Coupling Reaction of Azulenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes with Haloazulenes

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Abstract: In order to study the physicochemical properties of azulene oligomers, the synthesis and a coupling reaction of 2-(2-amino-1,3-bisethoxycarbonyl-6-azulenyl)-4,4,5,5-tetramethyl-1,3,2-diox-aborolane (1) and 2-(2-azulenyl)-4,4,5,5-tetramethyl-1,3,2-diox-aborolane (2) were examined.

Key words: arenes, azulene, boron, borylazulene, cross-coupling

Azulene oligomers and polymers are considered to be intriguing molecules from the viewpoint of the construction of functional substances, since azulene exhibits high redox potential, together with a moderate dipole moment vector. As for the dimers of azulene, some synthetic studies and physicochemical behavior have been reported,¹ and some novel functionalities of azulene oligomers seem to have been indicated. The synthetic methods, however, were considered to restrict the development of further studies. Thus, the Ullman coupling reactions at high temperature² or more sophisticated reactions that are based on Hafner's azulene synthesis, starting from bipyridyls, were used.³ Though the coupling reaction catalyzed with nickel dihalides was reported, it was effectively applied only to 1-bromoazulene.^{4a} The excellent Suzuki coupling⁵ using boryl-aromatic compounds which are derived from metalated aromatic compounds has been excluded, since the metalated azulene, such as azulenyl lithium⁶ and azulenyl magnesium halide, has not been reported in synthetic chemistry.

Recently, Miyaura has reported replacement of the halogen atom bonded to an aromatic ring by the pinacolatoboryl group with use of bis(pinacolato)diboron and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium.^{7a} This method was considered not to involve free metalated aromatic compounds. Hence, we decided to apply this reaction to the introduction of a boryl group to the azulene nucleus. It is important to study how the polarized electronic structure of azulene affects the introduction of the pinacolatoboryl group as well as the subsequent coupling reaction.

The nickel-catalyzed coupling reaction has been shown to be applicable to the synthesis of 1,1'-biazulene.^{4a} Application of this reaction to 2-amino-6-bromo-1,3-bisethoxy-carbonylazulene (**3**), however, resulted in the loss of the

bromine atom to give 2-amino-1,3-bisethoxycarbonylazulene (4) in 53% yield (Scheme 1). Less polarized 2-amino-6-bromoazulene (5) was likewise transformed into 2aminoazulene (6) in 26% yield. In contrast, 2-iodoazulene (7) was transformed into 2,2'-biazulene (8) in 42% yield, although the formation of azulene (28%) was observed. The reaction using 2-chloroazulene (9) also gave 8 in 60% yield together with a small amount of azulene. Comparison of the results for 3, 5, 7 and 9 is indicative of the difference between the reactivities at the 2- and 6-position, which could be definitely ascribed to the polarized structure of the azulene nucleus.



Scheme 1 Reagents and conditions: a) $(Ph_3P)_2NiCl_2$, tris(2-furyl)-phosphine, Zn, Et₄NI, THF

With the difference between the reactivities due to the positions of the azulene nucleus known, 2-(2-amino-1,3bisethoxycarbonyl-6-azulenyl)-4,4,5,5-tetramethyl-1,3,2dioxaborolane (1) and 2-(2-azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2) were examined in the coupling reactions (Scheme 2). Application of the Miyaura method^{7a} to the compounds 3 and 7 effectively yielded 1 and 2, respectively. The success of this simple application of the Miyaura method is considered to be a fair contribution in azulene chemistry.

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Scheme 2 Reagents and conditions: a) bis(pinacolato)diboron, Pd(dppf)Cl₂, KOAc, DMSO, 80 $^\circ C$

Treatment of **1** with iodobenzene in the presence of dichlorobis(triphenylphosphine)palladium and barium hydroxide⁸ gave 2-amino-1,3-bisethoxycarbonyl-6-phenylazulene in 91% yield. 2-Amino-1,3-bisethoxycarbonyl-6,2'-biazulene (**10**) was obtained by the treatment of **2** and **3** under the same conditions. Compound **10** was also formed by the coupling reaction of **1** with **7**; however, the yield was very low (28%). 2,2'-Diamino-1,1',3,3'-tetrakisethoxycarbonyl-6,6'-biazulene (**11**) was synthesized in the same manner using **1** and **3** (Scheme 3). The coupling reaction of **1** with 2,6-dibromopyridine (**12**) which consists of an electron-withdrawing pyridine nucleus and the bromine atoms effectively gave 2,6-bis(2-amino-1,3-bisethoxycarbonyl-6-azulenyl)pyridine (**13**) in 85% yield (Scheme 4). A pyrrole derivative which pos-



