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# Selective Insertion of Alkynes into C−C σ Bonds of Indolin-2-ones: Transition-Metal-Free Ring Expansion Reactions to Seven-Membered-Ring Benzolactams or Chromone Derivatives

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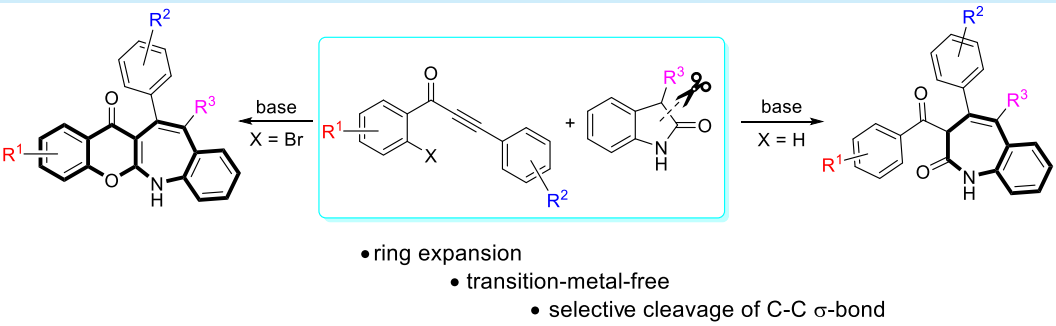
Supporting Information




**ABSTRACT:** An unprecedented ring expansion reaction of indolin-2-ones with alkynyl ketones under transition-metal-free conditions has been developed. Base-promoted selective cleavage of a C−C σ bond of the amide is the key in this process, which provides a straightforward and efficient way to synthesize seven-membered-ring benzolactams or chromone derivatives. The significant advantages of this method include readily accessible starting materials, wide scope and functional group tolerance, and high atom economy.

Carbon−carbon and carbon−nitrogen bonds are widely present in organic molecules and biomacromolecules. Transformations via cleavage reactions of C−C or C−N bonds are highly atom-economical methods with skeleton rearrangement. However, it is difficult to achieve C−C or C−N bond cleavage reactions, which usually require transition metal catalysts[1,2] or activated substrates, such as in situ-generated arynes[3] or cyclohexynes.[4] Therefore, it is of great significance to develop transition-metal-free cleavage reactions of C−C or C−N bonds under mild conditions. Amides are readily available compounds containing both C−C and C−N bonds. The cleavage reactions of amide C−N bonds are well-known.[2,5] Most of these reactions were developed by employing various transition metals, such as Ni,[2a−e] Pd,[2f−k] or others.[2l−p] Base-promoted C−N bond cleavage reactions of amides with highly reactive substrates have also been disclosed. For example, Liu and Larock reported a transition-metal-free amide C−N bond cleavage reaction with in situ-generated arynes (Scheme 1a).[3g] More recently, an amide C−N bond cleavage process in the presence of LiHMDS was developed by the Szostak group (Scheme 1b).[6] Generally, the C−N bond of amides is believed to be more reactive than the C−C bond. In this context, the development of selective transition-metal-free C−C bond cleavage reaction of amides remains a great challenge. Recently, our group disclosed a transition-metal-free cleavage reaction of the amide C−N bond (Scheme 1c).[7] On the basis of that research, we envisaged that cyclic amides such as indolin-2-ones could be expanded into seven-membered-ring compounds by an amide C−N bond insertion reaction (Scheme 1d), which may serve as a platform for producing various seven-membered N-heterocyclic compounds. Seven-membered-ring benzolactams are core structures found in many alkaloids and pharmaceutically related molecules, such as diazepam (**I**) and oxazepam (**II**), with enhancement of antianxiety activity, and darenzepine (**III**), an antiulcer agent (Figure 1).[8] The syntheses of seven-membered-ring benzolactams usually require metal catalysis or a multistep strategy.[9] Therefore, the development of efficient, transition-metal-free synthetic procedures starting from easily accessible starting materials is very appealing. Herein, we report a base-promoted, atom-economic approach which involves the selective insertion of ynones into C−C σ-bonds of cyclic amides (Scheme 1e), for the synthesis of seven-membered-ring benzolactams. Moreover, alkynones containing an *ortho*-halogenated aryl ring could also be used, resulting in seven-membered ring-fused chromone derivatives in good yields. Chromones are also commonly found in naturally occurring compounds.[10]

We initially tried the reaction of 3-phenyl-1-(*p*-tolyl)prop-2-yn-1-one (**1a**) with indolin-2-one (**2a′**). However, only **3a′**

