PALLADIUM-CATALYZED HETEROARYLAMINATION OF ETHYL 2-CHLORO-1-AZAAZULENE-3-CARBOXYLATE AND ANNULATION OF HETEROARYLAMINO-1-AZAAZULENES†

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Abstract – The palladium catalyzed heteroarylamination of ethyl 2-chloro-1-azaazulene-3-carboxylate was achieved using a catalyst based on Pd₂(dba)₃ / Xantphos system. Treatment of ethyl 2-(heteroarylamino)-1-azaazulene-3-carboxylates with a PPA-POCl₃ mixture gave corresponding annulation products. 2-(2-Benzothiazolylamino)-1-azaazulene (3h) showed anticancer activity against HeLa S3 cells (IC₅₀: 6.5 μM).

In recent years Pd-catalyzed amination of aryl halides has attracted attention,¹ because aryl amines have a potential functionality in pharmaceutical drug candidates.²⁻⁶ The chemistry of azaazulenes⁷ is of interest for their physiological properties⁸⁻⁹ as well as physical and chemical properties. Therefore, it is expected that heteroarylamino-1-azaazulenes have potential bioactivities. It is known that ethyl 2-chloro-1-azaazulene-3-carboxylate (1) reacted with good nucleophile, such as

† Dedicated to the memory of late Dr. John Daly.
alkoxide, amine, and sulfoxide, to give corresponding 2-substituted-1-azaazulenes. Indeed, when 1 was treated with aniline (2a) in EtOH under reflux for 30 min, ethyl 2-anilino-1-azaazulene-3-carboxylate (3a) was obtained in 88% yield. Whereas, the reaction of 1 with inferior nucleophile did not undergo well, and reactions of 1 with 2-aminopyridine (2b) or 4-aminopyridine (2c) did not give corresponding substituted products.

\[
\begin{align*}
1 & \quad \text{EtOH, reflux, 30 min} \quad 2a \\
\quad \rightarrow \quad 3a
\end{align*}
\]

Therefore, we tried to use pyridinium aminide as superior nucleophile, which was produced by treating aminopyridine with NaH in dioxane under argon atmosphere. Reaction of 1 with 2-aminopyridine (2b) in the presence of NaH in dioxane at 120 °C for 24 h gave a complex mixture, and a trace amount of 3b was isolated along with 1 (47%). On the other hand, when 1 was treated with 4-aminopyridine (2c) in the presence of NaH in dioxane for 6 h at 140 °C, 3c was isolated in 40% yield.

\[
\begin{align*}
1 & \quad + \quad \text{ArNH}_2 \quad \text{NaH} \quad \text{in dioxane} \\
2b : \text{Ar} = 2-\text{Py} & \quad \rightarrow \quad 3b : \text{Ar} = 2-\text{Py} \\
2c : \text{Ar} = 4-\text{Py} & \quad \rightarrow \quad 3c : \text{Ar} = 4-\text{Py}
\end{align*}
\]

Recently, metal-catalyzed cross coupling of aryl halides with amines are extensively investigated. Therefore, we adopted metal catalyzed amination of 2-chloro-1-azaazulene. At first, Ullmann-type Cu-mediated cross coupling was examined. Treatment of 1 with 2b in the presence of Cul, PPh₃, and 'BuOK in toluene gave a complex mixture, and 3b was obtained only 1% yield together with 1 (55%).

\[
\begin{align*}
1 & \quad + \quad \text{ArNH}_2 \quad \text{Cul, PPh₃} \quad \text{'BuOK in toluene} \\
2b : \text{Ar} = 2-\text{Py} & \quad \rightarrow \quad 3b : \text{Ar} = 2-\text{Py}
\end{align*}
\]

