Synthesis of 3,3-Disubstituted-2-Aminoindolenines by Palladium-Catalyzed Allylic Amidination with Isocyanide

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Abstract: Synthesis of 3,3-disubstituted-2-aminoindolenines was achieved by palladium-catalyzed allylic amidination with an isocyanide. It was found that isocyanides are effective building blocks in palladium-catalyzed allylic functionalizations, analogous to carbon monoxide. This approach enables the direct construction of the indolenine ring along with the formation of a quaternary carbon and the introduction of an amino substituent in one step under mild conditions.

Key words: palladium, isocyanide, allylic amidination, cyclization, indoles

3,3-Disubstituted indole skeletons are one of the most important structures in alkaloid chemistry and are present in a wide range of natural products and pharmaceuticals. Among these derivatives, 3,3-disubstituted-2-aminoindolenines and 2-aminoindolines are substructures found in biologically active natural products such as flustramine C, perophoramidine and quinadoline B (Figure 1). These compounds are structurally complex, and much effort has been put into the synthetic study toward them. There are three key aspects in the synthesis of 3,3-disubstituted-2-aminoindolenines: (i) construction of the indole ring, (ii) formation of the quaternary carbon at the 3-position, and (iii) introduction of the amino substituent at the 2-position (Scheme 1). A direct, one-step method would be an efficient approach to these structures, but to date there have been no published reports on the direct construction of 3,3-disubstituted-2-aminoindolenines.

![Image](324x518 to 392x569)

Figure 1 Bioactive 3,3-Disubstituted-2-Aminindole Derivatives

Our group has previously developed a synthetic method for indole derivatives which involves the formation of a C2-C3 bond. Based on this characteristic retrosynthetic analysis, the efficient construction of various 3,3-disubstituted indole derivatives was achieved. We also applied this strategy to the synthesis of 2-aminoindolines via SmI₂-mediated reductive cyclization of carbodiimides. Although this method is an effective approach for 3,3-disubstituted-2-aminoindolene derivatives, stepwise introduction of the nitrogen unit and construction of the indolenine skeleton was required, meaning a one-step method was still needed. Herein we describe a direct and general approach for the construction of 3,3-disubstituted-2-aminoindolenines by palladium-catalyzed allylic amidination with an isocyanide (Scheme 1).

The reaction shown in Eq. (1) was designed to develop the direct method. Reaction of isocyanide 1 bearing an allyl ester moiety with an amine in the presence of a palladium catalyst would give 3,3-disubstituted-2-aminoindoline 2 via oxidative addition and allylic amidination. Recent publications disclosed that isocyanides are useful building blocks for multicomponent reactions (e.g., Passerini and Ugi reactions) as well as for palladium-catalyzed reactions. However, there are only a few reports of palladium-catalyzed allylic functionalization reactions with isocyanides, unlike the well-developed chemistry of carbon monoxide, which is isoelectronic with an isocyanide. Usually, palladium-catalyzed allylic functionalization reactions occur at the less sterically hindered site. Our approach, however, would enable formation of a quaternary carbon at the more sterically hindered site under mild conditions, owing to intramolecular cyclization. This method would also enable the introduction of various amino substituents at the 2-position by using a range of amines.

To investigate the allylic amidination, we synthesized substrate 1a bearing an isocyanide and an allyl carbonate moiety. Treatment of 1a with piperidine and 10 mol % of Pd(PPh₃)₄ in toluene at room temperature afforded 2-aminoindolene 2a in 18% yield (Table 1, entry 1). Using Pd(dba)₂ and PPh₃ instead of Pd(PPh₃)₄ increased the yield of 2a to 35% (entry 2). Next, several ligands were screened. It was found that monodentate triarylphosphines were not effective for this process. Therefore, we decided to develop a catalytic system where monodentate triarylphosphines were not effective for this process. Therefore, we decided to develop a catalytic system where monodentate triarylphosphines were
effective, and P(2-furyl)$_3$ gave the best results in this reaction (entries 3-6), however, the yield of 2a was still below 50%. We assumed that the low yields were caused by high reactivity of the allyl carbonate moiety in substrate 1a, thus substrate 1b bearing an allyl acetate moiety was used instead. As a result, the yield of the desired product 2a increased to 55% (entry 7). When substrate 1a was used, additional base was not necessary for this reaction, but the addition of two equivalents of Et$_3$N when using 1b increased the yield of 2a (entries 7, 8). Further optimization revealed that THF was the best solvent (entries 9-13). Although lowering the amount of catalyst slightly decreased the yield of 2a, catalyst loadings as low as 2 mol % were sufficient for complete conversion (entries 14, 15).