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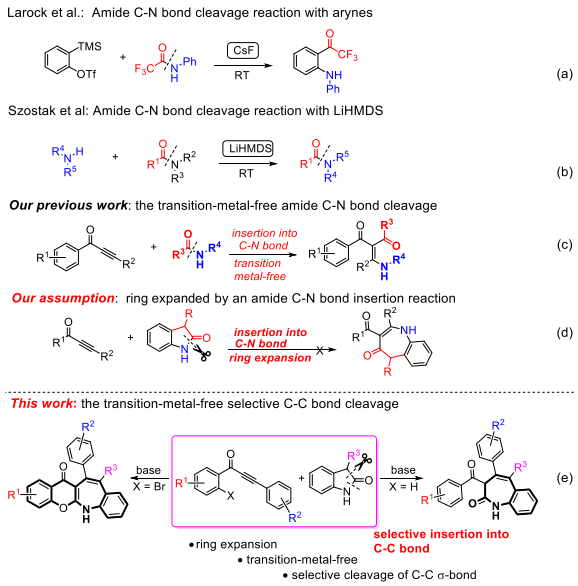
**Scheme 1. C−N or C−C Bond Activation of Amides**



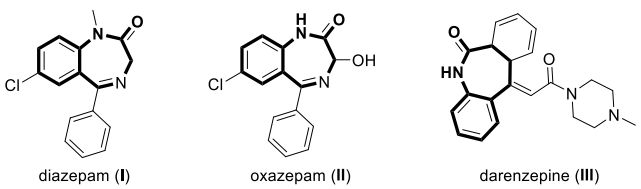
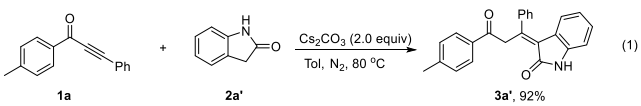



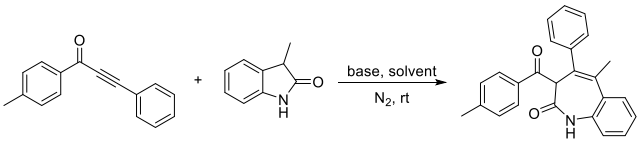

**Figure 1.** Representative bioactive molecules with seven-membered-ring benzolactams.

was obtained after screening of various reaction parameters (eq 1; for details, see SI). This product was formed via the Michael




addition of **2a′** to **1a** in the presence of a base followed by isomerization. We reasoned that the isomerization could be inhibited by employing 3-methyl-substituted indolin-2-one, and the desired ring-expansion product might be formed. Then we attempted the reaction of **1a** with 3-methylindolin-2-one (**2a**) (1.0 equiv) under air in the presence of 2.0 equiv of $Cs_2CO_3$ at room temperature in DMF. The results are shown in Table 1. To our delight, the ring expansion product **3a** was formed within 2 h, although in a low yield (Table 1, entry 1). Surprisingly, characterization of **3a** by NMR spectroscopy revealed that the C−C bond instead of the C−N bond of **2a** was selectively cleaved during the reaction process. This may because that the $\alpha$-H of **2a** is more acidic than *N*-H. The yield of **3a** was increased to 42% under a nitrogen atmosphere (entry 2). $K_2CO_3$ was almost ineffective for this reaction (entry 3). The yield was slightly increased to 44% when a stronger base such as *t*-BuOK was used (entry 4). The reaction was better in other dipolar aprotic solvents, such as DMAc or DMSO, with the best outcome occurring in DMSO (entries 5 and 6). Toluene as the solvent gave no desired product at all (entry 7). Increasing the amount of **2a** led to a significantly higher yield (entries 8 and 9). **3a** was obtained in up to 74% yield with 1.5 equiv of **2a** (entry 8). Finally, the effect of the amount of alkali was investigated (entries 10−12). It was

