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Rhodium-catalyzed intramolecular annulation via C-H activation leading to fused tricyclic indole scaffolds

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The rhodium(III)-catalyzed intramolecular annulation of alkyne-tethered acetanilides for the synthesis of fused tricyclic indole scaffolds via C-H activation has been developed, which has the potential for the synthesis of many indole alkaloids. This reaction proceeds under mild reaction conditions and with tolerance to a variety of functional groups.

The 3,4-fused tricyclic indole nucleus are found in a number of biologically active natural products and pharmaceuticals, such as lysergic acid,1 rugulosamine A,2 decarbocyclopentauramine,3 clavicipitic acid,4 decursivine,4 and indolactam V (Figure 1).6 Accordingly, the syntheses of these natural products have been the subject of intensive research, and a number of strategies are now available.7 However, the development of conceptually different synthetic approaches is still of great interest.8

Figure 1 Selected examples of 3,4-fused indole alkaloids.

In connection with some of our work on the total synthesis of 3,4-fused indole alkaloids,9a,b,12a,b,13 we have recently developed a new strategy for the construction of such skeleton via intramolecular Larock indolization,9 and achieved the total synthesis of fargesine by using this methodology (Scheme 1, eq 1).10 Meanwhile, Boger independently reported a similar work (Scheme 1, eq 2).11 However, these methods require ortho-halogenated anilines as starting materials thus adding cost12 and limiting its further application. Recently, the rhodium-catalyzed C-H activation has received significant interest because of its high atom-economy, selectivity, and functional-group tolerance.13 In 2008, Fagnou and co-workers reported an elegant method for the synthesis of indoles via rhodium-catalyzed oxidative annulation of acetanilides with internal alkenes. (Scheme 1, eq 3).14 A major advance of this method is that it employs more readily available N-acetyl anilines as starting materials thus minimizing the substrate preactivation. Based on these observations, we became interested in the rhodium-catalyzed intramolecular reaction of alkyne-tethered acetanilides (Scheme 1, eq 4). Although the rhodium-catalyzed intramolecular C-H activation reactions have been very recently reported, to the best of our knowledge, the intramolecular reaction of alkyne-tethered acetanilides has never been reported.15 The successful development of this reaction would lead to a more efficient and economical synthesis of 3,4- and 3,5-fused tricyclic indoles. Herein, we wish to report these results.

Our previous work (ref 10):

Scheme 1 Intramolecular annulation strategies for the synthesis of fused tricyclic indoles.
To test our hypothesis, compound 1a was employed as a model substrate and subjected to the first-generation Fagnou's intermolecular reaction conditions. We found that treatment of 1a with \([\text{Cp}^*\text{Rh(MeCN)}_3][\text{SbF}_6]_2\) (10 mol%) and \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (210 mol%) in \(t\)-AmOH at 80 °C under Ar atmosphere afforded the desired 3,4-fused tricyclic indole 2a in 31% yield (Table 1, entry 1). Increasing the reaction temperature to 100 °C gave almost the same result (Table 1, entry 2). When compound 1a was treated with the second-generation Fagnou's intermolecular reaction conditions by using molecular oxygen as the terminal oxidant \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (210 mol%) in acetone (0.01 M) at room temperature (Table 1, entry 3), To our delight, when acetone was used as the solvent at room temperature, the desired indole 2a could be obtained in 61% yield (Table 1, entry 4). Further optimization of the amount of catalyst showed that: when 5 mol% \([\text{Rh}^\cdot\text{H}][\text{SbF}_6]_2\) was used, the yield of 2a was remained to 37% (Table 1, entry 5). When the amount of [Rh] catalyst was decreased to 2.5 mol%, a slight decrease of the yield was observed (Table 1, entry 6). The yield of 2a was slightly improved with a 30% yield (Table 1, entry 7). When cyclohexanone was used as the solvent, the reaction did not work at all (Table 1, entry 8). It was worthy to mention that treatment of 1a under the first-generation Fagnou’s intermolecular reaction conditions by simply changing the solvent to acetone at room temperature provided the desired indole 2a in 62% yield. Considering the use of molecular oxygen more green and economical than the use of stoichiometric amounts of a metal oxidant (2.1 equiv of \(\text{Cu(OAc)}_2\)), the reaction condition was optimized as \([\text{Cp}^*\text{Rh(MeCN)}_3][\text{SbF}_6]_2\) (5 mol%), \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (20 mol%) under \(\text{O}_2\) in acetone (0.01 M) at room temperature (Table 1, entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of [Rh]</th>
<th>Equiv. of [Cu]</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.10</td>
<td>2.10</td>
<td>(t)-AmOH</td>
<td>80 °C</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>0.10</td>
<td>2.10</td>
<td>(t)-AmOH</td>
<td>100 °C</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>0.10</td>
<td>0.50</td>
<td>Acetone</td>
<td>60 °C</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>0.50</td>
<td></td>
<td>RT</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>0.20</td>
<td>Acetone</td>
<td>RT</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>0.025</td>
<td>0.20</td>
<td>Acetone</td>
<td>RT</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>0.20</td>
<td>DCE</td>
<td>RT</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>0.05</td>
<td>0.20</td>
<td>Cyclohexanone</td>
<td>RT</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0.05</td>
<td>2.10</td>
<td>Acetone</td>
<td>RT</td>
<td>62</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (0.1 mmol), \([\text{Cp}^*\text{Rh(MeCN)}_3][\text{SbF}_6]_2\), Cu(OAc)\cdot\text{H}_2\text{O}, under \(\text{O}_2\), acetone (10 mL), room temperature. Isolated products are given. 

