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Stereoselective preparation of methylenecyclobutane-fused angular tetracyclic spiroindolines via photosensitized intramolecular [2+2] cycloaddition with allene

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Stereoselective Preparation of Methylenecyclobutane-Fused Angular Tetracyclic Spiroindolines via Photosensitized Intramolecular [2+2] Cycloaddition with Allene

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Irradiation of 3-(hexa-4,5-dienyl)indole derivatives in the presence of 3',4'-dimethoxyacetophenone by a high-pressure mercury lamp through Pyrex glass gave the corresponding [2+2] cycloaddition products stereoselectively in high yields. The major product was a methylenecyclobutane-fused angular tetracyclic spiroindoline derivative produced by the [2+2] cycloaddition through a parallel orientation. The minor product was a hexahydropyridinocarbazole derivative through a crossed orientation. Electron-withdrawing substituents, such as acyl or alkoxycarbonyl, on the indole nitrogen were suitable for this reaction.

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Graphical Abstract
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Indoline-fused polycyclic compounds are frequently seen in bioactive natural products, and they have also attracted much attention as typical structural motifs in several useful pharmaceuticals. Novel fused cyclic indoline frameworks are of interest in bioactive screening for new pharmaceutical candidates. To date, a number of synthetic methods have been reported for this important class of compounds, whereas potential methods for synthesizing cyclobutane-fused indolines have been much less explored.

The [2+2] photocycloaddition between 1-acylindoles and substituted ethenes is known to proceed under the sensitization of acetophenone with Pyrex-filtered irradiation (>300 nm) to yield cyclobutane-fused indolines. These reactions can also be performed with 1-arylidinolines in the absence of the sensitizer. From a synthetic point of view, an intramolecular dearomatizing [2+2] cycloaddition of indole derivatives seems to be the most straightforward method to construct the cyclobutane-fused indolines. In fact, intramolecular [2+2] photocycloadditions have been investigated by tethering the alkene to the acylsubstituent of the indoles. This strategy gave the [2+2] adducts regio- and stereoselectively, while the resulting cyclobutane ring often did not have any functional groups useful for further molecular transformation (Scheme 1, top). More recently, You and collaborators reported an intramolecular dearomatization of indole derivatives based on visible-light-promoted [2+2] cycloaddition via an energy transfer mechanism. This elegant method provides a rare example of indole functionalization by exploiting visible-light-induced reactivity; however, the reaction requires 2-arylindoles in many cases that have ΔG(T-S0) values appropriate for the visible-light-excited energy transfer system.

In the course of our investigation on the photochemistry of 5-membered heteroaromatic compounds, we recently disclosed that irradiation of 1-(hexa-4,5-dienoyl)indole derivatives in the presence of an aromatic ketone, particularly 3',4'-dimethoxyacetophenone, by a high-pressure mercury lamp through Pyrex glass gave all-cis-fused methylenecyclobutane-containing compounds through [2+2] cycloaddition. To the best of our knowledge, photochemical [2+2] cycloaddition between indole and allene has not been reported previously. Prompted by this result, we envisaged that installation of the allene moiety on the C3 side chain of indoles instead of the side chain on the indole nitrogen would lead to various angular tetracyclic spiroindolines accompanied by inversion of the regioselectivity with respect to the allene moiety (Scheme 1, bottom). We report herein the novel photocyclization of 3-(hexa-4,5-dienyl)indole derivatives sensitized by 3',4'-dimethoxyacetophenone, which yields methylenecyclobutane-fused angular tetracyclic indoline derivatives in a highly stereoselective manner.

Our investigation began with elucidating the effect of the nitrogen protecting group on the reaction. We chose a series of indole derivatives linked with an allene moiety through diethylmalonate due to their ease of preparation. Referring to our previous result, we carried out reactions of N-acetyl derivative 1a–g sensitized by 3',4'-dimethoxyacetophenone (4, 50 mol%) in ethyl acetate under irradiation by a high-pressure mercury lamp through Pyrex glass (Table 1). Gratifyingly, our initial attempt to irradiate the N-acetyl derivative 1a gave the expected [2+2] cycloaddition product 2a (through parallel orientation) in 71% yield accompanied by a small amount of hydrocarbazole-type product 3a (through crossed orientation) (entry 1). It should be noted that each isomer was obtained as a diastereomerically pure form. The relative configurations of 2a and 3a were determined by NOE experiment. Next, the acetyl group was replaced with a propanoyl group with the expectation that the chromatographic separation of the regioisomers would be easier. Since the insufficient recovery of the sensitizer 4 (44%) and formation of unidentified messy products in entry 1 implied an undesirable side reaction that proceeded after the desired reaction was complete, we shortened the irradiation time in the subsequent experiments.