Table 1 Investigation of Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>CO$_2$Me</td>
<td>None</td>
<td>none</td>
<td>toluene</td>
<td>18%</td>
</tr>
<tr>
<td>2</td>
<td>CO$_2$Me</td>
<td>PPh$_3$</td>
<td>none</td>
<td>toluene</td>
<td>35%</td>
</tr>
<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td>DPPP$^b$</td>
<td>none</td>
<td>toluene</td>
<td>15%</td>
</tr>
<tr>
<td>4</td>
<td>CO$_2$Me</td>
<td>BINAPA$^p$</td>
<td>none</td>
<td>toluene</td>
<td>20%</td>
</tr>
<tr>
<td>5</td>
<td>CO$_2$Me</td>
<td>P(o-tolyl)$_3$</td>
<td>none</td>
<td>toluene</td>
<td>36%</td>
</tr>
<tr>
<td>6</td>
<td>CO$_2$Me</td>
<td>P(2-furyl)$_3$</td>
<td>none</td>
<td>toluene</td>
<td>42%</td>
</tr>
<tr>
<td>7</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>none</td>
<td>toluene</td>
<td>55%</td>
</tr>
<tr>
<td>8</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>toluene</td>
<td>65%</td>
</tr>
<tr>
<td>9</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>MeCN</td>
<td>19%</td>
</tr>
<tr>
<td>10</td>
<td>Ac</td>
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<td>Et$_3$N</td>
<td>DCE</td>
<td>16%</td>
</tr>
<tr>
<td>11</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>DMF</td>
<td>30%</td>
</tr>
<tr>
<td>12</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>1,4-dioxane</td>
<td>71%</td>
</tr>
<tr>
<td>13</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>THF</td>
<td>73%</td>
</tr>
<tr>
<td>14$^{cd}$</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>THF</td>
<td>64%</td>
</tr>
<tr>
<td>15$^{cd}$</td>
<td>Ac</td>
<td>P(2-furyl)$_3$</td>
<td>Et$_3$N</td>
<td>THF</td>
<td>63%</td>
</tr>
</tbody>
</table>

$^a$ Yield of isolated product.
$^b$ Pd[PPh$_3$)$_4$ was used instead of Pd(dba)$_2$.
$^c$ The reaction was performed at 50 °C.
$^d$ ≤ 1 mol % of Pd(dba)$_2$ and 10 mol % of P(2-furyl)$_3$ were used.
$^e$ 2 mol % of Pd(dba)$_2$ and 4 mol % of P(2-furyl)$_3$ were used.

Next we investigated the substrate scope of the reaction under the optimal conditions (Scheme 2). Initially, a range of amines were examined as the nucleophile. The reactions of simple cyclic amines gave the desired products 2b and 2c in 58% and 50% yields respectively. Morpholine could also be used in this reaction (2d). The reaction of acyclic amines such as diethylamine and benzylmethylamine also gave good results (2e, 2f). However, using a primary amine gave a low yield of the desired 2-aminoindolenine 2g. When N-methylaniline was used, the desired product 2h was not obtained, probably because of the weaker nucleophilicity. Next the reaction was performed using several isocyanides. The reactions of substrates bearing trifluoromethyl and methoxy groups at the para position of the aromatic ring gave the corresponding products 2i and 2j in 45% and 69% yields, respectively. An alkyl substituent on the olefin did not significantly influence the yield of the products (2k, 2l).

Scheme 2 Investigation of Substrate Scope

Next we performed the reactions using a chiral amine and an allyl acetate 1g derived from a secondary alcohol (Scheme 3). The optimal conditions were applied to the reaction using L-proline methyl ester as the nucleophile and interestingly, the desired product 2m was obtained as a 3:1 mixture of diastereomers at the 3-position of the indolenine ring (Eq. 2). This result indicates that the configuration of the quaternary carbon was influenced by the steric effect of the nucleophile. When allyl acetate 1g was used, the desired product 2n was obtained as a 2:1 mixture of olefin geometric isomers (Eq. 3).

