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### Construction of Isoquinolin-1(2*H*)-ones by Copper-Catalyzed Tandem Reactions of 2-(1-Alkynyl)benzaldimines with Water

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The Cu(OAc)<sub>2</sub>-catalyzed tandem reaction of 2-(1-alkynyl)benzaldimines with water for the synthesis of isoquinolin-1(2*H*)-ones was developed. Moreover, 4-halogen-substituted isoquinolin-1(2*H*)-ones were obtained in good yields simply by including *N*-halosuccinimides (NXS: X = Cl, Br, I) in the reaction system. Mechanistic studies indicated that the reactions are probably initiated by highly regioselective intramolecular cyclization of 2-(1-alkynyl)benzaldimines to give the corresponding isoquinolinium intermediates.

#### Introduction

The isoquinolin-1(2H)-one skeleton represents an important heterocyclic structure that is found in numerous biologically active compounds and pharmaceuticals.<sup>[1]</sup> Significant effort has been devoted to develop efficient methods for its construction.<sup>[2,3]</sup> Among these methods, intramolecular cyclization of 2-alkynylbenzamides, as one of the most straightforward strategies, has attracted considerable attention.<sup>[4]</sup> It has been found that both transition-metal catalysts and electrophilic reagents can promote this cyclization.<sup>[5]</sup> However, this route suffers from several limitations, especially the lack of regioselectivity and chemoselectivity, see Scheme 1, Equation (1).<sup>[5,6]</sup> Notably, Too and Chiba recently developed an efficient CuBr-mediated aerobic reaction of 2-alkynylbenzaldehydes with primary amines for the direct synthesis of 4-bromoisoquinolones<sup>[7]</sup> that proceeds selectively through 6-endo cyclization of hemiaminal intermediates generated in situ, see Scheme 1, Equation (2). However, a large excess amount of CuBr·SMe<sub>2</sub> is required, and the reaction fails with aromatic amines. Herein, we report a highly selective and efficient copper-catalyzed tandem cyclization process for the synthesis of isoquinolin-1(2H)-ones starting from 2-(1-alkynyl)arylaldimines, see Scheme 1, Equation (3).

2-(1-Alkynyl)arylaldimines are a class of useful organic molecules and are widely used to construct isoquinolines and 1,2-dihydroisoquinolines.<sup>[8–10]</sup> Starting from 2001, Larock and co-workers reported the formation of 3,4-di-substituted isoquinolines through the palladium-catalyzed

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Previous work: Intramolecular cyclization of 2-alkynylbenzamides<sup>[5,6]</sup> ο R NR 5-exo or 6-endo NHR cyclization ·R' (1)nucleophilic addition NR of N or O atoms R' 'n Chiba's work<sup>[7]</sup> 2.2 equiv. CuBr·SMe<sub>2</sub> R benzene/pyridine (5:1) ·NH<sub>2</sub> (2) SiO<sub>2</sub>, 80 °C, O<sub>2</sub> (1 atm) R<sup>2</sup>  $R^1 \neq Ar$ . H Br This work: Cu-catalyzed tandem reaction cat. Cu(OAc)<sub>2</sub>·H<sub>2</sub>O <sub>≷N</sub>∕R¹ 5 equiv. H<sub>2</sub>O, PhMe, air (3) with or without NXS X = CI, Br, I; R<sup>1</sup>, R<sup>2</sup> = Ar, alkyl ... Ή(X) [M] or

Scheme 1. Construction of isoquinolin-1(2H)-ones through intramolecular cyclization strategies.

Ή(X)

 $\dot{M}(X)$ 

carboamination of the *tert*-butylimines of 2-(1-alkynyl)aryl aldehydes.<sup>[8a-8g]</sup> Later, they found that electrophilic reagents could also promote the cyclization to give substituted isoquinolines.<sup>[8h,8i]</sup> During the same time, Asao and coworkers reported the synthesis of 1,3-disubstituted 1,2-dihydroisoquinolines by Ag<sup>I</sup>-promoted cyclization of 2-alkynylarylimines followed by intermolecular nucleophilic addition.<sup>[9a]</sup> In addition, Takemoto et al. developed a carbophilic Lewis acid catalyzed method for the synthesis of 1,2dihydroisoquinolines through tandem nucleophilic addition/cyclization of 2-(1-alkynyl)arylaldimines.<sup>[10a,10b]</sup> Inspired by these results, we envisioned that the tandem cyclization of 2-(1-alkynyl)arylaldimines and nucleophilic addition of water followed by oxidation might lead to the selective formation of isoquinolin-1(2H)-ones, see Scheme 1, Equation (3).