Thus, the reaction with 2b in the same manner gave the corresponding addition products in improved yields (entry 2). The sensitizer 4 was recovered quantitatively in this case. A substrate protected with Boc group 1c afforded the product in nearly quantitative yield (entry 3). Unfortunately, separation of the products 2c and 3c was not achievable, and these compounds...
gave a broadened $^1$H NMR spectrum likely due to slow movement around the Boc moiety. Since these properties of 2c and 3c made studying the product difficult, we replaced the Boc group with a methoxycarbonyl group (Moc) and attempted the reaction. Irradiation of 1d under the same conditions afforded a nice result, comparable to that by irradiation of 1c (entry 4). In this case, separation of the regioisomer 2d and 3d was possible by repeated preparative thin layer chromatography. The reaction was significantly retarded in the absence of the sensitizer 4 (entry 5). The reaction with the sulfonamide derivative 1e resulted in complete decomposition, giving no characterizable product (entry 6). The reaction with non-protected indole 1f and Me-protected 1g was quite sluggish and caused gradual decomposition of the starting material and the sensitizer (entries 7 and 8). We checked the stability of the major product 2d by irradiating isolated 2d under the same irradiation conditions, and observed very little decomposition of 2d was observed (Scheme 2). Based on these results, we selected the Moc group as the protecting group of choice in this reaction.

### Table 1. Screen of the nitrogen protecting group

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R</th>
<th>time (min)</th>
<th>yield (%)</th>
<th>recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ac</td>
<td>60</td>
<td>71±4</td>
<td>9±1</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>COEt</td>
<td>45</td>
<td>76±5</td>
<td>19±1</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>Boc</td>
<td>45</td>
<td>&gt;99</td>
<td>86:14</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Moc</td>
<td>45</td>
<td>84±6</td>
<td>12±2</td>
</tr>
<tr>
<td>5*</td>
<td>1d</td>
<td>Moc</td>
<td>45</td>
<td>9±1</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>1e</td>
<td>Ts</td>
<td>60</td>
<td>decomposition</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1f</td>
<td>H</td>
<td>45</td>
<td>trace</td>
<td>75±5</td>
</tr>
<tr>
<td>8</td>
<td>1g</td>
<td>Me</td>
<td>45</td>
<td>30±3</td>
<td>46±4</td>
</tr>
</tbody>
</table>

*All reactions were carried out using 0.10 mmol of 1a–g in a Pyrex test tube by external irradiation with a high-pressure mercury lamp at a concentration of 10 mM.

*Isolated yield or recovery.

*Chromatographic separation of 2c and 3c was quite difficult.

*Moc = methoxycarbonyl.

*The reaction was carried out in the absence of the sensitizer. The products were not separated.

*Not quantified, but only a small amount was recovered.

*Not quantified, but almost all the sensitizer remained.

*Not clearly detected in $^1$H NMR analysis.

With a suitable protecting group in hand, we next explored the reaction using a variety of indole derivatives (Table 2). Some of the reactions shown in Table 2 were carried out in a photochemical reaction vessel for internal irradiation. The reactions were discontinued as soon as possible after consumption of the starting materials. The reaction with 1d under internal irradiation at a concentration 5-times higher than that of the initial study proceeded as well (entries 1 and 2). A 1 mmol scale reaction for 1d was performed without problem to afford the products in good yields (entry 3). The amount of the sensitizer 4 could be reduced to 20 mol% with a slight sacrifice of the yield (entry 4). The sensitizer 4 was recovered almost quantitatively in each case. The reaction also worked well when the allene moiety was substituted by a methyl group. Irradiation of a substrate with two terminal methyl groups 5a gave the [2+2] adducts in a relatively large population of the cross-type product 7a (entry 5). When indole 5b, which had a methyl group at the internal allenyl carbon, was irradiated under the typical conditions, the cycloaddition products 6b and 7b were obtained in comparable yields (entry 6). It is worth mentioning that a sterically congested framework that contains contiguous quaternary sp$^3$ carbons can be constructed by this reaction. We were able to employ linker moieties other than a diethyl malonate moiety. Thus, compounds linked with Boc-protected nitrogen or oxygen (5c, 5d) gave the corresponding products in moderate to high yields (entry 7). In the case of substrates with a heteroatom linker, parallel-type adducts (6c, 6d) were produced in a population larger than that of 1d. This is likely because the more strained transition state leading to the cross-type adduct is made unfavorable by having a C–N or C–O bond shorter than the C–C bond.

