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Arylacetylenes as Two-carbon Synthons: Synthesis of Eight-membered Rings via C≡C Bond Cleavage

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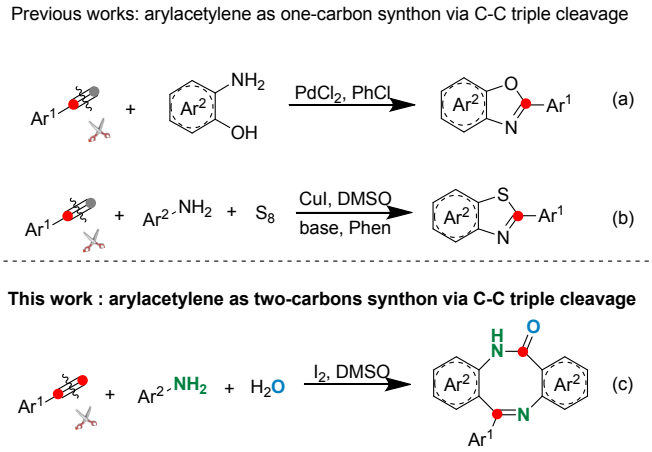
The first synthesis of eight-membered *N*-containing heterocycles by oxidative bicyclization/ring extension of arylacetylenes and aryl amines has been achieved. This protocol uses arylacetylene as an unusual two-carbon synthon by incorporating the two parts of the cracked C≡C bond into the final product, which provides a new method for using arylacetylenes as two-carbon synthons and further enriches C≡C bond cleavage methodology. Moreover, this multi-component reaction can provide diverse fused elegant eight-membered *N*-heterocycles under mild conditions with wide substrate scopes.

Medium-ring heterocycles hold an indispensable role in modern organic chemistry because they are one of the most important structural motifs in academia and industry.[1] In particular, medium-ring nitrogen heterocycles exhibit high biological activities.[2] Nevertheless, straightforward access to medium-ring heterocycles is still a formidable challenge, mainly because of some entropic and enthalpic reasons.[3] Thus, developing simple and efficient protocols for synthesis of a variety of medium-ring heterocycles, such as in situ cyclization followed by ring extension,[4] using readily available substrates is still important.

Arylacetylenes are one of the most common multi-functional synthons used in organic synthesis because of their readily availability and high reactivity. In the past few decades, direct cleavage of the C≡C bond of arylacetylenes has been a research hotspot, because it provides a great opportunity to produce other motifs through unusual routes. For example, a large number of excellent approaches are available to convert arylacetylenes to acids,[5] ketones,[6] nitriles,[7] amides,[8] and amidines[9] by cleaving the C≡C bond. However, direct use of the C≡C bond of arylacetylenes as one-carbon synthons through cleavage processes to construct heterocycles has rarely been realized. In 2014, Pan and co-workers[10] reported an interesting work in which arylacetylene was split into two parts by Pd-catalyzed cleavage of the C≡C bond and subsequently as one-carbon synthons assembled in the final products (Scheme 1a). More recently, Jiang's group[11] reported an appealing example of Cu-catalyzed tandem cyclization to assemble the benzothiazole frameworks using arylacetylenes as one-carbon synthons through cleaving the C≡C bond (Scheme 1b). Despite the great progress in cleavage of the C≡C bond,[12] reported methods usually focus on using arylacetylenes as one-carbon synthon by C≡C bond cleavage, and directly using arylacetylenes as unusual two-carbon synthons by C≡C bond cleavage is still a challenge. To the best of our knowledge, methods using arylacetylenes as two-carbon synthons have been well developed,[13] but cleaving the C≡C bond of arylacetylenes to produce two-carbon synthons for formation of heterocycles, especially medium-ring heterocycles, remains unexplored. In this work, we first developed an atom-economic strategy for synthesis of various eight-membered *N*-heterocycles using arylacetylene as an unusual two-carbon synthon, which provides a new method for cleaving the C≡C bond of arylacetylenes to produce two-carbon synthons (Scheme 1c). Notably, this transformation provides another way to construct 1,5-benzodiazocines through in situ cyclization followed by a ring extension process.[14]



