SYNTHESIS OF 2,6-DIAMINOAZULENES BY THE S_NAr REACTION WITH CYCLIC AMINES†

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Abstract – 2-Amino-6-bromoazulene derivatives reacted with cyclic amines (pyrrolidine, piperidine and morpholine) under the sealed-tube conditions to afford the corresponding 2,6-diaminoazulenes in excellent yields.

Aromatic compounds with multiple-amino functional groups have been of great interest owing to their potential applications in organic electronic devices, such as hole transport materials for organic light-emitting diodes.¹ Therefore, a large number of synthetic procedures for aromatic compounds with multiple-amino groups were found in literatures.²

In the pioneering works of azulene chemistry by Nozoe et al., 2,6-diaminoazulenes were first synthesized from an aminotropolone derivative, but the procedure requires a multistep reaction for the preparation of the starting tropolone derivatives which are essential to the preparation of 2,6-diaminoazulenes with different amino functions.³ They have also reported that the most promising intermediate, diethyl 2-amino-6-bromoazulene-1,3-dicarboxylate (1) that could be obtained much easier, does not react with

† Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday
amines to give the corresponding 2,6-diaminoazulenes, although the related diethyl 6-bromoazulene-1,3-dicarboxylate is easily reacted with amines to give the corresponding 6-aminoazulene derivatives.\textsuperscript{4} Difference of the reactivity at the 6-bromo groups is explained by the enhancement of electron-density of 1 owing to the electron-donating 2-amino group at the 6-position. Although we have reported an efficient preparation of 2- and 6-aminoazulene derivatives by utilizing palladium-catalyzed amination of 2- and 6-haloazulenes with several amines under the Hartwig–Buchwald conditions,\textsuperscript{5} the conditions has never been applied to the preparation of diaminoazulene derivatives due to the low availability of 2,6-dihaloazulenes.\textsuperscript{6} Thus, the development of an efficient and versatile preparation method for azulene derivatives with multiple-amino functional groups is one of the remained subjects in azulene chemistry for the applications of the aminoazulene derivatives to organic electronic materials. Recently, the sealed-tube conditions have been revealed by Li et al. as a good expedient for the amination reaction with volatile amines to provide aromatic amines that could not be obtained by the straightforward reaction.\textsuperscript{7} Thus, the amination reaction using the sealed-tube conditions will open a new and efficient strategy for the preparation of azulene derivatives with multiple-amino functional groups.

Herein, we describe novel synthetic procedures for 2,6-diaminoazulene derivatives 2–4 by the \textit{SN}$_{Ar}$-type amination reaction of 1 with cyclic amines (i.e., pyrrolidine, piperidine and morpholine) under the sealed-tube conditions, and by three-step amination reaction of 1 involving a protection and deprotection sequence of 2-amino group by trifluoroacetic anhydride. The outline of synthetic pathways for 2,6-diaminoazulene derivatives is shown in Scheme 1. The reaction conditions and yield of the products are summarized in Table 1. The reaction of 1 with cyclic amines (i.e., pyrrolidine, piperidine and morpholine) was examined under the sealed-tube conditions for the first time.\textsuperscript{8} The \textit{SN}$_{Ar}$ reaction of 1 with pyrrolidine at 130 °C in a sealed-tube and subsequent chromatographic purification on silica gel afforded the presumed product 2\textsuperscript{9} in 94% yield (Entry 1). Likewise, the reaction of 1 with piperidine afforded 3\textsuperscript{10} in 89% yield (Entry 2). The amination of 1 with morpholine under the sealed-tube conditions gave 4\textsuperscript{11} in 91% yield (Entry 3). Although Nozoe \textit{et al.} have reported that these amines do not react with 1 to afford the 2,6-diaminoazulenes,\textsuperscript{5} we found that they could be obtained by the \textit{SN}$_{Ar}$ reaction under the sealed-tube conditions. The reaction of 1 with alkylamines (i.e., \textit{tert}-butylamine, diethylamine, dibutylamine and diisopropylamine) was also examined under the same conditions, but the compound 1 was recovered, quantitatively, in all cases. The amination of ethyl 2-amino-6-bromoazulene-1-carboxylate (8) was also investigated, but the reaction did not undergo at all under the same conditions. Therefore, both high nucleophilicity of cyclic amines and electron-withdrawing groups at the 1,3-positions on azulene ring are essential to accelerate this \textit{SN}$_{Ar}$-type reaction. To explore the milder reaction condition, 2-amino group of 1 was protected by trifluoroacetyl
group that exhibits high electron-withdrawing nature. The trifluoroamidation reaction of 1 was established by using 3.0 equiv. of trifluoroacetic anhydride (TFAA) in the presence of excess pyridine as a base to afford the N-protected product 5 in 95% yield. As expected, amination reaction at the 6-position of 5 with cyclic amines was readily proceeded under much milder reaction conditions and short reaction period. Reaction of 5 with piperidine and morpholine was achieved at room temperature within 30 min to afford 6 and 7 in 60% and 81% yields, respectively, along with the deprotected 1 (Entries 5 and 6). The generation of 1 should exhibits the competition of the S$_{N}$Ar and deprotection reactions in these cases. In contrast, pyrrolidine reacted with 5 to give the deprotected-substitution product 2 in 74% yield, due to the consequence of the successive S$_{N}$Ar and deprotection reactions in one-pot (Entry 4). These results should be attributable to the higher nucleophilicity of pyrrolidine than that of piperidine and morpholine.$^{12}$ Deprotection of N-trifluoroacetyl group of 6 and 7 was readily established by the treatment with K$_2$CO$_3$ in EtOH to give the corresponding 2,6-diaminoazulenes 3 and 4, quantitatively (6: 99%, 7: 99%).