**Table 1. Optimization Studies for the Synthesis of 3a**[a]



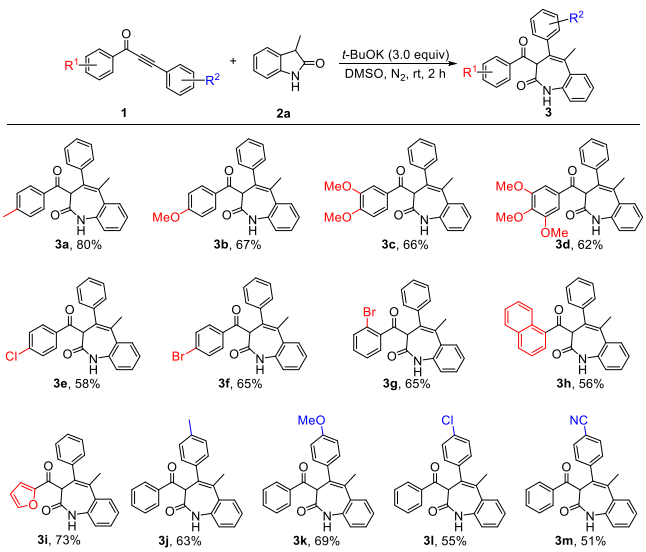

| entry | base (equiv) | solvent | yield (%)[b] |
|---|---|---|---|
| 1[c] | $Cs_2CO_3$ (2.0) | DMF | 13 |
| 2 | $Cs_2CO_3$ (2.0) | DMF | 42 |
| 3 | $K_2CO_3$ (2.0) | DMF | trace |
| 4 | *t*-BuOK (2.0) | DMF | 44 |
| 5 | *t*-BuOK (2.0) | DMAc | 46 |
| 6 | *t*-BuOK (2.0) | DMSO | 56 |
| 7 | *t*-BuOK (2.0) | toluene | NP[f] |
| 8[d] | *t*-BuOK (2.0) | DMSO | 74 |
| 9[e] | *t*-BuOK (2.0) | DMSO | 68 |
| 10[d] | *t*-BuOK (1.0) | DMSO | 52 |
| 11[d] | *t*-BuOK (3.0) | DMSO | 80 |
| 12[d] | *t*-BuOK (4.0) | DMSO | 41 |

[a]All reactions were performed on a 0.2 mmol scale with **1a**:**2a** = 1:1 in 2 mL of solvent under $N_2$ for 2 h, unless otherwise noted. [b]Isolated yields. [c]In air. [d]**1a**:**2a** = 1:1.5. [e]**1a**:**2a** = 1:2. [f]No product.

found that a high yield of 80% was observed using 3 equiv of *t*-BuOK (entry 11).

After the best conditions were determined (Table 1, entry 11), the substrate scope of this selective C−C insertion reaction was explored (Scheme 2). The results showed that

**Scheme 2. Substrate Scope of Alkynones 1**[a]




[a]Reaction conditions: 3.0 equiv of *t*-BuOK, 3 mL of DMSO, 0.3 mmol scale, **1**:**2a** = 1:1.5.

electron-donating $R^1$ groups (4-Me, 4-MeO, 3,4-$(MeO)_2$, 3,4,5-$(MeO)_3$) worked well, affording the desired ring-expansion products **3a**, **3b**, **3c**, and **3d** in 80, 67, 66, and 62% yield, respectively. Electron-withdrawing $R^1$ groups (4-Cl, 4-Br, 2-Br) also gave the corresponding seven-membered-ring benzolactams **3e**, **3f**, and **3g** in good yields. The 1-naphthyl-substituted alkynone readily delivered the corresponding product **3h** in 56% yield. The 2-furyl-containing alkyne



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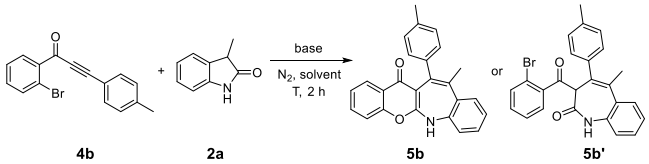
afforded the desired product **3i** in 73% yield. Alkynones with different $R^2$ substituents also worked well (**3j–l**). Notably, a *p*-CN functional group was tolerable as well, affording **3m** in 51% yield.

Having prepared a series of seven-membered-ring benzolactams, we envisioned that if alkynones bearing an *o*-bromide-substituted phenyl ring on the carbonyl carbon were used, further intramolecular cyclization would occur through nucleophilic aromatic substitution ($S_NAr$) to give fused-ring compounds. As we expected, the reaction of 1-(2-bromophenyl)-3-(*p*-tolyl)prop-2-yn-1-one (**4b**) with **2a** took place smoothly at 140 °C, affording the desired chromone **5b** in 22% yield (Table 2, entry 1). In order to increase the yield of **5b**,

