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# TBAI-mediated regioselective 5-*exo*-*dig* iodinative oxocyclization of 2-alkynylbenzamides for the synthesis of isobenzofuran-1-imines and isobenzofurans

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ABSTRACT

Alkyne-based regioselective functionalization is an important transformation method for the synthesis of a wide variety of organic products. In this work, a regioselective TBAI-mediated oxidative 5-*exo*-*dig* iodo-*oxy*cyclization of 2-alkynylbenzamide is used for the synthesis of various isobenzofuran derivatives with excellent functional group tolerance and high reaction efficiency. We hypothesized that using water in a mixed solvent could change the reaction pathway and realize a high reaction regioselectivity. Furthermore, the application of the developed procedure was demonstrated by the synthesis of phthalazin-1(2*H*)-one and aryl-substituted isobenzofurans.



The regioselective functionalization of alkynes is of great significance for the synthesis of a variety of organic products [1]. Importantly, intramolecular annulation has been extensively studied for their ability to synthesize the privileged structural cores, which always starts from a dual-function substrate [2].

As one of versatile dual-function synthons, 2-alkynylbenzamide is well-recognized as a powerful building block to synthesize various *N*-heterocyclic architectures through four reaction systems [3–7], including base-mediated 5-*exo azo*-cyclization [3], Lewis acid-catalyzed 6-*endo oxy*-cyclization [4], transitional metal-catalyzed 5-*exo oxy*-cyclization [5], and electrophilic cyclization [6]. Based on these pioneer works, we aim at determining the regioselectivity of cyclization reaction on alkynes. Larock and co-workers observed that both 5-*exo oxy*-cyclization and 6-*endo oxy*-cyclization could be found in the electrophilic cyclization of 2-alkynylbenzamide, which resulted in a mixture of 3-methyleneisobenzofuran-1-imine and isochromen-1-imine (Scheme 1, Eq. (1)) [6b]. Therefore, it is highly desirable to realize regioselective electrophilic cyclization of 2-alkynylbenzamide.

Over the past years, our group has devoted much endeavour on the regioselective functionalization of alkynes [8]. To construct 4-bromomethylene-4*H*-benzo[*d*][*1,3*]oxazine under a milder condition, we conducted a trial reaction involving KBr-mediated oxidative cyclization of *N*-acyl-2-alkynylacetoaniline using water as solvent [8a]. However, it is surprising that the reaction pathway was changed when water was used as solvent. This transformation uniquely produced *N*-(2-(2,2-dibromo-2-arylacetyl)aryl)acetamide via bromonative 6-*endo oxy*-cyclization and water-based nucleophilic ring-opening, whereas the desired 4-bromomethylene-4*H*-benzo[*d*][*1,3*]oxazine was not observed. Inspired by these findings, we hypothesized that this strategy could be employed to realize regioselective electrophilic halocyclization of 2-alkynylbenzamide (Scheme 1, Eq. (2)). However, the preliminary result indicated that KBr-mediated electrophilic cyclization of 2-alkynylbenzamide at 80 °C was regioselective in a fashion of 5-*exo oxy*-cyclization, which only provided isobenzofuran-1-imines in a good yield. To improve

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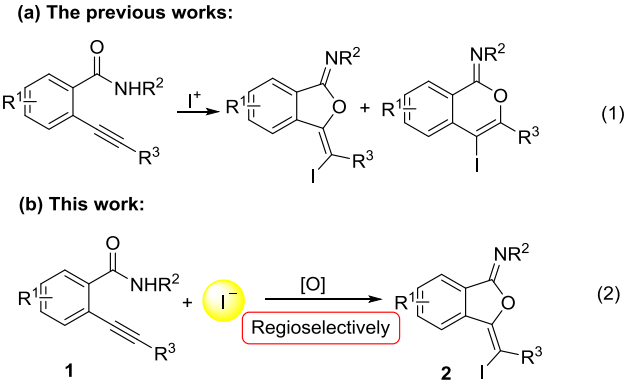



**Scheme 1.** Proposed route for the regioselective 5-*exo-dig iodo*-oxycyclization of 2-alkynylbenzamides.

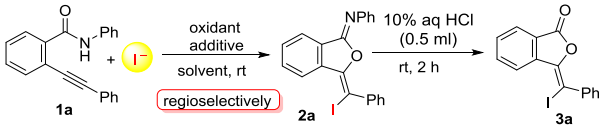
the reaction efficiency and broaden the reaction scope under a milder reaction condition, we next optimized the iodide-mediated electrophilic 5-*exo oxy*-cyclization of 2-alkynylbenzamide for the synthesis of iodo-containing isobenzofuran-1-imines (Scheme 1, Eq. (2)).

Based on the reported findings on the TBAB-mediated brominative regioselective functionalization of alkynes [9], we first employed *tetra-n*-butyl ammonium iodide (TBAI) as a source of iodide salt in the model reaction of *N*-phenyl-2-(phenylethynyl) benzamide **1a**. The result in the optimization experiments shows that the iodo-containing isobenzofuran-1-imines was partially hydrolysed into iodo-containing isobenzofurans. To the best of our knowledge, isobenzofuran-1-imines could be hydrolysed to isobenzofurans in the presence of HCl [6b,10]. Considering the importance of isobenzofuran core [11], we herein focused on the synthesis of isobenzofuran derivatives from 2-alkynylbenzamide via regioselective 5-*exo iodo-oxy*cyclization and *in situ* hydrolysis.