#### **Results and Discussion**

Our investigation began with the reaction of iminoalkyne 1a with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol-%) in toluene at 130 °C in air. To our delight, desired cyclization product 2a was obtained in 64% yield and no isoquinolines-type product was observed (Table 1, entry 1). Upon performing the reaction under an  $O_2$  atmosphere instead of in air, product 2a was isolated in 41% yield along with N-phenylphthalimide (2')in 36% yield (Table 1, entry 2).<sup>[11]</sup> As the reaction time was extended from 6 to 12 h, the yield of 2a increased to 73% (Table 1, entry 3). Increasing the loading of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O to 30 mol-% further boosted the yield of 2a to 79% (Table 1, entry 4). No reaction took place in the absence of the copper catalyst (Table 1, entry 5). Gratifyingly, the addition of H<sub>2</sub>O (5 equiv.) to the reaction system led to an optimal yield (89%; Table 1, entry 6). However, increasing the amount of water to 10 equiv. resulted in inferior results (Table 1, entry 7). Further screening of the amount of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O and water revealed that 2a could be obtained in 86% yield if 10 mol-% of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O and 3 equiv. of H<sub>2</sub>O were used (Table 1, entry 8).<sup>[12]</sup> In addition, a series of other metal catalysts, such as CuCl<sub>2</sub>, Cu(OTf)<sub>2</sub> (Tf =  $CF_3SO_2$ ), CuI, and Fe(OAc)<sub>2</sub>, were evaluated and were found to be less efficient (Table 1, entries 9-12). Inter-

Table 1. Selected results from screening of the optimal conditions.[a]



[a] Reaction conditions: **1a** (0.2 mmol), [M] (5–30 mol-%), and solvent (1.5 mL) in air for 12 h, sealed tube, 130 °C. DCE = 1,2-dichloroethane. [b] Yield of isolated product. [c] 6 h. [d] Under  $O_2$  atmosphere. [e] Fe(OAc)<sub>2</sub> (95% purity).



estingly, the reaction also performed smoothly in the presence of  $Fe(OAc)_2$  (30 mol-%) to afford the desired product in 73% yield. Subsequently, various solvents were also screened, and toluene proved to be the best choice (Table 1, entries 13–16).

After the establishment of the optimal reaction conditions, the scope of the substrates was surveyed (Table 2). Both electron-withdrawing and -donating substituents (e.g., MeO-, Cl-, F-) on the phenyl ring were well tolerated (see products **2b-d**). Moreover, iminoalkynes derived from a variety of aromatic amines were also suitable substrates, and the corresponding isoquinolin-1(2*H*)-ones were obtained in high yields (see products **2e**–i). In contrast, the reactions of iminoalkynes derived from aliphatic amines were less successful. Whereas the phenethylamine-derived

Table 2. Substrate scope.<sup>[a,b]</sup>



[a] Reaction conditions: 1 (0.2 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.06 mmol), PhMe (1.5 mL), air, sealed tube, 130 °C, 12 h. [b] Yields of isolated products are given; yields of the products obtained for reactions performed in the presence of Cu(OAc)<sub>2</sub> (10 mol-%) and H<sub>2</sub>O (3 equiv.) are shown in parentheses. [c] Yield of the product obtained for the reaction performed in the presence of Fe(OAc)<sub>2</sub> (30 mol-%). [d] Al<sub>2</sub>O<sub>3</sub> (20 mg).

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substrate reacted with water to afford product 2j in 36% yield, iminoalkynes derived from *tert*-butylamine and benzylamine did not afford any isoquinolin-1(2*H*)-one products. In the latter two cases, corresponding isoquinoline  $2''^{[8f,8g,13]}$  was formed instead, which suggests that the reactions may be proceeded through isoquinolinium intermediates. Furthermore, both aromatic and aliphatic functional groups on the alkynyl part were well tolerated (see products 2m-t), although aliphatic substituents gave relatively lower yields (see products 2s and 2t). Notably, 2d, 2f, 2m, and 2rwere also obtained in good yields in the presence of Fe(OAc)<sub>2</sub> (30 mol-%) as the catalyst.