Scheme 1. Transformation of Arylacetylenes to Heterocycles by Cleaving the C≡C Bond

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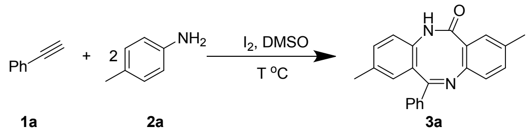
Because we are interested in heterocycles,[15] we started by reacting arylacetylene **1a** with *p*-toluidine **2a** in the presence of I_2 at 120 °C, which gave 1,5-benzodiazocine **3a** in 40% yield (entry 1, Table 1). Next, we investigated the effect of the temperature on the yield of the reaction, and 130 °C gave the best results (entries 2–6, Table 1). After determining the optimal temperature, we investigated the effect of the amount of iodine on the yield of the reaction. We found that slightly decreasing the amount of iodine gave better results, but the reaction did not occur without iodine (entries 7–11, Table 1). The results showed that iodine played an important role in this reaction. Subsequently, a series of acid additives (TFA, TfOH, HCl, $Cu(OTf)_2$ and $Fe(OTf)_3$) were investigated. It was found that $Fe(OTf)_3$ gave the best yield for this cleavage reaction (entries 12–16, Table 1). Notably, DMSO was an irreplaceable solvent in this reaction, because it also played the role of an oxidant in Kornblum oxidation sequence. Finally, we tested the effect of the amount of water on the yield of the reaction. The results showed the 2.0 mmol of water gave the best results (entry 17, Table 1).

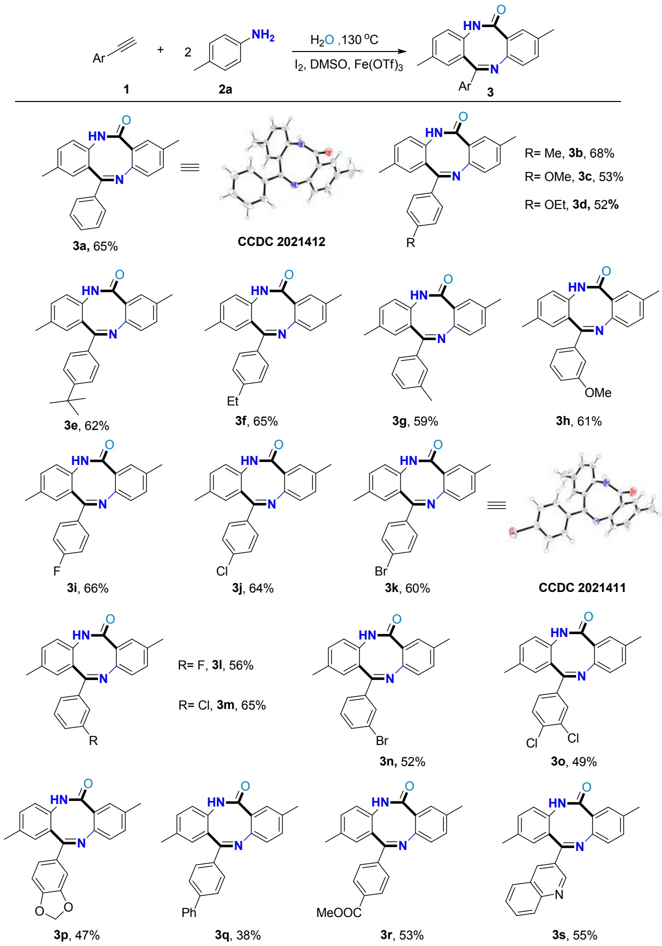
Table 1. Representative Optimization of the Dicyclization Reaction[a]