Scheme 3 Reagents and conditions: a) 3, (Ph₃P)₂PdCl₂, Ba(OH)₂, DME–H₂O (50:1), reflux

sesses an electron-withdrawing butoxycarbonyl group on the nitrogen atom likewise reacted with 1 to afford *N*-Boc-2,5-bis(2-amino-1,3-bisethoxycarbonyl-6-azulenyl)pyrrole (14) in 41% yield. The reaction of 1 with 2,5-dibromothiophene, however, resulted in recovery of the starting materials. Using the same method, an azulene trimer, that is, 2,2"-diamino-1,1",3,3"-tetrakisethoxycarbonyl-6,1':3',6"-terazulene (15), was, for the first time, synthesized in 46% yield.

In conclusion, we feel azulene oligomers with the desired structures in arrangement and length can be synthesized with the use of the Miyaura method, together with control of the reactivities of the substituents based on the polarity of the azulene nucleus.



Scheme 4 Reagents and conditions: a) 1, (Ph₃P)₂PdCl₂, Ba(OH)₂, DME-H₂O (50:1), reflux

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All reactions were carried out under argon. THF, DME and DMSO were distilled from CaH₂ under nitrogen before use. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a BRUKER AVANCE 400S (400 MHz) spectrometer with tetramethylsilane as an internal standard. IR spectra were obtained as KBr pellets on a Nicolet Impact 410 spectrophotometer. Mass spectra (EI) were determined on a Waters LC–MS Integrity System at an ionization potential 70 eV. UV/VIS spectra were measured by means of a Shimadzu UV-1600PC spectrophotometer.

Nickel-Catalyzed Reaction; General Procedure

To a flask charged with $(Ph_3P)_2NiCl_2$ (0.1 mmol), Zn (1.4 mmol), Et₄NI (1.0 mmol) and tris(2-furyl)phosphine (0.2 mmol) was added THF (6 mL) and then haloazulene (1.0 mmol). The suspension was stirred at 50 °C for 12 h (for **3** and **5**), at r.t. for 4 h (for **7**) and 24 h (for **9**), the reaction was quenched with brine, and the resulting mixture was extracted with Et₂O (3 × 5 mL). The combined extracts were dried (Na₂SO₄) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 5:1) to give the dehalogenated and/or coupling product.

Preparation of Azulenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes; General Procedure

To a flask charged with Pd(dppf)Cl₂ (0.03 mmol), KOAc (3.0 mmol) and bis(pinacolato)diboron (1.1 mmol) was added DMSO (6 mL) and then haloazulene (**3** or **7**)⁹ (1.0 mmol). The mixture was stirred at 80 °C for 5 h, the reaction was quenched with H₂O (20 mL), and the resulting mixture was extracted with benzene (3×5 mL). The combined extracts were dried (MgSO₄) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 5:1) to give the product.

2-(2-Amino-1,3-bisethoxycarbonyl-6-azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1)

Yield: 73%; orange solid; mp 167-170 °C.

IR: 1670 (CO) cm⁻¹.

¹H NMR: δ = 1.38 (12 H, s), 1.47 (6 H, t, J = 7.1 Hz), 4.43 (4 H, q, J = 7.1 Hz), 7.93 (2 H, s), 8.05 (2H, d, J = 10.6 Hz), 9.08 (2 H, d, J = 10.6 Hz).

 13 C NMR: δ = 14.55, 24.89, 59.82, 84.52, 99.69, 130.26, 138.63, 147.33, 144.86, 163.50, 166.60.

UV/VIS (cyclohexane): λ_{max} (ϵ) = 249 (33910), 319 (52820), 329 (65570), 374 (sh) (8080), 414 (11970), 454 (sh) (1660) nm.

MS: m/z (%) = 295 (M⁺ – CO₂Et – OEt, 100), 367 (M⁺ – OEt – 1, 21), 413 (M⁺, 56).