Next, we examined Pd-mediated amination. It is known that Pd₂(dba)₃-catalyzed amination of aryl halides in the presence of Xantphos as a ligand is excellent method. Therefore, we treated 1 with 2b in the presence of Pd₂(dba)₃, Xantphos, and Cs₂CO₃ in dioxane at 120 °C for 24 h, and 3b was obtained in 72% yield along with 1 (10%). When above reaction was carried out in the presence of 'BuOK as base, 3b was obtained in 40% yield together with 1 (7%) and ethyl 2-oxo-1,2-dihydro-1-azaazulene-3-carboxylate (4) (15%). Similar reaction of 1 with 2c in the presence of Pd₂(dba)₃, Xantphos, and Cs₂CO₃ in dioxane at 120 °C for 24 h, gave 3c in 59% yield.
Table 1. Coupling reaction of 1 with heteroaryl amines in the presence of Pd$_2$(dba)$_3$, Xantphos, and Cs$_2$CO$_3$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArNH$_2$</th>
<th>Product</th>
<th>Yield / % (recovery %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td><img src="3b.png" alt="Image" /></td>
<td>3b : 72 (10)</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td><img src="3c.png" alt="Image" /></td>
<td>3c : 59 (-)</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td><img src="3d.png" alt="Image" /></td>
<td>3d : 50 (trace)</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td><img src="3e.png" alt="Image" /></td>
<td>3e : 73 (-)</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td><img src="3f.png" alt="Image" /></td>
<td>3f : 67 (-)</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td><img src="3g.png" alt="Image" /></td>
<td>3g : 52 (trace)</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td><img src="3h.png" alt="Image" /></td>
<td>3h : 65 (-)</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td><img src="3i.png" alt="Image" /></td>
<td>3i : 70 (-)</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td><img src="3j.png" alt="Image" /></td>
<td>3j : 52 (-)</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td><img src="5k.png" alt="Image" /></td>
<td>5k : 44 (-)</td>
</tr>
</tbody>
</table>
In a similar manner, reactions of 1 with some heteroarylamines were examined. Some results were shown in Table 1. Interestingly, in the reaction of 1 with 2k, auto-Tandem catalysis occurred and annulated product (5k) was obtained in 44% yield in one-pot.

Next, we examined the annulation of 3b-3i. When 3b was treated with polyphosphoric acid (PPA) at 150 °C for 5 h, cyclized product (5b) was obtained in 83% yield together with 2-(2-pyridylamino)-1-azaazulene (6) (10%), which was a deestrification product. For enhance the annulation yield, we treated 3b with POCl₃-PPA mixture at 150 °C for 5 h, and obtained 5b in 98% yield. Similar treatment of 3c-3j gave corresponding annulated products (7 and 5d-5j) in moderate to good yields.

**Biological evaluation**

Some newly synthesized products (3d, 3g, 3h) were evaluated for their anticancer activity (cytotoxic activity) against HeLa S3 cells. The IC₅₀ values [μM] are summarized in Table 2. In a case (denoted >), the minimum inhibitory concentration could not be determined due to limited solubility of the
compound in the testing medium. The results revealed that the compound \(3h\) showed moderate activity and the compound \(3d\) showed weak activity against HeLa S3 cells (It is considered that IC\(_{50}\) > 30 \(\mu\)M is inactive).

Table 2. Cytotoxic evaluation of compounds \(3d, 3g, 3h\) expressed in \(\mu\)M.

<table>
<thead>
<tr>
<th></th>
<th>(3d)</th>
<th>(3g)</th>
<th>(3h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC(_{50})</td>
<td>23 ± 3</td>
<td>&gt;7.5</td>
<td>6.5 ± 1.4</td>
</tr>
</tbody>
</table>

Conclusion

In summary, the Pd-mediated coupling of ethyl 2-chloro-1-azaazulene-3-carboxylate (1) with wide range of heteroarylamines was described. Annulation of ethyl heteroarylamino-1-azaazulene-3-carboxylates using a POCl\(_3\)-PPA mixture is useful for preparing new numerical heterocycles. Some ethyl heteroarylamino-1-azaazulene-3-carboxylates showed anticancer activity against HeLa S3 cells.

