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# Hydroiodination-Triggered Cascade Reaction with I<sub>2</sub>/PPh<sub>3</sub>/H<sub>2</sub>O: a Metal-Free Access to 3-Substituted Phthalides from 2-Alkynylbenzoates

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**Abstract:** Phthalide is an important scaffold found in several biologically active compounds. Therefore, effective synthetic methods for phthalides are strongly desired. Herein, we describe the metal-free synthesis of 3-substituted phthalides by the reductive hydroiodination of 2-alkynylbenzoates via an I<sub>2</sub>/PPh<sub>3</sub>/H<sub>2</sub>O-triggered cascade reaction. A variety of 3-substituted phthalides were synthesized in excellent yields via a one-pot reaction involving four processes: desilylation, hydroiodination, cyclization, and reduction.

Phthalide (isobenzofuranone) is an important scaffold found in many biologically active and naturally occurring substances.<sup>[1]</sup> Therefore, numerous synthetic methods for phthalides have been reported in the last decade. Notably, the construction of the ybutyrolactone scaffold is a key step in the synthesis of phthalides, and numerous lactonization reactions were reported including the 1-(1-hydroxyalkyl)benzaldehyde cyclization of and its derivatives,<sup>[1b],[2]</sup> cyclization of o-aroylbenzoic acids,<sup>[3]</sup> and other methods.<sup>[4]</sup> To accomplish efficient synthesis of phthalides, a number of transition-metal-catalyzed reactions have been recently reported.<sup>[5]</sup> However, metal-free efficient syntheses of phthalides were still rare. Cyclization using 2-alkynylbenzoates 1 is an attractive route for synthesizing phthalides 2, but the reduction of intermediate alkylidene phthalides<sup>[4b]</sup> is required [Eq. (1)]. Therefore, the metal-free synthesis of phthalides from 2alkynylbenzoates is unexplored.





Synthetic methods using cascade reactions<sup>[6]</sup> have garnered considerable attention because multiple purification steps are avoided and they produce less waste and require less time. Our group recently reported that the hydroiodination of alkynes with  $I_2$ , PPh<sub>3</sub>, and H<sub>2</sub>O afforded iodoalkenes.<sup>[7]</sup> Furthermore, the hydroiodination was successfully applied to a one-pot Pdcatalyzed cross-coupling reaction; notably, the hydroiodination residues did not prevent the subsequent cross-coupling reactions.<sup>[7]</sup> When the hydroiodination of various alkynes was attempted, methyl 2-(trimethylsilylalkynyl)benzoate (1a) gave 3methylphthalide (2a) [Eq. (2)]. This novel lactonization should contain four steps, i.e., desilylation, hydroiodination, cyclization<sup>[8]</sup>, and reduction. Therefore, we investigated the hydroiodinationtriggered cascade reaction of 2-alkynylbenzoates using I<sub>2</sub>/PPh<sub>3</sub>/H<sub>2</sub>O.



First, we optimized the reaction conditions of the lactonization of methyl 2-(trimethylsilylalkynyl)benzoate **1a** with I<sub>2</sub>, PPh<sub>3</sub>, and H<sub>2</sub>O (Table 1). When equimolar amounts of I<sub>2</sub>, PPh<sub>3</sub>, and H<sub>2</sub>O (0.1 mmol) were used, 3-methylidene phthalide (**3a**) was obtained in 19% yield (Entry 1).<sup>[9]</sup> When the amounts of I<sub>2</sub>, PPh<sub>3</sub>, and H<sub>2</sub>O were increased (from 1 to 2 equiv.), **2a** was obtained as the major product in 70% yield (Entry 2). Further increases in the amounts of I<sub>2</sub>, PPh<sub>3</sub> (3 equiv.), and H<sub>2</sub>O improved the yield of **2a** (Entry 3). With higher concentrations of **1a** (0.25 M), **2a** was obtained in an excellent yield (95%) (Entry 4). When HI aq.(hydroiodic acid 57%, 6 equiv.) was used instead of I<sub>2</sub> / PPh<sub>3</sub> / H<sub>2</sub>O, the yields of **2a** and **3a** were low (0%, and 23%). Comparatively, I<sub>2</sub> / PPh<sub>3</sub> / H<sub>2</sub>O system is efficient for the desired cascade reaction.