As presented in Table 1, when THF:$H_2O$ (v/v, 1:1) was employed as solvent, the desired product isobenzofuran **3a** was produced with the yield of 70% at room temperature (entry 3, Table 1), whereas other mixed solvents such as DCE:$H_2O$, MeCN:$H_2O$, and pure water only afforded **3a** in 46%, 20% and 53% respectively. The decrease of ratio between water and THF made significant impact on reaction yield and regioselectivity (entry 5, Table 1). 6-*endo* cyclization isomer was observed in 11% yield. When changing the oxidant from oxone to $H_2O_2$, the reaction was totally shut down (entry 6, Table 1). Moreover, the uses of $NaHCO_3$ as additive provided an inferior yield (entry 7, Table 1). Meanwhile, blank experiment was also performed to demonstrate the importance of using additive for the reactions (entry 8, Table 1). In addition, changing TBAI to KI was not favourable for the reaction, affording the desired product **3a** in 39% yield (entry 9, Table 1). The result was possibly ascribed to the dual role of TBAI both as an iodo source and phase transfer catalyst. When reducing the loading of TBAI and $K_2CO_3$, the yields were decreased accordingly (entries 9–10, Table 1). As a result, 2.0 equivalent of TBAI, 3.0 equivalent of $K_2CO_3$, 2.0 equivalent of oxone in THF:$H_2O$ (v/v, 1:1) and 10% of aqueous HCl (0.5 mL) at room temperature were selected as an optimized condition for the subsequent transformations.

After optimization, we then examined the reaction scope and the results were illustrated in Table 2. Encouragingly, a series of isobenzofuran derivatives **3** were synthesized as expected. The substituents $R^1$ were equal to aryl, alkyl, and silyl groups. For example, the reaction of *N*-phenyl-2-(phenylethynyl)benzamide **1a** provided isobenzofuran **3a** in a 70% yield under standard conditions. Electronic effect of aryl $R^1$ had a significant impact on the reaction results. Based on these results, we believed that the electron-rich aryl groups were more favourable than the electron-deficient aryl groups. For instance, the reaction of 4-methylphenyl-connected substrate **1b** leading to a desired product **3b** in a 73% yield, while the 4-chlorophenyl- and 4-fluorophenyl-linked substrates (**1c** and **1d**) only afforded isobenzofuran **3d** and **3e** in 55% and 63% yields, respectively. To our surprise, a mixed product of 5-*exo* cyclization **3c** and 6-*endo* cyclization **3c'** was formed when 2-((4-methoxyphenyl)ethynyl)-*N*-phenylbenzamide **1c** was used as substrate (total yield: 74%, ratio = 1:1). The reaction of 2-((4-nitrophenyl)ethynyl)-*N*-phenylbenzamide failed to produce a desired product. Interestingly, heteroaryl-connected substrate was also compatible for the reaction under standard conditions. The reaction of thiophene-attached starting material **1f** proceeded smoothly with the formation of thiophene-connected isobenzofuran **3f** in a 82% yield.

**Table 1**
Preliminary studies for regioselective 5-*exo-dig iodo*-oxycyclization of 2-alkynylbenzamide **1a** with iodide[a].




| entry | $[I]^-$ | additive (3.0 eq.) | oxidant | solvent | 3a of yield (%)[a,b] |
|---|---|---|---|---|---|
| `1 | TBAI | $K_2CO_3$ | oxone | DCE:$H_2O$ (v/v,1:1) | 46 |
| 2 | TBAI | $K_2CO_3$ | oxone | MeCN:$H_2O$ (v/v,1:1) | 20 |
| **3** | **TBAI** | **$K_2CO_3$** | **oxone** | **THF:$H_2O$ (v/v,1:1)** | **70** |
| 4 | TBAI | $K_2CO_3$ | oxone | $H_2O$ | 53 |
| 5 | TBAI | $K_2CO_3$ | oxone | THF:$H_2O$ (v/v,4:1) | 41[e] |
| 6 | TBAI | $K_2CO_3$ | $H_2O_2$ | THF:$H_2O$ (v/v,1:1) | N. R. |
| 7 | TBAI | $NaHCO_3$ | oxone | THF:$H_2O$ (v/v,1:1) | 61 |
| 8 | TBAI | – | oxone | THF:$H_2O$ (v/v,1:1) | Complex |
| 9 | KI | $K_2CO_3$ | oxone | THF:$H_2O$ (v/v,1:1) | 39 |
| 10[c] | TBAI | $K_2CO_3$ | oxone | THF:$H_2O$ (v/v,1:1) | 62 |
| 11[d] | TBAI | $K_2CO_3$ | oxone | THF:$H_2O$ (v/v,1:1) | 65 |

[a] Reaction conditions: **1a** (0.2 mmol), iodide source (2.0 equiv), additive (3.0 equiv), oxidant (2.0 equiv), 8 h.
[b] Isolated yield based on 2-alkynylbenzamide **1a**.
[c] 1.5 equiv TBAI.
[d] 2.0 equiv $K_2CO_3$.
[e] 6-endo cyclization isomer was observed in 11% yield. DCE = 1,2-dichlorethane; THF = tetrahydrofuran; MeCN = acetonitrile; N. R. = no reaction.