A Synthesis of Multifunctionalized Indoles from [3 + 2] Annulation of 2-Bromocyclopropenes with Anilines

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Supporting Information

ABSTRACT: A new regioselective method for the synthesis of multifunctionalized indoles from [3 + 2] annulation of 2-bromocyclopropenes with anilines has been developed. By employing a nickel complex as a catalyst, 27 examples of indole products were obtained in good yields with excellent regioselectivity. Synthetic utility of the resulting product was demonstrated in a concise synthesis of biologically active compound Paullone.

The indole unit is one of the most important structural components that is present in abundant natural products and drug molecules.1 2,3-Disubstituted indoles are very important synthetic intermediates that could be further transformed to various biologically active compounds, such as Paullone, Kenpaullone, and Cilansetron (Figure 1).

Paullone, Kenpaullone, and their analogues are potent inhibitors of the cyclin-dependent kinases (CDKs) and glycogen synthase kinase-3β (GSK-3β), which have become promising agents for the treatment of neurodegenerative and proliferative disorders.2 Cilansetron is a 5HT-3 antagonist, considered as a promising drug to treat irritable bowel syndrome (IBS).3

The synthesis of multifunctionalized indole and its derivatives arouses intense interest from chemists.4 New generations of more efficient and more practical indole synthesis methods continue to emerge. For example, the Fischer indole synthesis, developed in 1883, has proven to be one of the most powerful routes.6 Recently, instead of using carcinogenic hydrazines, by employing more readily available imines and enamines, the cross-dehydrogenative coupling strategy was developed for the synthesis of indoles by palladium catalysis.7 Another example is the classic Bischler indole synthesis, which was first reported in 1892.8 In modern synthesis, remarkable developments in the Bischler indole synthesis have been achieved involving N−H insertion reaction from diazo compounds with anilines,9a as well as the Ru(0) or Zn(II) catalyzed Bischler indole synthesis of propargylic alcohols with anilines.9b In 1991, Larock and co-workers developed a palladium catalyzed regioselective formation of 2,3-disubstituted indoles by employing internal alkyynes with 2-iodoaniline.10 In a Larock indole synthesis, the aryl group of the aniline prefers to attach to the less bulky end (R3) of the triple bond while the nitrogen moiety is more liable to assemble on the sterically more hindered end (R1) (eq a, Scheme 1). Since the 2,3-disubstituted indole is a key structural motif of various biologically active natural and unnatural molecules, the synthetic methods that provide the 2,3-disubstituted indoles with an alternative regioselectivity is still highly in demand.

Cyclopropenes, as the smallest unsaturated cyclic molecule, exhibit a unique chemical property.11 The vinylic carbon atoms of cyclopropene are sp2 hybridized, indicating that the cyclopropene sometimes could serve as an alkyne equivalent.

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With continuing effort and interest in the field of both indole derivatives and small ring compounds, in this study, we have developed an unexpected synthesis of 2,3-disubstituted indoles from [3 + 2] annulation of donor–acceptor cyclopropenes with anilines, which displays different regioselectivity, compared with the Larock indole synthesis, for the larger diester moiety to be installed at the 3-position and the smaller aryl group to be placed at the 2-position of indole (eq b, Scheme 1). In the presence of nickel(II) as the catalyst, various multifunctionalized indoles were furnished in up to 86% yield with excellent regioselectivities. Herein, we report the preliminary results.

Initially, we employed a bipyridine–Lewis acid complex as the catalyst to start our investigation of the [3 + 2] annulation reaction by using tetrahydroquinolines (Scheme 1). In the presence of nickel(II) as the catalyst, various multifunctionalized indoles were furnished in up to 50% yield with >20/1 rr after 23 h (Table 1, entry 9 vs 5). To our delight, with 20 mol % of Ni(ClO₄)₂·6H₂O, the reactivity of the [3 + 2] annulation was increased to 70%, and the reaction time was shortened to 11 h (Table 1, entry 10).

Under the optimized reaction conditions, various aniline derivatives were reacted with cyclopropenes bearing different ester groups, affording good to high yields with excellent regioselectivities. As shown in Scheme 2, N-Bn-anilines containing different substituents, such as Cl, Me, MeO, Bu- at the para-position, could reacted smoothly, leading to the corresponding multifunctionalized indoles 3a–e in 65–77% yields. N-Me-anilines were also suitable substrate, delivering the N-Me-indole derivatives 3f–j in 61–70% yields, while anilines with a strong electron-withdrawing substituent such as CF₃ and NO₂ could also afford the desired products but with lower yields (3f–g). Multisubstituted anilines such as 3,5-dimethoxyanilines and 3,4,5-trimethoxyanilines were tolerated in the current catalyst system. In both cases, the N-Me-3,5-dimethoxyindoles 3l and the N-Me-3,4,5-trimethoxyindoles 3n were obtained in 70–81% yields. Furthermore, cyclopropenes bearing different substituents at both para- and ortho- positions of aryl groups (3o–q) also worked well, affording the corresponding indoles in 70–76% yields.

