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Synthesis of Dibenzoxepine Lactams via a Cu-Catalyzed One-Pot Etherification/Aldol Condensation Cascade Reaction: Application toward the Total Synthesis of Aristoyagonine

Hye Sun Lim,[†,‡] Young Lok Choi,[†] and Jung-Nyoung Heo*[,†,‡]

Medicinal Chemistry Research Center, Korea Research Institute of Chemical Technology, 141 Gajeong-ro, Daejeon 305-600 Korea, and Graduate School of New Drug Discovery and Development, Chungnam National University, 99 Daehak-ro, Daejeon 305-764 Korea

heojn@krict.re.kr

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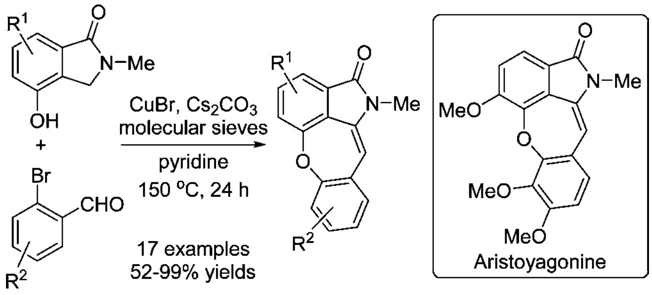
ABSTRACT



A general synthesis of dibenzoxepine lactams has been developed using a one-pot Cu-catalyzed etherification/aldol condensation cascade reaction. The reaction of 4-hydroxyisoindolin-1-one with a wide range of 2-bromobenzaldehydes in the presence of a copper catalyst provided various aristoyagonine derivatives in good yields.

Polycyclic heterocycles are frequently found in natural products and pharmaceutical agents.[1] In particular, the dibenzoxepine motif has been found to be important in a wide range of therapeutics.[2] From a structural point of view, natural products with an additional ring system in the dibenzoxepine framework traditionally play a key role in medicinal chemistry. Among these products, a family of the diverse cularine alkaloids that includes aristoyagonine (**1**), yagonine (**2**), and oxosarcocapnine (**3**) in different oxidation states has shown interesting biological activity against cancer cell lines (Figure 1).[3] Aristoyagonine was isolated from *Sarcocapnos* plants in 1984 and is the only known product in this family that contains a five-membered lactam ring.[4] Previously, Castedo et al. accomplished the first synthesis of aristoyagonine using lithium−halogen exchange followed by internal trapping with carbamates.[5]

[†] Korea Research Institute of Chemical Technology.

[‡] Chungnam National University.

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Couture and co-workers reported the total synthesis of aristoyagonine through an intramolecular Ullman coupling reaction, which is an effective method, but it is somewhat limited by the low yield of the Horner-type reaction used to prepare the isoindolinone precursor.[6]

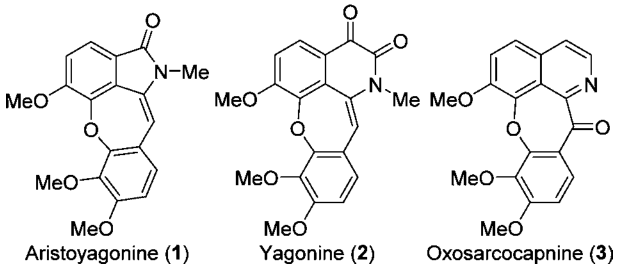
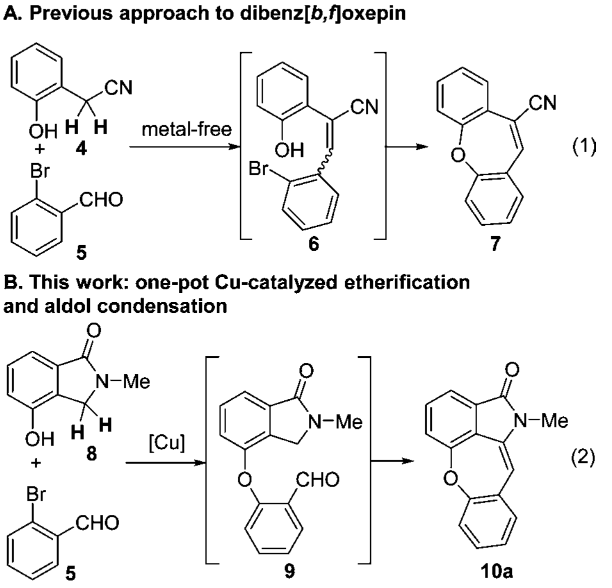


Figure 1. Members of an aristocularine family.