**Scheme 1.** Synthesis of 2,6-diaminoazulene derivatives

**Table 1.** Reaction of 2-amino-6-bromoazulenes 1 and 5 with cyclic amines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Amine</th>
<th>Reaction time [h]</th>
<th>Product, Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>pyrrolidine</td>
<td>6</td>
<td>2, 94</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>piperidine</td>
<td>6</td>
<td>3, 89</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>morpholine</td>
<td>6</td>
<td>4, 91</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>pyrrolidine</td>
<td>0.5</td>
<td>2, 74 and 1, 23</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>piperidine</td>
<td>0.5</td>
<td>6, 60 and 1, 34</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>morpholine</td>
<td>0.5</td>
<td>7, 81 and 1, 15</td>
</tr>
</tbody>
</table>

In conclusion, three new 2,6-diaminoazulene derivatives 2–4 have been prepared by the S$_{N}$Ar reaction of compound 1 with cyclic amines under the sealed-tube conditions. Although a protection-deprotection
sequence was required, 2,6-diaminoazulene derivatives 2–4 were also obtained from 1 under much milder reaction conditions. Since compound 1 is readily available as a starting material by the selective bromination of diethyl 2-aminoazulene-1,3-dicarboxylate at the 6-position, our synthetic methodologies have potentials to be an efficient procedure for the synthesis of azulene derivatives with multiple-amino functional groups.

ACKNOWLEDGEMENTS
This work was partially supported by a Grant-in-Aid for Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (Grant No. 25810019 to T. S.).

REFERENCE AND NOTE
8. **General procedure**: The solution of 1 (366 mg, 1.00 mmol) in the corresponding amines (5 mL) was stirred at 130 °C in a sealed-tube for 6 h under an Ar atmosphere. The reaction mixture was poured into a 1M HCl solution and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried with Na$_2$SO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with CH$_2$Cl$_2$ to give 2,6-diaminoazulenes 2–4 (yield of the products is summarized in Table 1).
9. **Selected data of compound 2**: mp 208.0 – 210.0 °C (MeOH); $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 9.01 (d, 2H, J = 11.7 Hz, 4,8-H), 7.05 (br s, 2H, NH$_2$), 6.87 (d, 2H, J = 11.7 Hz, 5,7-H), 4.42 (q, 4H, J = 7.2 Hz, CO$_2$Et), 3.53 (t, 4H, J = 6.3 Hz, 2,5-H of pyrrolidine), 2.13 (t, 4H, J = 6.3 Hz, 3,4-H of pyrrolidine), 1.45 (t, 6H, J = 7.2 Hz, CO$_2$Et).
10. **Selected data of compound 3**: Orange oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 8.97 (d, 2H, J = 11.8 Hz, 4,8-H), 7.32 (br s, 2H, NH$_2$), 7.12 (d, 2H, J = 11.8 Hz, 5,7-H), 4.42 (q, 4H, J = 7.2 Hz, CO$_2$Et), 3.49 (t, 4H, J = 5.5 Hz, 2,6-H of piperidine), 1.72 (br s, 6H, 3,4,5-H of piperidine), 1.45 (t, 6H, J = 7.2 Hz, CO$_2$Et).
11. **Selected data of compound 4**: mp 139.0 – 140.0 °C (MeOH); $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 9.02 (d, 2H, J = 11.8 Hz, 4,8-H), 7.40 (br s, 2H, NH$_2$), 7.15 (d, 2H, J = 11.8 Hz, 5,7-H), 4.43 (q, 4H, J = 7.2 Hz, CO$_2$Et), 3.88 (t, 4H, J = 4.9 Hz, 3,5-H of morpholine), 3.43 (t, 4H, J = 4.9 Hz, 2,6-H of morpholine), 1.45 (t, 6H, J = 7.2 Hz, CO$_2$Et).