-(Trimethylsilanyl ethynyl)benzoic acid was isolated as major product in 47% yield.

with 1-octyne yielded the corresponding phthalides in only 47%.

In summary, we have developed a phosphine- and copper-free condition for the synthesis of phthalides via Pd/CNTs-catalyzed tandem coupling-cyclization process. The palladium immobilized on CNTs showed high catalytic effect on the reaction, and various phthalides were formed in moderate to good yields in the presence of 0.1% mmol Pd/CNTs. This protocol not only tolerates a range of functional groups but also does not require any additives such as phosphine ligands or CuI. Since the catalytic system is cheap and easy to handle, it should find practical usage in the synthesis of phthalides, an important class of molecules. Mechanistic studies of this method, as well as the further applications in the preparation of biologically interesting compounds, are actively under investigation in our laboratory.

Acknowledgments

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16. *Representative experimental procedure for the synthesis of* **3j**: A mixture of *o*-iodobenzoic acid **1** (0.248 g, 1 mmol), 10% Pd/CNTs (1 mg, 0.1% mmol), NaOAc (164 mg, 2 mmol), and DABCO (45 mg, 0.4 mmol) in DMF/H_2O (5 mL, v:v = 20:1) was stirred at 25 °C for 10 min under nitrogen. Then 2-methyl-but-3-yn-2-ol (**2j**, 0.168 g, 2 mmol) was added slowly to the mixture with stirring. The reaction mixture was then stirred at 100 °C for 12 h, cooled to room temperature, diluted with EtOAc (20 mL), and filtered through celite. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether–EtOAc v:v = 4:1) to afford the desired product **3j** as a white soild (0.153 g, 75% yield).
(Z)-3-(1-Benzylidene)phthalide (**3a**):[8a] white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (1H, s), 7.31 (1H, tt, $J = 7.2$ Hz, 1.2 Hz), 7.40–7.46 (2H, m), 7.52–7.56 (1H, m), 7.69–7.78 (2H, m), 7.83–7.85 (2H, m), 7.92–7.94 (1H, dt, $J = 7.2$ Hz, 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.1, 119.8, 123.4, 125.3, 128.4, 128.7, 129.5, 130.1, 133.1, 134.5, 140.6, 144.6, 167.1. MS (70 eV) *m*/*z* (%): 222 (100), 194 (20), 165 (68); IR (KBr) *v*: 3059, 2959, 1768, 1482, 1086, 976 cm^{-1}.
(3-Oxo-3H-isobenzofuran-1-ylidene)-acetic acid methyl ester (**3b**):[5b] white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s), 5.90 (1H, d, $J = 12.8$ Hz), 7.22 (1H, t, $J = 7.8$ Hz), 7.45 (1H, t, $J = 7.2$ Hz), 8.04 (1H, dd, $J = 8$ Hz, 1.2 Hz), 8.51 (1H, d, $J = 12.4$ Hz); MS (70 eV) *m*/*z* (%): 204 (21), 173 (100), 89 (24); IR (KBr) *v*: 3078, 1744, 1707, 1648, 1229, 1106 cm^{-1}.
3-(4-Fluoro-benzylidene)-3H-isobenzofuran-1-one (**3c**):[17] white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (1H, s), 7.09 (2H, t, $J = 8.8$ Hz), 7.54–7.56 (1H, m), 7.72–7.76 (2H, m), 7.81–7.84 (2H, m), 7.93 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.8, 115.8, 116.0, 119.7, 123.4, 125.7, 129.8, 131.9, 134.5, 140.2, 144.2, 163.8, 166.9; MS (70 eV) *m*/*z* (%): 240 (100); IR (KBr) *v*: 2922, 1784, 1651, 1009 cm^{-1}.
3-(4-Methyl-benzylidene)-3H-isobenzofuran-1-one (**3d**):[18] white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s), 6.40 (1H, s), 7.20–7.27 (2H, m), 7.50–7.54 (1H, m), 7.72–7.79 (4H, m), 7.93 (1H, d, $J = 8.0$ Hz); MS (70 eV) *m*/*z* (%): 236 (100), 225 (72); IR (KBr) *v*: 2990, 1782, 1235, 857, 751 cm^{-1}.