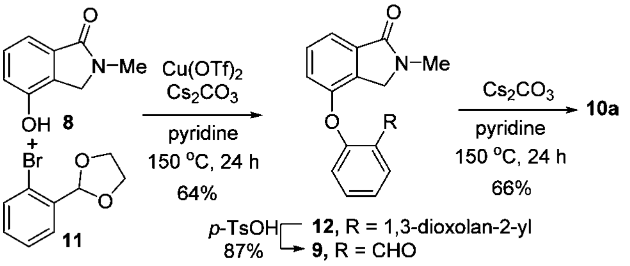
As part of our ongoing drug discovery program to develop novel scaffolds,[7] we recently reported the direct one-pot synthesis of dibenzoxepine **7** via a transition-metal-free base-mediated aldol condensation and nucleophilic aromatic substitution pathway (Scheme 1, eq 1).[8] Following this strategy, our next challenge was the introduction of an additional lactam ring in the dibenzoxepine framework. However, our preliminary attempts with isoindolin-1-one **8** and 2-bromobenzaldehyde (**5**) in the absence of transition metals were not successful in achieving the desired result. We believe that this failure illustrates that the primary factor is the difference in the acidities of the benzylic protons of **4** and **8** in the first aldol condensation step. With this in mind, we revised our synthetic plan to employ a Cu-catalyzed etherification followed by an aldol condensation cascade reaction (eq 2).[9]

To verify our synthetic strategy, we performed the stepwise reaction sequence using acetal-protected 2-bromobenzene **11**. The coupling of isoindolin-1-one **8**[10] with **11**[11] in the presence of a $Cu(OTf)_2$ catalyst provided biaryl ether **12** in 64% yield (Scheme 2). After deprotection of the acetal group under weakly acidic conditions, the intramolecular aldol-type cyclization of aldehyde **9** under basic conditions (Cs_2CO_3/pyridine) at 150 °C successfully afforded the corresponding dibenzoxepine lactam **10a** in 66% yield.

Scheme 1. One-Pot Synthesis of Dibenz[*b,f*]oxepine and Dibenzoxepine Lactam



Scheme 2. Stepwise Synthesis of Dibenzoxepine Lactam



After screening a variety of conditions, we found that the one-pot coupling reaction of isoindolin-1-one **8** with 2-bromobenzaldehyde (**5**) in the presence of a Cu catalyst, with Cs_2CO_3 as the base and pyridine as the solvent, afforded the desired dibenzoxepine lactam **10a** in good yield (Table 1). Notably, little or no biaryl ether aldehyde **9** was observed via GC/MS analysis. Various copper sources proved to be excellent catalysts in this type of one-pot reaction, with yields greater than 90%. Of the potential copper catalysts, we chose CuBr because it is inexpensive and highly effective (entry 5).

Having determined the optimal conditions, we examined the scope of this one-pot Cu-catalyzed etherification and aldol condensation reaction (Figure 2). However, substituted 2-bromobenzaldehydes other than **5** gave poor yields. For example, the coupling with 2-bromo-4-methylbenzaldehyde provided **10b** in only 52% yield. Eventually, we found that the addition of molecular sieves (4 Å) improved the reaction

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(10) Isoindolin-1-one **8** was readily prepared from 3-acetoxy-2-methylbenzoic acid in three steps. See Supporting Information for details.