**Table 2. Optimization Studies for the Synthesis of 5b**[a]



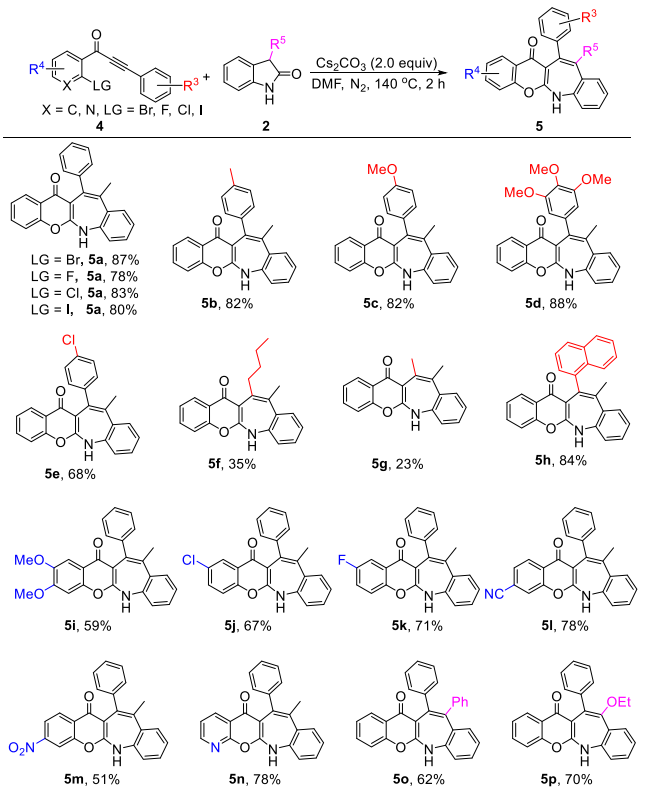

| | | | | yield (%)[b] | |
|---|---|---|---|---|---|
| entry | base (equiv) | solvent | *T* (°C) | **5b** | **5b′** |
| 1[c] | $Cs_2CO_3$ (2.0) | DMAc | 140 | 22 | –[f] |
| 2 | $Cs_2CO_3$ (2.0) | DMAc | 140 | 57 | –[f] |
| 3 | *t*-BuOK (2.0) | DMAc | 140 | 41 | –[f] |
| 4 | $Cs_2CO_3$ (2.0) | DMAc | 140 | 65 | –[f] |
| 5 | $K_2CO_3$ (2.0) | DMAc | 140 | 36 | –[f] |
| 6 | DABCO (2.0) | DMAc | 140 | trace | –[f] |
| 7 | $Cs_2CO_3$ (2.0) | DMF | 140 | 73 | –[f] |
| 8 | $Cs_2CO_3$ (2.0) | DMSO | 140 | 66 | –[f] |
| 9 | $Cs_2CO_3$ (2.0) | toluene | 140 | –[f] | 44 |
| 10 | $Cs_2CO_3$ (3.0) | DMF | 140 | 68 | –[f] |
| 11 | $Cs_2CO_3$ (1.0) | DMF | 140 | 71 | –[f] |
| 12[d] | $Cs_2CO_3$ (2.0) | DMF | 140 | 82 | –[f] |
| 13[e] | $Cs_2CO_3$ (2.0) | DMF | 140 | 78 | –[f] |
| 14[d] | $Cs_2CO_3$ (2.0) | DMF | 120 | 70 | –[f] |
| 15[d] | $Cs_2CO_3$ (2.0) | DMF | 100 | –[f] | 26 |
| 16[d] | $Cs_2CO_3$ (2.0) | DMF | 80 | –[f] | 51 |

[a]Reaction conditions: **4b**:**2a** = 1:1, 2 mL of solvent, under $N_2$, 2 h, 0.2 mmol scale. [b]Isolated yields. [c]In air. [d]**4b**:**2a** = 1:1.5. [e]**4b**:**2a** = 1:2. [f]No product.

optimization of the reaction conditions was conducted by adjusting reaction parameters, including the base, solvent, and ratio of the reactants (Table 2). Uncyclized product (**5b′**) was mainly produced at lower reaction temperatures (Table 2, entries 15 and 16). The results show that the reaction temperature has a great influence on the reaction process. The structure of **5b′** was fully confirmed by X-ray crystallography. It was found that the optimal conditions for the preparation of **5b** were 2.0 equiv of $Cs_2CO_3$ in DMF at 140 °C (Table 2, entry 12).