### Scheme 2. Irradiation to isolated 2d.

With a suitable protecting group in hand, we next explored the reaction using a variety of indole derivatives (Table 2). Some of the reactions shown in Table 2 were carried out in a photochemical reaction vessel for internal irradiation. The reactions were discontinued as soon as possible after consumption of the starting materials. The reaction with 1d under internal irradiation at a concentration 5-times higher than that of the initial study proceeded as well (entries 1 and 2). A 1 mmol scale reaction for 1d was performed without problem to afford the products in good yields (entry 3). The amount of the sensitizer 4 could be reduced to 20 mol% with a slight sacrifice of the yield (entry 4). The sensitizer 4 was recovered almost quantitatively in each case. The reaction also worked well when the allene moiety was substituted by a methyl group. Irradiation of a substrate with two terminal methyl groups 5a gave the [2+2] adducts in a relatively large population of the cross-type product 7a (entry 5). When indole 5b, which had a methyl group at the internal allenyl carbon, was irradiated under the typical conditions, the cycloaddition products 6b and 7b were obtained in comparable yields (entry 6). It is worth mentioning that a sterically congested framework that contains contiguous quaternary sp$^3$ carbons can be constructed by this reaction. We were able to employ linker moieties other than a diethyl malonate moiety. Thus, compounds linked with Boc-protected nitrogen or oxygen (5c, 5d) gave the corresponding products in moderate to high yields (entry 7). In the case of substrates with a heteroatom linker, parallel-type adducts (6c, 6d) were produced in a population larger than that of 1d. This is likely because the more strained transition state leading to the cross-type adduct is made unfavorable by having a C–N or C–O bond shorter than the C–C bond.
Table 2. Substrate screen.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>Z</th>
<th>conditions</th>
<th>concentration (mM)</th>
<th>R1</th>
<th>R2</th>
<th>parallel (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>cross (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1d</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A</td>
<td>10</td>
<td>H</td>
<td>H</td>
<td>2d, 84</td>
<td>3d, 12</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>B</td>
<td>50</td>
<td>H</td>
<td>H</td>
<td>2d, 85</td>
<td>3d, 12</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>B</td>
<td>50</td>
<td>H</td>
<td>H</td>
<td>2d and 3d, 98 (85:15)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10</td>
<td>H</td>
<td>H</td>
<td>2d and 3d, 94 (85:15)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>B</td>
<td>10</td>
<td>Me</td>
<td>H</td>
<td>6a, 63</td>
<td>7a, 32</td>
</tr>
<tr>
<td>6</td>
<td>5b</td>
<td>C(CO2Et)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A</td>
<td>10</td>
<td>H</td>
<td>Me</td>
<td>6b, 73</td>
<td>7b, 13</td>
</tr>
<tr>
<td>7</td>
<td>5c</td>
<td>NBoc</td>
<td>B</td>
<td>10</td>
<td>H</td>
<td>H</td>
<td>6c and 7c, 95 (93:7)&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5d</td>
<td>O</td>
<td>A</td>
<td>10</td>
<td>H</td>
<td>H</td>
<td>6d, 97</td>
<td>7d, &lt;2%&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>A: The reaction was carried out using 0.10 mmol of the substrate in a Pyrex test tube by external irradiation with a high-pressure mercury lamp for 45 min. B: The reaction was carried out using 0.10 mmol of the substrate in a Pyrex reaction vessel for photochemical reaction by internal irradiation with a high-pressure mercury lamp for 30 min.

<sup>b</sup>Isolated yield.

<sup>c</sup>The reaction was carried out using 1.0 mmol of 1d.

<sup>d</sup>Separation of the regioisomeric products was not carried out.

<sup>e</sup>The reaction was carried out using 20 mol% of 4.

<sup>f</sup>Detected by <sup>1</sup>H NMR analysis, but not fully characterized.

Scheme 3. Irradiation to secondary alcohol derivatives 8a and 8b.

In order to show the versatility of this method for the construction of a fused indoline framework, we attempted a reaction with a substrate that had a carbon linker other than the malonate moiety. Irradiation to a secondary alcohol substrate 8a under the typical conditions afforded four addition products in 96% total yield: 9a (46%), 10a (26%), 11a (15%), and 12a (9%) (Scheme 3). The parallel (9a+10a) / cross (11a+12a) ratio was somewhat smaller than that of the reaction with 1d. The diastereomeric selectivity with respect to the stereochemical relationship between the hydroxy group and the cyclobutane moiety was 2:1. When TBS ether 8b was irradiated in the same manner, the corresponding products were obtained in almost the same population as in the case of 8a. Unexpectedly, the steric hindrance around the hydroxy moiety scarcely affected the product distribution.


To obtain information on the significance of the linker length, we carried out a reaction with allenyl indole 13, which has a linker moiety longer than 1d by a methylene (Scheme 4). The reaction was sluggish and gave a hardly separable mixture of many products. The predominant product was a cross-type adduct 14 (18% isolated yield), and the 13 was recovered in 40% yield. The formation of a parallel-type product was not ruled out due to the complexity of the mixture, but such a product would have been produced in only a small amount, if any.
Supplementary Material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151252

References and notes