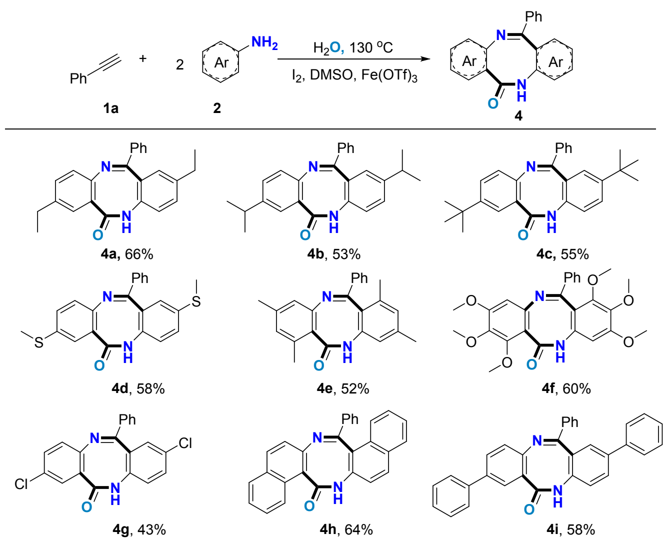
Entry	I_2 (mmol)	Temp (°C)	Additive	Yield (%)[b]
1	1.6	120	-	40
2	1.6	80	-	trace
3	1.6	100	-	15
4	1.6	110	-	23
5	1.6	130	-	45
6	1.6	140	-	32
7	1.0	130	-	55
8	0.8	130	-	38
9	0.5	130	-	20
10	2.0	130	-	37
11	-	130	-	ND
12	1.0	130	TFA	60
13	1.0	130	TfOH	46
14	1.0	130	HCl	35
15	1.0	130	$Cu(OTf)_2$	38
16	1.0	130	$Fe(OTf)_3$	62
17	1.0	130	$Fe(OTf)_3$	65[c](60)[d](57)[e]

[a]Reaction conditions: **1a** (1.2 mmol), **2a** (2.0 mmol), I_2 (mmol), additive (1.0 mmol), indicated temperature, DMSO 4 mL, 3 h, unless otherwise noted. [b]Isolated yields. [c]2.0 mmol of water was added. [d]4.0 mmol of water was added. [e]6.0 mmol of water was added.

After determining the optimal reaction conditions, the substrate scope of this multi-component reaction was investigated with a series of arylacetylenes (Scheme 2). Overall, the series of substituted arylacetylenes were compatible with this cyclization/ring-extension reaction, giving the corresponding eight-membered *N*-containing fused heterocycles. Arylacetylenes bearing electron-donating groups (–Me, –OMe, –OEt, –^{t}Bu and –Et) showed good reactivity under the optimal conditions, giving the corresponding eight-membered frameworks in good yields (**3a**–**3h**, 52%–68%). Next, halogenated substrates **1i**–**1n** were treated with *p*-toluidine (**2a**) under the optimal reaction conditions, and they gave various halogenated eight-membered rings (**3i**–**3n**, 52%–66%). We have also tested polysubstituted arylacetylenes in this reaction, and giving the products **3o** and **3p** in 49% and 47% yield, respectively. Furthermore, we also investigated some arylacetylenes bearing electron-deficient groups (–Ph, –COOMe).