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[a] Reaction conditions: substrate **1a** (0.1 mmol), CDCl<sub>3</sub> (0.6 mL). [b] Determined by <sup>1</sup>H NMR analysis. [c] Substrate 1a (0.3 mmol), CDCl<sub>3</sub> (1.2 mL). [d] HI (3 equiv.) was used instead of  $I_2$ / PPh<sub>3</sub>/ H<sub>2</sub>O.

Next, the scope and limitations of the cyclization of methyl 2-(trimethylsilyl)ethynyl benzoates **1** were investigated (Table 2). First, the cascade reaction was carried out on the gram scale and **2a** was successfully obtained. When methyl-, methoxy-, chloro-, trifluoromethyl-, and fluoro-substituted 2-(trimethylsilyl)ethynyl benzoates **1b–g** were used, the cascade reaction gave the corresponding 3-methylphthalides **2b–g** in good to excellent yields (74–91%). Nitro groups and pyridyl rings prevented the cascade reaction. In the case of **1j**, which has two cyclization sites, the corresponding double cyclization product, 3,7-dimethyl-3,7dihydro-1*H*,5*H*-benzo[1,2-c:4,5-c']difuran-1,5-dione (**2j**), was obtained in 80% yield.

Table 2. Synthesis of 3-methyl phthalides via cyclization of 2-(trimethylsilyl)ethynyl benzoates.  $^{[a],[b]}$ 





[a] Reaction conditions: methyl 2-(trimethylsilyl)ethynyl benzoate (1, 0.3 mmol),  $l_2$  (0.9 mmol), PPh<sub>3</sub> (0.9 mmol),  $H_2O$  (0.9 mmol), CDCl<sub>3</sub> (1.2 mL). [b] Isolated yield. [c] 10 mmol scale in CHCl<sub>3</sub>. [d] 1j (0.3 mmol),  $l_2$  (1.8 mmol), PPh<sub>3</sub> (1.8 mmol), and  $H_2O$  (1.8 mmol) were used.

Ethyl ester **1k** was also a viable substrate in the cascade reaction [Eq. (3)].



When methyl 2-ethynylbenzoate (11) without a silyl group was used, 2a was obtained successfully [Eq. (4)].



As shown in Scheme 1, several methyl 2-ethynylbenzoates with aliphatic or aromatic groups instead of trimethylsilyl groups were subjected to the lactonization under the same conditions. When methyl 2-(1-hexynyl)benzoate (1m) was employed, 3pentyl phthalide (2m) and 3-butyl isocoumarin (4m) were obtained in 20% and 70% yields, respectively. With methyl 5chloro-2-(1-hexynyl)benzoate corresponding (**1n**), the isocoumarin 4n was obtained as the major product. Benzoate substituted with a methoxy group at the 5-position 1o afforded the corresponding phthalide 20 as the major product. Methyl 2-(arylethynyl)benzoates 1p and 1q afforded the corresponding isocoumarins with excellent selectivities (2/4 = 0/100). The phthalide/isocoumarine selectivity depended on the regioselectivity of the hydroiodination of the internal alkyne;[10] 2-(1-alkynyl)benzoates bearing electron donating group on aromatic ring preferentially afford phthalides, and 2-(2arylethyny)lbenzoates are converted to isocoumarins with excellent selectivities.

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Scheme 1. Cyclization of 2-ethynyl benzoates. Isolated yields are shown. The values in parentheses are corresponded to <sup>1</sup>H NMR yields.

Table 3 shows the scope of 2-ethynyl benzoates that gave phthalides as the major product. Chloro, nitro, phenyl, and ester groups were tolerated, and the corresponding phthalides 2r-2x were obtained in good yields with good phthalide selectivity. Notably, an aliphatic hydroxy group was displaced with an iodo group under the reaction conditions,<sup>[11]</sup> affording 3-(iodoalkyl)phthalide (**2y**).