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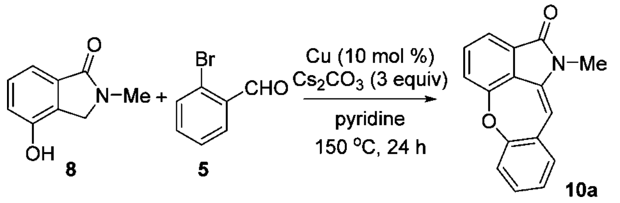
Table 1. One-Pot Synthesis of Dibenzoxepine Lactam[a]



entry	Cu	yield (%)[b]
1	none	no reaction
2	$Cu(OTf)_2$	94
3	Cu_2O	91
4	CuI	94
5	**CuBr**	**99**
6	CuCl	97

[a] Reaction conditions: **8** (0.3 mmol), **5** (0.6 mmol), CuBr (10 mol %), Cs_2CO_3 (3 equiv), pyridine, 150 °C, 24 h. [b] Isolated yield.

yield (83%), presumably by trapping H_2O that was generated in situ during the aldol condensation[12] [CuBr (10 mol %), Cs_2CO_3 (3 equiv), molecular sieves (4 Å), pyridine, 150 °C, 24 h]. A range of 2-bromobenzaldehyde derivatives were coupled with 4-hydroxyisoindolin-1-one **8** in modest to high yields. Both electron-rich and electron-deficient substrates were converted to the desired dibenzoxepine lactams. No interconversion between chloride-substituted benzaldehyde and the existing bromide was observed (**10d**). This protocol was also expanded to the naphthyl (**10g**) and heteroaromatic carboxaldehydes, including pyridines (**10h** and **10i**) and a thiophene (**10j**), which exhibited no significant incompatibilities during the reaction.

After we efficiently accessed the tetracyclic framework of aristoyagonine via the one-pot Cu-catalyzed etherification and aldol condensation, the key remaining challenge toward the total synthesis of aristoyagonine involved the simple replacement of the starting isoindolin-1-one and 2-bromobenzaldehyde. Following this plan, we hypothesized that the palladium-catalyzed carbonylation reported by Orito would be appropriate to obtain the key intermediate, isoindolin-1-one **17a** (Scheme 3).[13] The protection of phenol **13a** with a benzyl group followed by a reductive amination provided benzylamine **15a** in excellent yield.[14] The intramolecular palladium-catalyzed carbonylation of **15a** smoothly produced isoindolin-1-one **16a**, which was subjected to debenzylation via catalytic hydrogenation. Finally, the one-pot Cu-catalyzed etherification/aldol condensation of **17a** with 2-bromobenzaldehyde **18**[15] under the optimized conditions provided aristoyaonine (**1**)

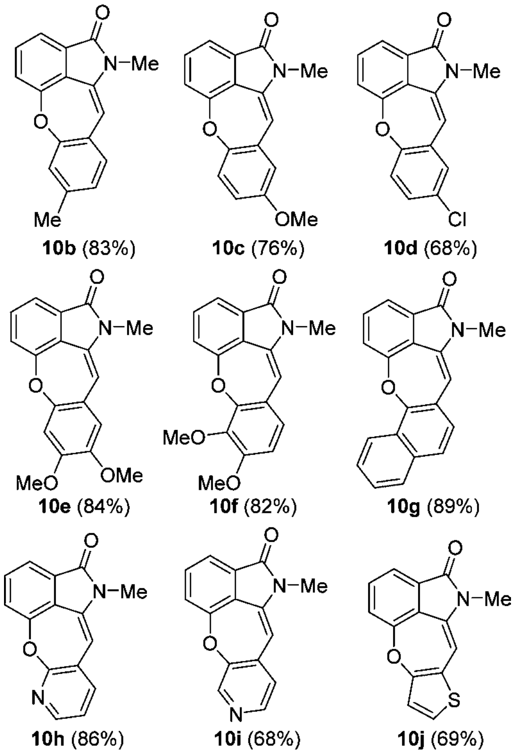
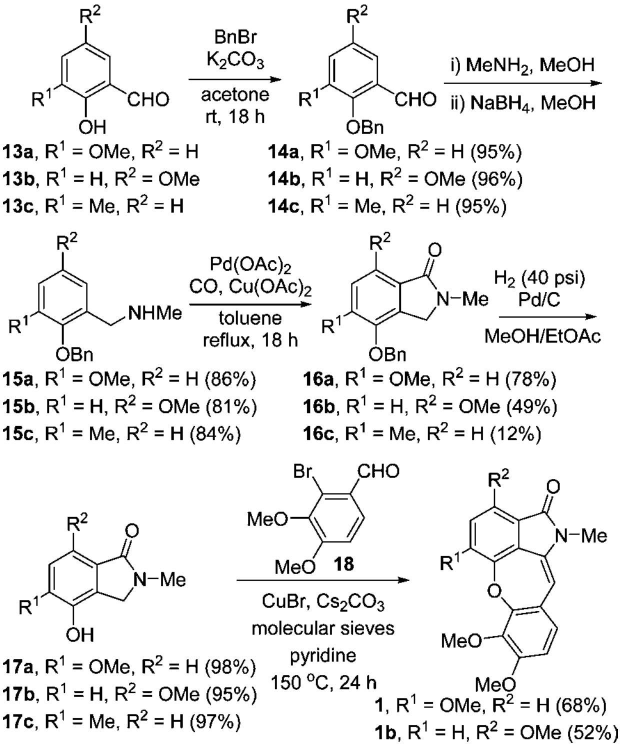