With the optimized reaction in hand, we next examined the substrate scope of the reaction. Under our optimized reaction conditions, the reaction proceeded smoothly to give a series of 3,4-fused tricyclic indoles in moderate to excellent yield (Table 5). Firstly, the electronic effects of aryl groups attached to the terminal alkylene were first examined (Table 2, 2a-e). Compounds 1a and 1b with electron-donating groups gave the desired products 2a and 2b in 63% and 60% yield, respectively. Compounds 1c with electron-neutral group provided the corresponding product 2c in 55% yield. Compounds 1d with electron-withdrawing group provided the corresponding product 2d in 48% yield. These results indicated that electronic factors of the phenyl moiety indeed affected the reactivity of this transformation. The triethylsilyl-group substrate also tolerated the reaction condition and produced the desired indole in 55% yield (Table 2, 2e).

Table 2 Substrate scope for the formation of 3,4-fused indoles

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>16 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>R = OMe</td>
<td>63%</td>
<td>64%</td>
</tr>
<tr>
<td>2b</td>
<td>R = Me</td>
<td>55%</td>
<td>57%</td>
</tr>
<tr>
<td>2c</td>
<td>R = H</td>
<td>60%</td>
<td>61%</td>
</tr>
<tr>
<td>2d</td>
<td>R = Cl</td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td>2e</td>
<td>R = OMe</td>
<td>63%</td>
<td>65%</td>
</tr>
<tr>
<td>2f</td>
<td>R = OMe</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

\(2a, \text{R} = \text{OMe}, 16 \text{ h}, 63\%\) 
\(2b, \text{R} = \text{Me}, 16 \text{ h}, 60\%\) 
\(2c, \text{R} = \text{H}, 16 \text{ h}, 65\%\) 
\(2d, \text{R} = \text{Cl}, 16 \text{ h}, 48\%\) 
\(2e, \text{R} = \text{OMe}, 16 \text{ h}, 63\%\) 
\(2f, \text{R} = \text{OMe}, 16 \text{ h}, 99\%\) 

\(2g, \text{R} = \text{Me}, 16 \text{ h}, 97\%\) 
\(2h, \text{R} = \text{Cl}, 16 \text{ h}, 89\%\) 

\(2i, 48 \text{ h}, 63\%\) 
\(2j, 48 \text{ h}, 64\%\) 

