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Palladium-catalyzed cyclization of benzamides with aryynes: application to the synthesis of Phenaglydon and N-Methylcrinasiadine

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N-Methyl or methoxy benzamides reacted with benzynes in the presence of Pd(OAc)₂, organic acid and K₂S₂O₈ in CH₃CN yielding tricyclic phenanthridinone derivatives in good yields.

Phenanthridinones are key core units found in various natural products and bioologically active molecules. This molecule is used as a potential PARP-1 inhibitor anticancer drug as well as neurotrophin activity enhancers for the treatment of nerve diseases. Traditionally, phenanthridinones are prepared by metal-catalyzed cyclization of nitrocarbonyl-biphenyls, Beckmann/Schmidt rearrangement of fluorenones and photoinduced rearrangement of 2-halobenzamides. However, in these reactions, the preparation of key starting materials need more steps and the overall yields observed were lower. Subsequently, phenanthridinones are prepared by a palladium-catalyzed homo coupling of ortho-halo benzamides and coupling of aromatic halides with ortho-halo benzamides. Very recently, Larock’s group reported the synthesis of phenanthridinones via a palladium-catalyzed cyclization of ortho-halo N-substituted benzamides with benzynes (eq 1). But, a preactivated carbon-halogen partner on the aromatic moiety is required for the reaction. Apart from these reactions, phenanthridinones are prepared by a metal-catalyzed ortho arylation of benzamides with iodobenzenes or aromatic boronic acids or electron-rich aromatics following by intramolecular C-N bond formation.

Transition metal-catalyzed cyclization of heteroatom substituted aromatics with carbon-carbon π-components via chelation-assisted C-H bond activation is a practical method to synthesize heterocyclic molecules in one pot. By using nitrogen containing chelating groups such as amide, oxime and imine mono- and bicyclic heterocycles are prepared through the consecutive C-C and C-N bond formation. In the cyclization reaction, alkynes, alkenes and allenes are extensively used as carbon-carbon π-components (eq 1). However, benzene as a π-component has not been well explored in the literature. In fact, there are several challenges to utilize benzene as a π-component in the reaction due to its high reactivity. It is very important to note that in the cyclization of substituted aromatics with benzynes, a tricyclic ring system can be constructed in one pot.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Additive</th>
<th>Oxidant</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuCl₃(c-p-cymene)]_2/AgSbF₆</td>
<td>Cu(OAc)₂</td>
<td>30/0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂/TFA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂/pivalic acid</td>
<td>-</td>
<td>10/35</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>Ag₂O</td>
<td>0/45</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>Ag₂CO₃</td>
<td>0/33</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>Ag₂CO₃</td>
<td>0/27</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>Ag₂CO₃</td>
<td>0/45</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>K₂S₂O₇</td>
<td>0/74</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>Ph₃P(OAc)</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)₂/Adm-1-COOH</td>
<td>(NH₂)₂S₂O₇</td>
<td>-</td>
</tr>
</tbody>
</table>

*Reactions conditions: 1a with 2a (1.5 equiv) in the presence of cat (5.0 mol %), additive (10.0 equiv) and oxidant (2.0 equiv) in CH₃CN at 100 °C for 12 h. GC yield. **AgSbF₆ (20 mol %) was used. ***Adm-1- COOH (30 mol %) was used.

We have focused on utilization of a highly reactive benzene as a π-component in the cyclization reaction. Initially, we have tried the cyclization of N-methoxy 4-methoxy benzamide (1a) with o-(trimethylsilyl)aryl trflate (2a) in the presence of [[RuCl₃(c-p-cymene)]_2], AgSbF₆ and Cu(OAc)₂ in CH₃CN at 100 °C for 12 h (Table 1, entry 1). CsF in CH₃CN was used to generate benzene from benzene precursor 2a. In the reaction, only N-arylated benzamide 3a was observed in 30% yield and the expected cyclization product 4a was not observed. Next, the cyclization reaction of 1a with 2a was examined in the presence of Pd(OAc)₂ (5 mol %) and acetic acid or CF₃COOH (10.0 equiv) in CH₃CN (entries 2 and 3). In the reaction, no N-arylation product 3a or cyclization product 4a was observed. It seems AcOH or CF₃COOH might quench the CsF base. Then, acetic acid was replaced by the sterically hindered pivalic acid (entry 4). Interestingly, in the reaction, the expected cyclization product 4a was observed in 35% yield and competitive product 3a was also observed in 10% yield. To avoid product 3a, the reaction was tested with a catalytic amount of L-adamantanecarboxylic acid (Adm-1-COOH) (30 mol %) (entry 5). Surprisingly, in the reaction, product 4a was observed in 45% yield and no N-arylated product 3a was observed. To increase the yield of...
product 4a, the reaction was examined with oxidants (1.0 equiv) (entries 6-11). Interestingly, using K2S2O8, product 4a was observed in 74% GC yield and 66% isolated yield (entry 9). Remaining oxidants were partially effective or totally ineffective, yielding 4a in 0-45% yields (entries 6-11).