Figure 2. Scope of the dibenzoxepine lactams.

Scheme 3. Total Synthesis of Aristoyagonine



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(16) According to the procedure reported by Couture and co-workers (ref 6), aristoyagonine **1** was prepared from 3-benzyloxy-2,4-dimethoxybenzoic acid in five steps with a 12.4% overall yield.

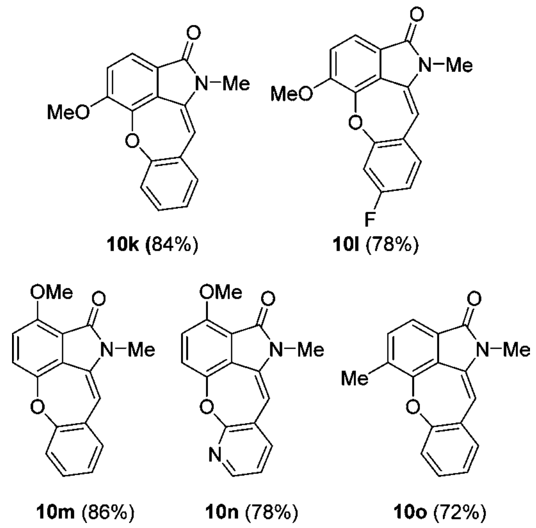

Figure 3. Scope of aristoyagonine derivatives.

in 68% yield. This route efficiently provided aristoyagonine in five steps with a 42.5% overall yield, starting from the commercially available benzaldehyde **13a**.[16] Following the same route, we obtained isoindolin-1-ones **17b** and **17c**, starting from phenols **13b** and **13c**, respectively. In the case of **17b**, the final one-pot cyclization with **18** provided the desired product **1b** in 52% yield.

Following the standard protocol, we finally evaluated the scope of the coupling reaction with respect to the isoindolin-1-one coupling partners. As illustrated in Figure 3, substituted isoindolin-1-ones (**17a**, **17b**, and **17c**) were found to be compatible with the reaction, providing the corresponding dibenzoxepine lactams in good to excellent yields. Notably, the presence of sterically hindered 5-OMe (**10k** and **10l**) and 5-Me (**10o**) groups in the substrates appeared to have little or no effect on the coupling with various 2-bromobenzaldehydes.

In summary, we developed an efficient, simple one-pot procedure for the synthesis of dibenzoxepine lactam via a Cu-catalyzed etherification/aldol condensation cascade reaction. The coupling reactions of isoindolin-1-ones with 2-bromobenzaldehydes in the presence of catalytic CuBr provided a wide range of dibenzoxepine lactams. The total synthesis of aristoyagonine was successfully achieved in a highly efficient manner using this protocol, which also afforded a variety of aristoyagonine derivatives.

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Supporting Information Available. Experimental procedures and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.