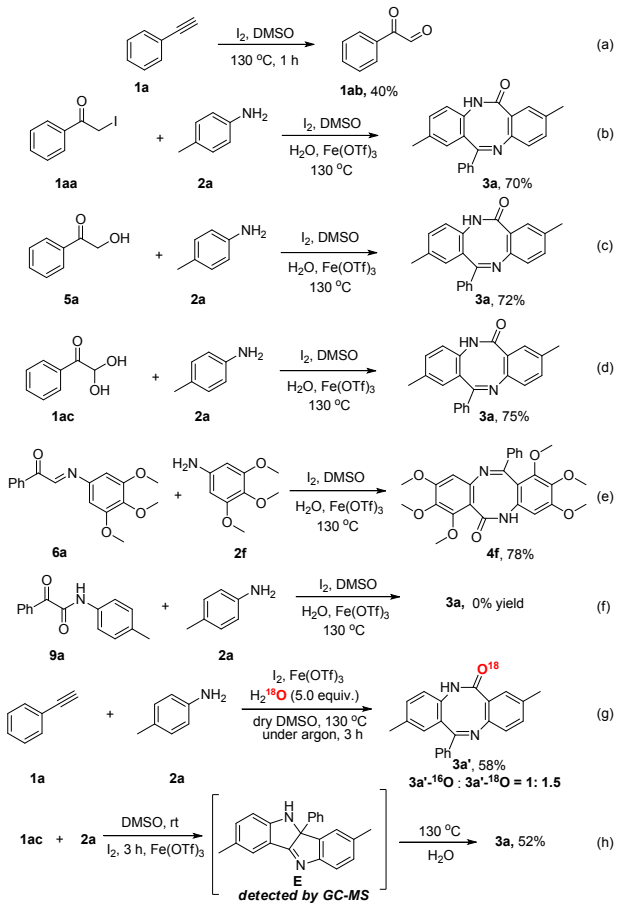
Scheme 2. Scope of Arylacetylenes. Reaction conditions: 1.0 mmol scale. Isolated yields.



Scheme 3. Scope of Aryl amines. Reaction conditions: 1.0 mmol scale. Isolated yields.

They afforded the final products in 38%–53% yields (**3q**–**3r**). Of note, 3-ethynylquinoline (**1s**) afforded eight-membered ring **3s** in 55% yield.

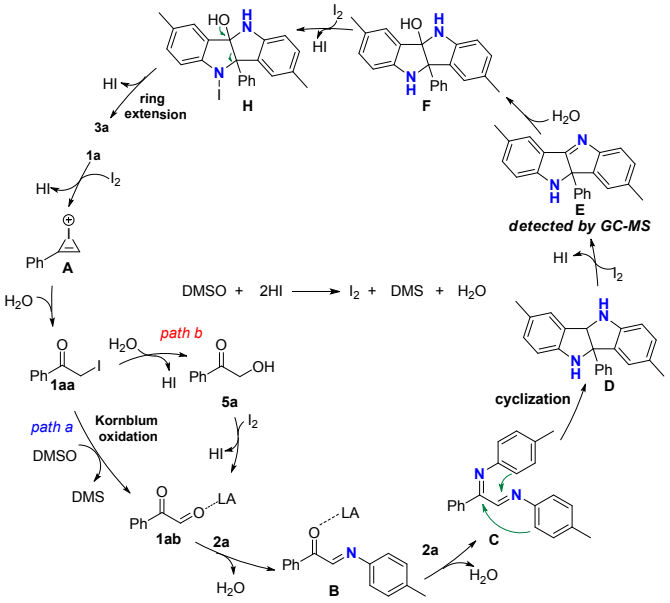
Next, to further expand the practicability of this method, various substituted aryl amines were investigated in this multi-component reaction (Scheme 3). Electron-donating group substituted aryl amines (–Et, –^{i}Pr, –^{t}Bu and –SMe) were compatible with this transformation, giving **4a**–**4d** in 53%–66% yields. Interestingly, when polysubstituted amine substrates were reacted with arylacetylene **1a** under the optimal reaction conditions, the corresponding polysubstituted eight-membered ring products were obtained (**4e**–**4f**, 52%–60%). In addition, halogenated amines with an aromatic ring (–Cl) easily transformed to halogenated eight-membered rings **4g** in 43% yield. Notably, naphthylamine **2h** was well tolerated in this reaction, affording **4h** in 64% yield. Finally, we tested an amine with an electron-deficient group (–Ph), which gave **4i** in 58% yield.