Table 3. Synthesis of 3-substituted phthalides<sup>[a],[b]</sup>



[a] Reaction conditions: 2-ethynyl benzoate (1, 0.3 mmol), l<sub>2</sub> (0.9 mmol), PPh<sub>3</sub> (0.9 mmol), H<sub>2</sub>O (0.9 mmol), CDCl<sub>3</sub> (1.2 mL), 30  $^{\circ}$ C, 17 h. [b] Isolated yield. The values in parentheses correspond to <sup>1</sup>H NMR yields.

To obtain further insight into this cascade reaction, the following three additional reactions were examined. When 1-

phenyl-2-(trimethylsilyl)acetylene (**5**) was treated with excess  $I_2$ , PPh<sub>3</sub>, and H<sub>2</sub>O (3 equiv.), sequential desilylation,<sup>[12]</sup> hydroiodination, and reduction occurred to give (1-iodoethyl)benzene (**6**) in 98% yield [Eq. (5)].<sup>[13]</sup> Notably, the reaction from phenylacetylene to (1-iodoethyl)benzene directly has never been reported.



On the other hand, treatment of 3-methylidene phthalide (**3a**) with PPh<sub>3</sub>, l<sub>2</sub>, and H<sub>2</sub>O led to a reduction and 3-methylphthalide (**2a**) was obtained in a good yield (83%) [Eq. (6)].



0.1 mmol

(Determined by <sup>1</sup>H NMR)

To confirm the hydrogen source, the cascade reaction of **1c** was conducted using D<sub>2</sub>O (>99 atom% D) instead of H<sub>2</sub>O [Eq. (7)]. This reaction afforded **2c-D**, deuterated at benzylic proton (86 atom% D) and 3-methyl proton (89 atom% D), respectively, in 56% yield. This result indicates that the reductive hydrogen source comes from H<sub>2</sub>O in the cascade reaction. However, the details for reduction mechanism with I<sub>2</sub>, PPh<sub>3</sub>, and H<sub>2</sub>O is still unclear.



The proposed reaction pathway for the synthesis of 3substuituted phthalides **2** from methyl 2-(trimethylsilyl)ethynyl benzoates **1** via the hydroiodination-triggered cascade reaction is shown in Scheme 2. As previously reported, <sup>[7]</sup> [<sup>14]</sup> I<sub>2</sub>, PPh<sub>3</sub>, and H<sub>2</sub>O gives HI and [Ph<sub>3</sub>POH]<sup>+</sup>[I]<sup>-</sup>, quantitatively. The generated species can cause the hydroiodination of alkynes. First, the desilylation of **1a** occurs to give terminal alkyne **1**. Subsequently, hydroiodination of **11** proceeds to give vinyl iodide **7**.<sup>[12b]</sup> Next, vinyl iodide **7** is quickly cyclized with the elimination of MeI to give 3methylidene phthalide (**3a**). The eliminated MeI is observed by <sup>1</sup>H NMR analysis after the cascade reaction. Finally, **3a** is reduced to give the desired product **2a** where reductive hydrogens are derived from H<sub>2</sub>O. Although an alternative pathway via reduction of **7**, which generates alkyl iodide **8**, followed by cyclization to give **2a** can be also considered, **8** is not observed by <sup>1</sup>H NMR analysis.

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b) Proposed Reaction Pathway for the Synthesis of Phthalides



Scheme 2. a) Hydroiodination of alkynes with I\_2, PPh\_3, and H\_2O. b) Proposed reaction pathway of the cascade reaction for the synthesis of phthalides

In conclusion, we developed a hydroiodination-triggered cascade reaction of 2-alkynylbenzoates. This one-pot cascade reaction involves four processes: desilylation, hydroiodination, cyclization, and reduction. Metal-free and readily available reagents ( $I_2$ /PPh<sub>3</sub>/H<sub>2</sub>O) are utilized in the cascade reaction, which offers a considerable advantage over conventional approaches.

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**Keywords**: Domino reactions • Cyclization • Reduction • Iodine • Phosphorus

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Phthalides are synthesized in excellent yields by a metal-free cascade reaction from 2-alkynylbenzoates with  $I_2/PPh_3/H_2O$ , which are easy-aviable reagents. This reaction includes 4 steps: desilylation, hydroiodination, cyclization, and reduction.

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