Anal. Calcd for C₂₂H₂₈BNO₆: C, 63.94; H, 6.83; N, 3.39. Found: C, 64.21; H, 7.01; N, 3.41.

2-(2-Azulenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2) Yield: 42%; blue solid; mp 99–101 °C.

IR: 2980, 1510, 1340, 1240, 1140 cm⁻¹.

¹H NMR: δ = 1.40 (12 H, s), 7.12 (2 H, t, *J* = 9.8 Hz), 7.58 (1 H, dd, *J* = 10.0, 9.8 Hz), 7.76 (2 H, s), 8.35 (2 H, d, *J* = 10.0 Hz).

 13 C NMR: $\delta = 24.93, 83.72, 122.72, 125.07, 138.17, 138.74, 140.68.$ One carbon signal due to the azulene skeleton was not observed.

UV/VIS (cyclohexane): λ_{max} (ϵ) = 203 (37240), 244 (34270), 284 (114360), 332 (9010), 347 (11300), 360 (4260), 434 (1530), 665 (1460).

MS: m/z (%) = 128 (C₁₀H₈, 29), 154 (C₁₀H₇BO, 99), 169 (19), 181 (84), 254 (M⁺, 100).

Anal. Calcd for $C_{16}H_{19}BO_2$: C, 75.62; H, 7.54. Found: C, 75.22; H, 7.55.

Cross-Coupling Reaction; Typical Procedure

To a suspension of $(Ph_3P)_2PdCl_2$ (0.014 mmol), **1** (0.1 mmol) and Ba(OH)₂·8H₂O (0.2 mmol) in DME–H₂O (50:1) (2 mL) was added iodobenzene (0.15 mmol), and the mixture was refluxed for 24 h. The reaction was quenched with water and the resulting mixture was extracted with CHCl₃ (3 × 5 mL). The combined extracts were dried (Na₂SO₄) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 2:1) to give 2-amino-1,3-bisethoxycarbonyl-6-phenylazulene.

Yield: 91%; yellow powder; mp 142–150 °C.

IR: 1655 (CO) cm⁻¹.

¹H NMR: δ = 1.49 (6 H, t, *J* = 7.1 Hz), 4.48 (4 H, q, *J* = 7.1 Hz), 7.42 (1 H, t, *J* = 7.3 Hz), 7.49 (2 H, t, *J* = 7.4 Hz), 7.63 (2 H, d, *J* = 7.1 Hz), 7.79 (2 H, d, *J* = 11.4 Hz), 7.81 (2 H, s), 9.19 (2 H, d, *J* = 11.4 Hz).

 13 C NMR: $\delta = 14.69, 59.86, 99.97, 127.92, 128.28, 128.86, 130.89, 132.82, 143.86, 144.86, 146.42, 162.42, 166.58.$

UV/VIS (dioxane): λ_{max} (ϵ) = 247 (31250), 338 (52030), 423 (11720), 461 (sh) (2390).

MS: m/z (%) = 245 (M⁺ – CO₂Et – OEt, 100), 317 (M⁺ – OEt – 1, 28), 363 (M⁺, 70).

Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.12; H, 5.80; N, 3.94.

2-Amino-1,3-bisethoxycarbonyl-6,2'-biazulene (10)

Yield: 71%; brown powder; mp 172–173 °C.

IR: 1682 (CO) cm⁻¹.

¹H NMR: δ = 1.51 (6 H, t, J = 7.1 Hz), 4.49 (4 H, q, J = 7.1 Hz), 7.19 (2 H, t, J = 9.8 Hz), 7.55 (1 H, t, J = 9.9 Hz), 7.74 (2 H, s), 7.84 (2 H, s), 8.25 (2 H, d, J = 11.5 Hz), 8.31 (2 H, d, J = 9.4 Hz), 9.18 (2 H, d, J = 11.5 Hz).

 ^{13}C NMR: δ = 15.10, 60.26, 100.56, 116.01, 124.67, 131.08, 133.03, 137.28, 137.75, 141.43, 141.86, 145.55, 152.03, 163.05, 166.96.

UV/VIS (dioxane): λ_{max} (ϵ) = 251 (71300), 295 (23960), 334 (94700), 358 (sh) (58530), 467 (54170), 576 (sh) (1180), 623 (sh) (830), 681 (sh) (320).