The structure of 3a was determined by the X-ray diffraction of the single crystal of the reaction product. As shown in Figure 2, the phenyl group from the cyclopropene was installed at the 2-position of the indole product, while the diester moiety was located at the 3-position.

Remarkably, tricyclic indoles are also accessible through this [3 + 2] annulation reaction by using tetrahydroquinolines instead of anilines (Scheme 3). It is worth mentioning that tricyclic indoles are found as a core structure in many natural products and biologically active molecules, such as Cilanse-

### Table 1. Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>L</th>
<th>t (h)</th>
<th>rr</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₁</td>
<td>45</td>
<td>6/1</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₂</td>
<td>45</td>
<td>5/1</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₃</td>
<td>45</td>
<td>5/1</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₄</td>
<td>24</td>
<td>5/1</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₅</td>
<td>23</td>
<td>20/1</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)₂</td>
<td>L₅</td>
<td>25</td>
<td>20/1</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>FeCl₃</td>
<td>L₅</td>
<td>24</td>
<td>3/1</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>Ga(OTf)₃</td>
<td>L₅</td>
<td>25</td>
<td>20/1</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>Ni(OTf)₂</td>
<td>L₅</td>
<td>25</td>
<td>20/1</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>Ni(ClO₄)₂·6H₂O</td>
<td>L₅</td>
<td>11</td>
<td>20/1</td>
<td>70</td>
</tr>
</tbody>
</table>

“Conditions in entry 10, Table 1; Isolated yields of 3; With >20/1 rr in all cases unless noted. With 11/1 rr, rr = regio metric ratio.”
As shown in Scheme 3, various tetrahydroquinolines with both electron-donating and electron-withdrawing groups substituted at the aryl ring could give the corresponding tricyclic indoles in up to 86% yield with excellent regioselectivity. Benzomorpholine is also a suitable substrate and gave the corresponding tricyclic indole in moderate yield. Moreover, the reaction can be extended to a larger cyclic amine, giving product bearing an eight-numbered ring in 32% yield with 6.4/1 rr.

This method was found to be synthetically promising. As shown in Scheme 4a, a scaled-up reaction was carried out, and 2.59 g of indole were obtained in 72% yield. The synthetic utility of this reaction was further demonstrated in a concise synthesis of Paullone, which was a potent cyclin-dependent kinase inhibitor and tau-protein kinase inhibitor (Scheme 4b).

In conclusion, we have developed a new method for the regioselective synthesis of 2,3-functionalized indoles via [3 + 2] annulation of anilines and 2-bromocyclopropenes. In the presence of a nickel complex as the catalyst, a variety of anilines as well as tetrahydroquinolines were found as compatible substrates, providing versatile multifunctionalized indoles (27 examples) in high yields with excellent regioselectivity. The current method is practical and potentially synthetically useful, which was demonstrated in a scaled-up reaction and synthesis of Paullone. Further application of this reaction in the construction of indole alkaloids is ongoing in our laboratory.

**Scheme 3. Substrate Scope of Tetrahydroquinoline Derivatives**

<table>
<thead>
<tr>
<th>R</th>
<th>X</th>
<th>Y</th>
<th>5a</th>
<th>5b</th>
<th>5c</th>
<th>5d</th>
<th>5e</th>
<th>5f</th>
<th>5g</th>
<th>5h</th>
<th>5i</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>O</td>
<td>10 h, 82%</td>
<td>10 h, 76%</td>
<td>10 h, 86%</td>
<td>11 h, 84%</td>
<td>12 h, 63%</td>
<td>12 h, 87%</td>
<td>11 h, 89%</td>
<td>12 h, 47%</td>
<td>13 h, 32%</td>
</tr>
</tbody>
</table>

"Conditions in entry 10, Table 1; Isolated yields of 5; With >20/1 rr in all cases unless noted. L4 was used with 10 mol % of Ni(ClO4)2·6H2O, 4i/2b = 1/1.2; with 6.4/1 rr, rr = regiomeric ratio.

**Scheme 4. Scaled-Up Reaction and Applications**

Experimental procedures and characterization data (PDF)

**Accession Codes**

CCDC 1014786 and 1909652 contain 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**
The authors declare no competing financial interest.

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