\(2k, 48 \text{ h}, 62\%\) 
\(2l, 48 \text{ h}, 64\%\) 

\(2m, 72 \text{ h}, 38\% (93\%)\) 
\(2n, 16 \text{ h}, 18\%\) 
\(2o, 16 \text{ h}, 18\% (99\%)\) 

\(2p, 16 \text{ h}, 62\% (99\%)\) 

\(2q, 48 \text{ h}, 62\% (99\%)\) 

\(2r, 48 \text{ h}, 64\% (97\%)\) 

\(2s, 48 \text{ h}, 62\% (99\%)\) 

\(2t, 48 \text{ h}, 64\% (97\%)\) 

\(2u, 48 \text{ h}, 62\% (99\%)\) 

\(2v, 48 \text{ h}, 64\% (97\%)\) 

\(2w, 48 \text{ h}, 62\% (99\%)\) 

\(2x, 48 \text{ h}, 64\% (97\%)\) 

\(2y, 48 \text{ h}, 62\% (99\%)\) 

\(2z, 48 \text{ h}, 64\% (97\%)\) 

\(2a, \text{R} = \text{OMe, 16 h, 63%}\) 

\(2b, \text{R} = \text{Me, 16 h, 60%}\) 

\(2c, \text{R} = \text{H, 16 h, 55%}\) 

\(2d, \text{R} = \text{Cl, 16 h, 48%}\)
The electronic effects of acetanilides were next examined (Table 2, 2f-h). Surprisingly, substrates 1f and 1g with electron-rich R¹ groups gave the desired products in excellent yield under the optimized reaction conditions (Table 2, 2f and 2g). However, substrate with electron-deficient R¹ group resulted in only moderate yield (Table 2, 2h). These results imply that the acetanilide metatalation step was extremely sensitive to electronic effects. Most likely, the electron-withdrawing effect of R₂ group (Table 2, reaction was examined for the preparation of 3,5-fused tricyclic indoles in better yield (Table 2, Table 3 Substrate scope for the formation of 3,5-fused indoles

Table 3 Substrate scope for the formation of 3,5-fused indoles

\[
\begin{array}{cccc}
\text{R} & \text{NHAc} & \text{O} & \text{H} \\
\text{Ac} & \text{OMe} & \text{OMe} & \text{Ac}
\end{array}
\]

\[\text{[Cp*Rh(MeCN)₂][SbF}_6\text{]₂} \rightarrow \text{R} \]

acetone (0.01 M) RT, time

Isolated products are given.

Encouraged by the results for the 3,4-fused tricyclic indoles, we next examined the electronic effects of acetanilides. The electronic effects of acetanilides were next examined (Table 2, 2f-h). Surprisingly, substrates 1f and 1g with electron-rich R¹ groups gave the desired products in excellent yield under the optimized reaction conditions (Table 2, 2f and 2g). However, substrate with electron-deficient R¹ group resulted in only moderate yield (Table 2, 2h). These results imply that the acetanilide metatalation step was extremely sensitive to electronic effects. Most likely, the electron-withdrawing effect of R₂ group had a strong influence on the C-H activation process. The reaction was then extended to prepare 3,4-medium ring (7- and 8-membered rings). We were pleased to find that the desired indole products were still obtained in good to excellent yield (Table 2, 2i-p), although the yield of substrate leading to 8-membered ring 2n was relatively low. As mentioned above, substrates with electron-rich R¹ groups gave the desired 3,4-fused tricyclic indoles in better yield (Table 2, 2k, 2l, 2o and 2p).

In summary, we have developed the first rhodium-catalyzed intramolecular annulation of alkyne-tethered acetanilides for the synthesis of fused tricyclic indoles via C-H bond activation. This reaction proceeds under mild reaction conditions (room temperature) and with tolerance to a variety of functional groups, and employs molecular oxygen as the stoichiometric terminal oxidant. We expect that this intramolecular protocol will find widespread use in chemical synthesis.

Acknowledgements

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Notes and references


12 ortho-Iodoaniline is $1070/mol, whereas aniline is $12/mol.

