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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

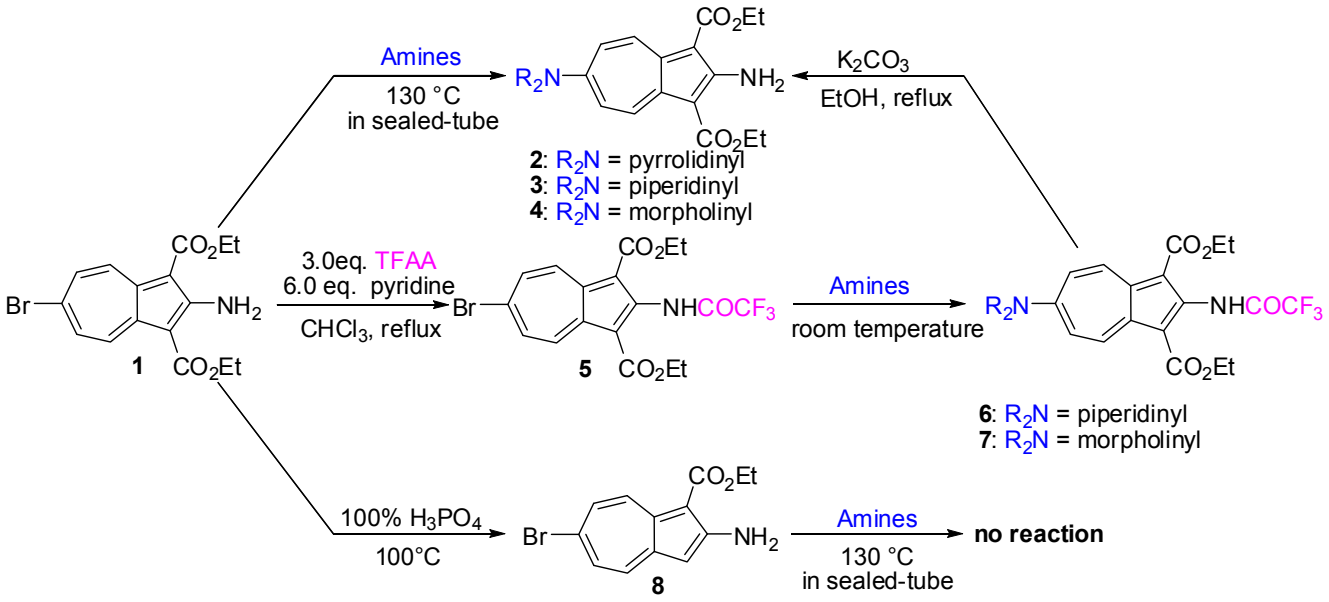
† Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

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.[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,[5] the conditions has never been applied to the preparation of diaminoazulene derivatives due to the low availability of 2,6-dihaloazulenes.[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.[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 S_NAr-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.[8] The S_NAr reaction of **1** with pyrrolidine at 130 °C in a sealed-tube and subsequent chromatographic purification on silica gel afforded the presumed product **2**[9] in 94% yield (Entry 1). Likewise, the reaction of **1** with piperidine afforded **3**[10] in 89% yield (Entry 2). The amination of **1** with morpholine under the sealed-tube conditions gave **4**[11] in 91% yield (Entry 3). Although Nozoe *et al*. have reported that these amines do not react with **1** to afford the 2,6-diaminoazulenes,[5] we found that they could be obtained by the S_NAr reaction under the sealed-tube conditions. The reaction of **1** with alkylamines (i.e., *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 S_NAr-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_NAr 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_NAr 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_2CO_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

Entry	Substrate	Amine	Reaction time [h]	Product, Yield [%]
1	**1**	pyrrolidine	6	**2**, 94
2	**1**	piperidine	6	**3**, 89
3	**1**	morpholine	6	**4**, 91
4	**5**	pyrrolidine	0.5	**2**, 74 and **1**, 23
5	**5**	piperidine	0.5	**6**, 60 and **1**, 34
6	**5**	morpholine	0.5	**7**, 81 and **1**, 15

In conclusion, three new 2,6-diaminoazulene derivatives **2**–**4** have been prepared by the S_NAr 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.

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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_2Cl_2. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with CH_2Cl_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, $CDCl_3$): δ_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_2Et), 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_2Et).
10. **Selected data of compound 3**: Orange oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ_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_2Et), 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_2Et).
11. **Selected data of compound 4**: mp 139.0 – 140.0 °C (MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ_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_2Et), 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_2Et).
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