Scheme 4. Control Experiments

To investigate the mechanism of this novel reaction, some control experiments were performed (Scheme 4). First, arylacetylenes reacted with iodine and DMSO at 130 °C to give phenylglyoxal in 40% yield (Scheme 4a). α-Iodophenone **1aa** reacted with *p*-toluidine **2a** under the optimal conditions giving product **3a** in 70% yield (Scheme 4b). 2-hydroxyacetophenone **5a** reacted with **2a** under the standard reaction conditions, obtained the **3a** in 72% yield (Scheme 4c). Furthermore, hydrated species **1ac** smoothly reacted with *p*-toluidine **2a** under the optimal reaction conditions to give **3a** in 75% yield (Scheme 4d). These results show that α-iodophenone **1aa**, 2-hydroxyacetophenone **5a** and ketoaldehyde **1ab** are potential intermediates in this transformation. Next, the pre-prepared substrate *C*-acylimine **6a** and ketoamide **9a** reacted with **2f**, **2a** respectively under the optimal conditions, only giving **4f** in 78% yield (Scheme 4e and 4f). These results showed that *C*-acylimine was a key intermediate in this cleavage reaction. Next, we added 5.0 equivalent of $H_2{}^{18}O$ to investigate the source of oxygen in **3a**, and the ^{18}O labeled product was obtained in 58% yield (Scheme 4g). Moreover, an oxygen atom exchange experiment excluded possibility of the oxygen atom exchange between ^{16}O-labeled product 3a and $H_2{}^{18}O$ under the reaction conditions (for details, see SI). Those results showed that oxygen in **3a** mainly is from water. Finally, hydrated species **1ac** reacted with *p*-toluidine **2a** in DMSO at room temperature with addition of $Fe(OTf)_3$ and H_2O for 3 h, giving bicyclization intermediate **E** (detected by GC-MS), which further transformed to eight-membered ring **3a** at 130 °C (Scheme 4h). This result showed that this protocol underwent bicyclization to generate the polycyclic intermediate in situ followed by a ring-extension process.

Based on the above results and previous studies,[4a,14,16] we proposed a possible mechanism (Scheme 5). Arylacetylene **1a** was activated by iodine to give iodonium cation **A** with release of HI. Subsequently, **A** was attacked by water to give α-iodophenone **1aa** Then, the **1ab** can be obtained via two pathways. In path a, **1aa** direct converted to **1ab** by a Kornblum oxidation sequence.[16a] In path b, the α-iodophenone **1aa** reacted with another water to generate **5a,** which further underwent iodine promoted oxidization to afford **1ab.** [16b, 16c] Next, the **1ab** was attacked by one molecule of *p*-toluidine **2a** to afford *C*-acylimine **B**. **B** was then attacked by another molecule of **2a** to give intermediate **C**, which further transformed to **D** by a cyclization process. The in situ formed bicyclization intermediate **D** via N-I bond formation, then eliminated HI to give intermediate **E**,[16d, 16e] followed by water attacking to generate **F**. The Intermediate **F** oxidization by iodine to **H,** followed transformation to product **3a** through a ring-extension process.



Scheme 5. Proposed Mechanism

In summary, we have developed an efficient strategy for synthesis of a variety of elegant eight-membered rings by an iodine-promoted bicyclization/ring-extension process. This transformation is characterized by using arylacetylenes as unusual two-carbon

synthons, which provides a new method for cleaving the C≡C bond of arylacetylenes to produce two-carbon synthons. Moreover, this transformation uses readily available starting materials to form polycyclic compounds in-situ, in which a tedious preparation process is avoided so that direct transform to eight-membered rings can be achieved. Further investigation of a cyclization in situ followed by ring extension strategy for preparation of other medium-ring heterocycles is underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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