The scope of the catalytic reaction was tested with substituted N-methoxy benzamides 1b-i (Scheme 1). 2-Methoxy (1b), 4-methyl (1c) and N-methoxy benzamides (1d) underwent cyclization with 2a, yielding phenanthridinones 4b-d in 55%, 62% and 61% yields, respectively. Next, the cyclization reaction was tested with unsymmetrical benzamides. N-Methoxy 3,4-dimethoxy benzamide (1e) and meta methoxy benzamide 1f afforded phenanthridinones 4e and 4f in 61% and 58% yields, respectively, in which the ortho C-H bond activation takes place selectively at a sterically less hindered side. Whereas, benzamide 1g provided mixtures of regioselective cyclization products 4g and 4g' in 60% combined yield in a 1:5.1 ratio. Further, the cyclization reaction was tested with 4-bromo and 4-chloro benzamides 1h and 1i. However, only N-arylated benzamides 3h and 3i were observed in 47% and 51% yields, respectively and the expected cyclization products 4 were not observed. Similarly, 4-trifluoromethyl, 4-cyano and 4-nitrobenzamides were also not compatible for the reaction. This result clearly reveals that electron-donating substituents on the aromatic moiety of benzamide favor the ortho C-H bond activation/cyclization reaction. But, halogen and electron deficient aromatic benzamides favor only competitive nucleophilic addition of free N-H moiety of benzamide with benzene. Surprisingly, the palladacycle of 4-chloro benzamide 5a reacted with benzene precursor 2a, yielding cyclization product 4h in 45% yield. This result clearly says that the ortho C-H bond activation process is very slow in the electron deficient benzamides, and the competitive nucleophilic addition is very fast. Although, at present, the catalytic reaction was compatible with only electron-rich benzamides, it has been shown that a highly reactive benzene can be used as a π-component for the cyclization reaction.

The cyclization reaction was also examined with benzene precursors 2b-e (Scheme 2). Treatment of benzamide 1a with benzene precursors 2b and 2c gave phenanthridinones 4i and 4j in 61% and 55% yields, respectively. Interestingly, synthetically useful benzene precursors 2d and 2e reacted with 1e, giving products 4l and 4m in 70% and 63% yields, respectively.

The catalytic reaction was further tested with other N-methyl benzamides (Scheme 3). N-Methyl benzamide (6a) underwent cyclization with 2a, providing N-methylphenanthridine 7a in 49% yield, in which ortho C-H bond activation takes place selectively at the sterically less hindered side. Further, N-methyl 4-methoxy benzamide (6b) and N-methyl benzamide (6c) reacted with 2a or 2c affording cyclization products 7b-d in 45%, 43% and 38% yields, respectively. Treatment of N-methyl benzamide 6d with 1a gave natural product N-methylcrinasiadine10 (7e) in 30% yield and other regioisomer 7e' in 25% yield, respectively. It is important to point out that natural product N-methylcrinasiadine (7e) shows several biological activities.1

Later, OMe group on the cyclic amides of 4c and 4d were cleaved into the natural product phenaglydon A,b 8a in 69% yield and 6(SH)-phenanthridine 8b in 67% yield under the
photochemical irradiation conditions \(^{2a,b}\) (eq 2). Later, compound \(8\) underwent nitration at C-5 position of phenanthridinone in the presence of \(\text{HNO}_3/\text{H}_2\text{SO}_4\), providing 5-nitro phenanthridinone \(9\) in 75\% yield. It is important to note that compound \(9\) is a key precursor for the preparation of anti-cancer drug PJ34.\(^{16}\)

A possible reaction mechanism is proposed in Scheme 4 to account for the present cyclization reaction. Coordination of the amidine nitrogen of benzamide \(1\) to the palladium species followed by ortho-metalation provides a five-membered palladacycle intermediate \(5\). Coordinative insertion of benzene \(10\) into the intermediate \(5\) yields a seven-membered palladacycle intermediate \(11\). Subsequent C-N bond formation and reductive elimination affords product \(4\) and regenerates the active palladium species in the presence of RCOOH and \(\text{K}_2\text{S}_2\text{O}_8\).

**Scheme 4** Proposed mechanism

Apart from the above proposed mechanism, other possible pathways such as ortho-arylation of benzamide with benzene yielding product \(12\) followed by intramolecular C-N bond formation or N-H arylation of benzamide with benzene providing compound \(3\) followed by intramolecular dehydrogenative aryl-aryl coupling are also possible.\(^{17}\) To support the proposed mechanism in Scheme 4, the following reactions were done (Scheme 5). ortho-Arylated benzamide \(12\) was prepared separately and treated with \(\text{Pd(OAc)}_2\), \(\text{CsF}\) and \(\text{K}_2\text{S}_2\text{O}_8\) in \(\text{CH}_3\text{CN}\) at 100 °C for 12 h. In the reaction, no cyclization product \(4a\) was observed. Subsequently, \(\text{N}\)-arylated benzamide \(3a\) was treated with \(\text{Pd(OAc)}_2\) and \(\text{K}_2\text{S}_2\text{O}_8\) under similar reaction conditions. However, no cyclization product \(4a\) was observed. Further, a five-membered palladacycle intermediate \(5b\) was prepared separately and treated with benzene precursor \(2a\) in the presence of \(\text{CsF}\) in \(\text{CH}_3\text{CN}\) at 100 °C for 12 h. As expected, the cyclization product \(4f\) was observed in 75% yield. These results clearly revealed that the present reaction proceeds via coordinative insertion pathway. To support the hypothesis that benzene is involved in the cyclization reaction, the reaction of benzamide \(1a\) with unsymmetrical benzene precursor \(2g\) was performed. In the reaction, a mixture of regioisomeric compounds \(4n\) and \(4m\) were observed in 53% combined yield in a 2:1 ratio. The lack of regioselectivity of the reaction is consistent with insertion of unsymmetrical benzene into a Pd-carbon bond in intermediate \(5\).

In conclusion, we have demonstrated a palladium-catalyzed oxidative cyclization of \(N\)-substituted benzamides with benzenes providing phenanthridinones with diverse substituents.

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**Notes and references**


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