Scheme 3 Investigation Using L-Proline Methyl Ester and an Allyl Acetate 1g

A plausible mechanism is shown in Figure 2. Firstly, oxidative addition of allyl acetate 1b to Pd(0) generates allylpalladium complex A. There are two possibilities for the next step. One is that intramolecular isocyanide insertion proceeds to form
intermediate B and then C–N reductive elimination regenerates the Pd(0) species and affords the desired 2-aminoindolenine 2a (Path A). The other possibility is that nucleophilic addition to the isocyanide activated by the Pd(II) occurs to give palladacycle C followed by C–C reductive elimination (Path B). Path B is analogous to the proposed catalytic cycle of the palladium-catalyzed decarboxylative cyclization reaction reported by Hayashi and co-workers. Considering the scope of this reaction and the nucleophilicity of the amine to isocyanide of intermediate A, we believe that Path B is dominant.

In summary, we have developed the synthesis of 3,3-disubstituted-2-aminoindolenine derivatives by palladium-catalyzed allylic amidination of isocyanides. This approach enables the direct construction of an indolenine ring along with the formation of a quaternary carbon and introduction of an amino substituent under mild conditions. We are currently investigating the mechanistic detail of the reaction and extending the strategy to an asymmetric reaction.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References


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12 Substrates 1a and 1b were synthesized by Suzuki-coupling of N-formyl-2-iodoaniline with vinyl boronic esters followed by formation of the carbonate or ester and then the isocyanide. See Supporting Information for more details.

13 General Procedure for Synthesis of 3,3-Disubstituted-2-Aminoindolenines: To a stirred solution of 1 (0.1 mmol), amine (0.2 mmol) and Et3N (0.028 mL, 0.201 mmol) in THF (2 mL) were added Pd(dba)2 (5.8 mg, 0.0101 mmol) and P(2-furyl)3 (4.6 mg, 0.0198 mmol). After stirring for 12 h at room temperature, the reaction mixture was diluted with toluene and extracted with 2N aqueous HCl. The combined extracts were basified with 2N aqueous NaOH and extracted with EtOAc. The resultant organic layers were washed with brine, dried over Na2SO4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc) to give 2.

14 Analytical Data for 2a: A colorless block, which was recrystallized from Et2O: m.p. 83.0-86.0 °C; 1H NMR (500 MHz, CDCl3) δ 7.16-7.12 (m, 2H), 6.92 (d, 1H, J = 7.2 Hz), 6.86 (ddd, 1H, J1 = J2 = 6.6 Hz, J3 = 1.7 Hz), 5.90 (dd, 1H, J1 = 17.5 Hz, J2 = 10.6 Hz), 5.35 (d, 1H, J = 17.5 Hz), 5.22 (d, 1H, J = 10.6 Hz), 3.71-3.63 (m, 4H), 1.67-1.58 (m, 9H); 13C NMR (126 MHz, CDCl3) δ 176.2, 154.7, 140.6, 138.9, 128.1, 121.2, 120.8, 115.7, 113.6, 55.6, 47.4, 26.0, 24.3, 20.7; IR (ATR) 2934, 1632, 1542, 1458, 1448 cm−1; MS (FAB) m/z = 241 ([M+H]+); HRMS (FAB+) C16H21N2: ([M+H]+) 241.1705: Found 241.1708.

15 As previous reports of the synthesis of amidines using palladium catalysis and isocyanides (ref. 9g, h), Path A is also possible. In this case, the diastereoselectivity of 2m would be derived from a selective reaction of one enantiomer of racemic B and L-proline methyl ester (i.e. matched pair).
Synthesis of 3,3-Disubstituted-2-Aminoindolenines

\[
\begin{array}{c}
R^1 \quad \text{NC} \quad \text{OAc} \quad \text{Pd catalyst} \\
\text{Oxidative} \quad \text{Addition} \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\text{N} \quad \text{N} \quad \text{N} \\
\text{R}^3 \\
\end{array}
\]

\[
3,3\text{-disubstituted-2-aminindolenine}
\]