3-Heptylidene-3H-isobenzofuran-1-one (**3e**):[19] Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 8.4$ Hz), 1.27–1.35 (8H, m), 2.51 (2H, t, $J = 7.8$ Hz), 6.23 (1H, s), 7.33 (1H, d, $J = 7.8$ Hz), 7.40–7.44 (1H, m), 7.62–7.67 (1H, m), 8.22 (1H, d, $J = 8.0$ Hz); MS (70 eV) *m*/*z* (%): 230 (48), 160 (100), 102 (19); IR (KBr) *v*: 3065, 2938, 1742, 1342 cm^{-1}.
3-(2-Hydroxy-ethylidene)-3H-isobenzofuran-1-one (**3f**):[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59 (2H, d, $J = 8.4$ Hz), 5.80 (1H, t, $J = 7.2$ Hz), 7.43–7.46 (1H, m), 7.51–7.57 (1H, m), 7.62–7.67 (1H, m), 7.79 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.1, 106.7, 120.2, 124.6, 125.5, 128.5, 130.3, 132.0, 134.6, 139.1, 146.3, 166.4; MS (70 eV) *m*/*z* (%): 176(49), 147 (100), 129 (44), 104 (71); IR (KBr) *v*: 3419, 2974, 1775, 1271, 1046 cm^{-1}.
3-(3-Hydroxy-propylidene)-3H-isobenzofuran-1-one (**3g**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (2H, t, $J = 6.4$ Hz), 3.72 (2H, t, $J = 6.4$ Hz), 6.37(1H, s), 7.31 (1H, d, $J = 8.0$ Hz), 7.40–7.46 (2H, m), 7.42–7.58 (1 H, m), 7.60–7.67 (1H, m),8.20 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 66.7, 104.8, 125.2, 127.9, 128.6, 129.5, 134.3, 137.3, 154.8, 162.9; MS (70 eV) *m*/*z* (%): 190 (64), 160 (100), 131 (66), 89 (47); IR (KBr) *v*: 3397, 2923, 1718, 1656, 1050 cm^{-1}.
3-(5-Hydroxy-pentylidene)-3H-isobenzofuran-1-one (**3h**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57–1.68 (4H, m), 2.84 (2H, t, $J = 7.2$ Hz), 3.65 (2H, t, $J = 6.0$ Hz), 6.27 (1H, s), 7.33 (1H, d, $J = 7.6$ Hz), 7.42–7.44 (1H, m), 7.62–7.67 (1H, m), 7.90 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 26.8, 34.2, 66.5, 103.7, 125.3, 127.9, 128.7, 129.4, 134.0, 137.5, 151.6, 164.1; MS (70 eV) *m*/*z* (%): 217 (39), 200 (33), 172 (100), 131 (35), 89 (43); IR (KBr) *v*: 3435, 2928, 1717, 1653, 1206, 1050 cm^{-1}.
3-(2-Hydroxy-heptylidene)-3H-isobenzofuran-1-one (**3i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 6.8$ Hz), 1.30–1.34 (4H, m), 1.59–1.63 (2H, m), 1.69–1.74 (2H, m), 1.93 (1H, br), 4.91 (1H, m), 5.63 (1H, d, $J = 8.4$ Hz), 7.52–7.56 (1H, m), 7.64–7.71 (2H, m), 7.89 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 24.9, 31.6, 37.2, 66.9, 110.9, 120.2, 124.5, 125.4, 130.2, 134.5, 139.2, 145,5, 166.5; MS (70 eV) *m*/*z* (%): 246 (12), 227 (10), 175 (100), 147 (94), 129 (36); IR (KBr) *v*: 3417, 3056, 2930, 1789, 1687, 1471, 1276 cm^{-1}.
3-(2-Hydroxy-2-methyl-propylidene)-3H-isobenzofuran-1-one (**3j**):[5e] white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (6H, s), 5.80 (1H, s), 7.51–7.55 (1H, m), 7.61 (1H, d, $J = 7.6$ Hz), 7.66–7.69 (1H, m), 7.89 (1H, d, $J = 7.6$ Hz); MS (70 eV) *m*/*z* (%): 204 (10), 189 (40), 147 (100); IR (KBr) *v*: 3413, 2981, 1764, 1681, 1370, 1164 cm^{-1}.
3-Methylene-3*H*-isobenzofuran-1-one (**3 k**):[5b] yellow solid, mp 55–56 °C (lit. 57–58 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 5.23 (2H, d, $J = 0.9$ Hz), 7.64–7.54 (2H, m), 7.73 (1H, d, $J = 3.8$ Hz), 7.92 (1H, d, $J = 7.8$ Hz); MS (70 eV) *m*/*z* (%): 147 (30), 133 (100); IR (KBr) *v*: 1782, 1670, 1154 cm^{-1}.
3-Heptylidene-5-nitro-3H-isobenzofuran-1-one (**3l**): ^{1}H NMR (400 MHz, $CDCl_3$): 0.87 (3H, t, $J = 8.4$ Hz), 1.29–1.37 (6H, m), 1.71 (2H, m), 2.57 (2H, t, $J = 7.2$ Hz), 6.35(1H, s), 7.48 (1H, d, $J = 8.8$ Hz), 8.46 (1H, dd, $J = 8.8$ Hz, 2.4 Hz), 9.08 (1H, d, $J = 7.2$ Hz); MS (70 eV) *m*/*z* (%): 275 (34), 205 (100), 146 (42); IR (KBr) *v*: 1738, 1644, 1338, 1088 cm^{-1}.
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