Next, a variety of *o*-bromo-substituted arenes on the carbonyl carbon were used to examine the scope of the reaction (Scheme 3). Not only bromo-substituted alkynones but also fluoro-, chloro-, or iodo-substituted ones could be used, delivering the desired product **5a** in 87, 78, 83, and 80% yield, respectively. *o*-Bromo-substituted arenes were selected to explore the substrate range since the highest yield of **5a** was achieved when it was used. For the substituents $R^3$ on the aryl ring attached to the triple bond, electron-donating groups such

**Scheme 3. Substrate Scope of 4 and 2**[a]




[a]Reaction conditions: LG = Br, 2.0 equiv of $Cs_2CO_3$, 3 mL of DMF, **4**:**2** = 1:1.5, 0.3 mmol scale.

as -Me, -OMe, and 3,4,5-$(OMe)_3$ afforded **5b–d** in >80% yield. An electron-withdrawing -Cl group resulted in a 68% yield of **5e**. An electron-poor aryl group gave a lower yield than electron-rich aryl groups (**5e** vs **5b–d**). Interestingly, alkyl-substituted substrates could also react with **2a** to give **5f** or **5g** in moderate yields. When a 1-naphthyl-substituted substrate was subjected to the reaction, the desired product **5h** was formed in 84% yield. Substituents on the aryl group attached to the carbonyl carbon could be electron-donating groups, such as 3,4-$(OMe)_2$, which gave **5i** in 59% yield. Electron-withdrawing functionalities such as 3-Cl, 3-F, 4-CN, and 4-$NO_2$ were also compatible with the reaction, producing the desired fused-ring compounds (**5j–m**) in 51–78% yield. The heteroaryl substituent 2-pyridine offered the desired product **5n** in 78% yield. When C3 of the indolin-2-one was substituted with other functional groups (-Ph, -OEt), the corresponding products were obtained in 62% and 70% yield, respectively.

In order to make clear the reaction mechanism, the reaction of **4b** with **2a** was performed at room temperature, and the intermediate **5b′** was isolated in 88% yield (Scheme 4a). The structure of **5b′** was confirmed by X-ray crystallography. Treatment of **5b′** with $Cs_2CO_3$ at 140 °C led to the formation of the desired product **5b** in 80% yield within 2 h (Scheme 4b). This indicates that the fused-ring compound **5b** was formed through a tandem sequence via **5b′**.

On the basis of the results of the control experiments and our previous reports, a possible reaction mechanism is proposed (Scheme 5). In the presence of a base, nucleophilic attack of 3-methylindoline-2-one (**2a**) on **4b** affords allene intermediate **A**. Then an intramolecular nucleophilic addition/ring opening occurs to give the formal alkyne insertion product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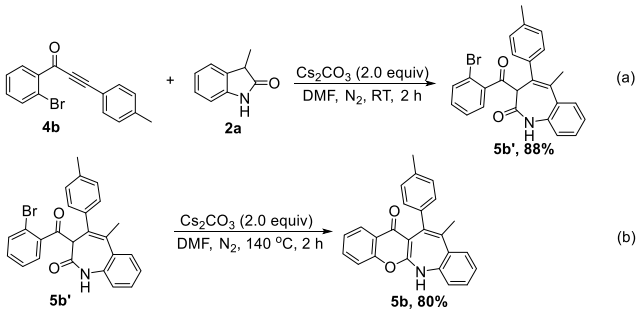
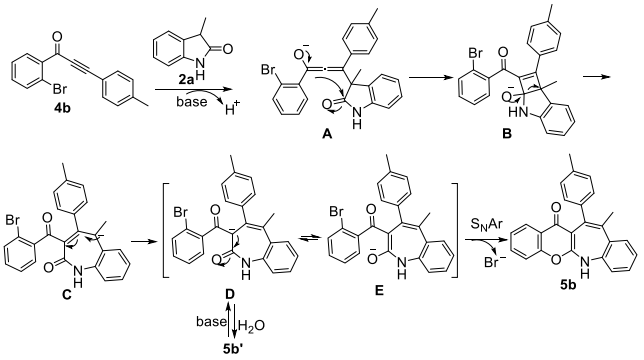
**Scheme 4. Control Experiments**




**Scheme 5. Plausible Reaction Mechanism**




**C**.[10c−e] Tautomerization of **C** offers **D**. Hydrolysis of **D** leads to product **5b′**. There are two possible routes from tautomer **E** to **5b**. One involves nucleophilic aromatic substitution ($S_NAr$) reaction, and the other is through conjugate addition followed by elimination of $Br^-$.

In summary, we have reported a transition-metal-free and atom-economical approach for the synthesis of seven-membered-ring benzolactams or chromone derivatives. The key step of this process is the selective insertion of ynones into C−C $\sigma$ bonds rather than C−N bonds of cyclic amides. Advantages such as good functional group tolerance, easily accessible starting materials, and high atom economy make this protocol appealing for the synthesis of N-containing seven-membered rings or fused-ring compounds.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04081.

Experimental procedures, characterization data, and spectra of new compounds (PDF)

### Accession Codes

CCDC 1951341 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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