REFERENCES AND NOTES


14. A representative procedure of the amination: A mixture of 1 (0.2228 g, 0.95 mmol), 2-aminobenzothiazol (3e) (0.1402 g, 0.093 mmol), Xantphos (0.0533 g, 0.0092 mmol), Pd2(dba)3 (0.0580 g, 0.0063 mmol), Cs2CO3 (0.3176 g, 0.980 mmol), and dry 1,4-dioxane (2.5 mL) in a sealed tube under argon atmosphere was heated at 120 °C for 22 h under stirring, then water (20 mL) was added. The mixture was extracted with CHCl3. The extract was dried over Na2SO4, and evaporated. Chromatography of the residue with EtOAc-hexane (1:8) gave 3h (0.2106 g, 65%). 3h: Orange needles (from CH2Cl2-hexane), mp 177-178 °C; 1H NMR (CDCl3) δ 10.71 (1H, s, NH), 9.09 (1H, d, J = 10.0, H-4), 8.48 (1H, d, J = 9.6, H-8), 7.82 (1H, d, J = 8.0, H-7), 7.81 (1H, dd, J = 10.0, 9.6, H-7), 7.77 (1H, dd, J = 10.0, 9.6, H-5), 7.74 (1H, dd, J = 7.2, 1.2, H-4'), 7.71 (1H, dd, J = 10.0, 9.6, H-6), 7.43 (1H, t, J = 7.2, H-5'), 7.27 (1H, ddd, J = 8.0, 7.2, 1.2, H-6'), 4.53 (2H, q, J = 7.2, CH2), 1.52 (3H, t, J = 7.2, CH3); 13C NMR (CDCl3) δ 165.2, 161.7, 159.4, 159.2, 149.6, 147.1, 135.1, 133.7, 133.5, 133.3, 133.2, 132.7, 126.0, 123.1, 121.0, 120.5, 99.1, 60.7, 14.7; νmax / cm⁻¹ 1653 (C=O), 3249 (NH); λmax nm (log ε) 277 (4.59), 308 (4.45, sh), 393 (4.78), 444 (3.71, sh). Anal. Calcd for C19H15N3O2S: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.73; H, 4.32; N, 11.88.
16. A representative procedure of the annulation: A mixture of 3h (0.0735 g, 0.21 mmol), PPA (5 mL), and POCl3 (1.5 mL) was heated at 150 °C for 4 h under stirring, and then ice-water (20 mL) was added. The mixture was neutralized with Na2CO3. Then the precipitate was collected by filtration, and 5h (0.0589 g, 92%) was obtained. 5h: Yellow prisms (CHCl3-EtOH), mp 259-261 °C; 1H NMR (DMSO-d6) δ 9.50 (1H, dd, J = 9.2, 1.6, H-12), 9.08 (1H, dd, J = 8.4, 1.2, H-1), 8.84 (1H, dd, J = 10.0, 1.6, H-8), 8.32-8.24 (3H, m, H-9,11,12), 8.10 (1H, dd, J = 8.4, 1.2, H-4), 7.66 (1H, ddd, J = 8.4, 7.6, 1.2, H-3), 7.58 (1H, ddd, J = 8.4, 7.6, 1.2, H-2); 13CNMR (TFA-d) δ 172.2, 159.1, 158.9, 151.7, 147.7, 144.6, 144.4, 144.0, 137.6, 136.2, 131.1, 130.9, 125.4, 124.6, 121.9, 103.7; νmax / cm⁻¹ 1690 (C=O); λmax nm (log ε) 288 (4.27), 322 (4.45), 375 (3.60, sh), 458 (3.14). Anal. Calcd for C17H9N3OS: C, 67.31; H, 2.99; N, 13.85. Found: C, 67.25; H, 3.22; N, 14.11.