To introduce halogen atoms at the C4 position of the isoquinolin-1(2H)-ones, N-halosuccinimides (NXS: X = Cl, Br, I) were added to the reaction system as a halogen atom source (Table 3). After optimization of the reaction conditions (see the Supporting Information), we found that in the presence of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (30 mol-%), NBS (1 equiv.), and H<sub>2</sub>O (3 equiv.) the tandem reaction of iminoalkyne 1a worked well at 100 °C in chlorobenzene. Therefore, the cyclization of several 2-(1-alkynyl)arylaldimines under these conditions was performed (Table 3). The corresponding 4bromo-, 4-iodo-, and 4-chloroisoquinolin-1(2H)-ones (see products 3a-c, 3r, 3a', and 3a'') were isolated in moderate to high yields (53-75%).<sup>[14]</sup> Notably, in the absence of  $Cu(OAc)_2 \cdot H_2O$ , 4-bromo-substituted isoquinolin-1(2H)one 3a was obtained in only 14% yield starting from 1a (see the Supporting Information).

Table 3. Substrate scope.[a,b]



[a] Reaction conditions: 1 (0.2 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.06 mmol), NXS (0.2 mmol), H<sub>2</sub>O (0.6 mmol), PhCl (1.5 mL), sealed tube, 100 °C. [b] Yields of the isolated products are given. [c] 1,2-Di-chloroethane (1.5 mL).

Several experiments were conducted to shine light on the reaction mechanism (Scheme 2). The reaction of **1a** in the presence of  $Cu(OAc)_2$  (30 mol-%) performed under an Ar atmosphere furnished desired product **2a** in only 10% yield, which suggests that O<sub>2</sub> is necessary for the transformation, see Scheme 2, Equation (4). The fate of D<sub>2</sub>O in the reaction shown in Equation (5) (Scheme 2) clearly indicates proton-

ation at the 4-position, which supports the formation of an intermediate with a C-Cu bond.<sup>[15]</sup> In addition, through the addition of H<sub>2</sub>O<sup>18</sup>, an O<sup>18</sup>-substituted product was observed (see the Supporting Information), which suggests that the oxygen in the product comes from water, see Scheme 2, Equation (6). On the basis of these results, a possible mechanism is proposed in Scheme 3.<sup>[16]</sup> First, complexation of Cu<sup>II</sup> with the alkynyl moiety of substrate 1 activates the triple bond for nucleophilic attack by the imine nitrogen atom to form isoquinolinium intermediate B. Subsequently, nucleophilic addition of water onto intermediate **B** followed by oxidation of hemiaminal **C** with  $Cu^{II}$  and  $O_2$ leads to final product 2. On the other hand, electrophiles could also promote the cyclization of substrate 1, which would lead to isoquinolinium intermediate  $\mathbf{B}'$ , and this intermediate could undergo nucleophilic addition with water to give C'.<sup>[17]</sup> Oxidation of C' affords corresponding halogenated product 3.



Scheme 2. Preliminary mechanism study.



Scheme 3. The proposed mechanism.

To further increase the synthetic utility of this transformation, we tried the direct reaction of 2-(1-alkynyl)benzaldehyde 1a' with aniline in the presence of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (30 mol-%). The reaction afforded corresponding isoquinolin-1(2*H*)-one 2a in 63% yield, see Equation (7).



#### Conclusions

We developed a copper-catalyzed tandem reaction of 2-(1-alkynyl)benzaldimines with water. This method provides straightforward and facile entry to various isoquinolin-1(2H)-one derivatives. Further study of the reaction scope and applications is still underway in our laboratory.

#### **Experimental Section**

General Procedures for the Synthesis of Isoquinolin-1(2H)-ones 2: A 25 mL tube was charged with 2-alkynylbenzaldehydeimine derivative 1 (0.2 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (0.06 mmol), H<sub>2</sub>O (1.0 mmol), and toluene (1.5 mL). The tube was sealed with a Teflon<sup>®</sup>-lined cap, and the mixture was stirred at 130 °C for 12 h. Subsequently, the mixture was purified by column chromatography (silica gel; petroleum ether/ethyl acetate, 5:1) to give the desired product.

General Procedures for the Synthesis of 4-Halogenoisoquinolin-1(2H)-ones 3: A 25 mL tube was charged with 2-alkynylbenzaldehyde derivative 1 (0.2 mmol),  $Cu(OAc)_2 \cdot H_2O$  (0.06 mmol), NXS (0.2 mmol),  $H_2O$  (0.6 mmol), and chlorobenzene (1.5 mL). The tube was sealed with a Teflon-lined cap, and the mixture was stirred at 100 °C for 12 h. Subsequently, the mixture was purified by column chromatography (silica gel; petroleum ether/ethyl acetate, 5:1) to give the desired product.

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- [12] Because other substrates gave worse results under these reaction conditions than the conditions in entry 6 (Table 1), we chose the latter as the standard conditions.
- [13] The structure of compound 2'' is as below:



- [14] For the crystal structure of 3b, see the Supporting Information. CCDC-1056204 (for 3b) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.
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