MS: m/z (%) = 295 (M⁺ – CO₂Et – OEt, 100), 367 (M⁺ – OEt + 1, 20), 413 (M⁺, 67).

Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.93; H, 5.81; N, 3.79.

2,2'-Diamino-1,1',3,3'-tetrakisethoxycarbonyl-6,6'-biazulene (11)

Yield: 24%; orange powder; mp 298 °C (decomp.).

IR: 1674 (CO) cm⁻¹.

¹H NMR: δ = 1.50 (12 H, t, *J* = 7.1 Hz), 4.48 (8 H, q, *J* = 7.1 Hz), 7.77 (4 H, d, *J* = 11.3 Hz), 7.86 (4 H, s), 9.16 (4 H, d, *J* = 11.3 Hz).

 ^{13}C NMR: δ = 14.67, 59.97, 100.34, 130.46, 133.34, 144.87, 148.33, 162.73, 166.47.

UV/VIS (dioxane): λ_{max} (ϵ) = 249 (57650), 357 (72470), 463 (39420).

MS: m/z (%) = 149 (100), 167 (C₁₀H₄CONH, 41), 279 (M⁺ - 4 CO₂Et - 1, 12), 572 (M⁺, 3).

Anal. Calcd for $C_{32}H_{32}N_2O_8{:}$ C, 67.12; H, 5.63; N, 4.89. Found: C, 67.50; H, 5.28; N, 5.13.

2,6-Bis(2-amino-1,3-bisethoxycarbonyl-6-azulenyl)pyridine (13)

Yield: 85%; brown powder; mp 223–225 °C. IR: (CO) 1670 cm⁻¹.

¹H NMR: δ = 1.49 (12 H, t, *J* = 7.1 Hz), 4.47 (8 H, q, *J* = 7.1 Hz), 7.73 (2 H, d, *J* = 7.9 Hz), 7.81 (1 H, t, *J* = 7.9 Hz), 7.85 (4 H, s), 8.27 (4 H, d, *J* = 11.3 Hz), 9.14 (4 H, d, *J* = 11.3 Hz).

 ^{13}C NMR: δ = 15.10, 60.32, 100.52, 120.77, 130.75, 132.31, 138.20, 142.96, 145.99, 158.83, 163.30, 166.89.

UV/VIS (dioxane): λ_{max} (ϵ) = 249 (78600), 344 (99770), 440 (51330).

MS: m/z (%) = 295 (M⁺ - 4 CO₂Et - 2 NH₂ - 1, 82), 412 (M⁺ - 2 CO₂Et - 1, 100), 649 (M⁺, 71).

Anal. Calcd for $C_{37}H_{35}N_3O_8$: C, 68.40; H, 5.43; N, 6.47. Found: C, 68.65; H, 5.30; N, 6.67.

N-Boc-2,5-Bis(2-amino-1,3-bisethoxycarbonyl-6-azulenyl)pyrrole (14)

Yield: 41%; red powder; mp 205-207 °C.

IR: 1746, 1674 (CO) cm⁻¹.

¹H NMR: δ = 1.13 (9 H, s), 1.48 (12 H, t, *J* = 6.8 Hz), 4.47 (8 H, q, *J* = 6.8 Hz), 6.43 (2 H, s), 7.67 (4 H, d, *J* = 11.8 Hz), 7.79 (4 H, s), 9.10 (4 H, d, *J* = 11.8 Hz).

 ^{13}C NMR: δ = 14.59, 27.19, 59.83, 85.08, 100.08, 114.58, 128.25, 129.90, 133.21, 138.17, 139.69, 144.93, 162.36, 166.42.

UV/VIS (dioxane): λ_{max} (ϵ) = 248 (74410), 322 (54240), 364 (47660), 457 (45100).

MS: m/z (%) = 108 (100), 149 (71), 184 (56), 571 (M⁺ - 2 CO₂Et - 2 OEt + 1, 24), 590 (M⁺ - CO₂t-Bu -OEt - 1, 20), 737 (M⁺, 3).

Anal. Calcd for $C_{41}H_{43}N_3O_{10}$: C, 66.74; H, 5.87; N, 5.70. Found: C, 67.10; H, 5.57; N, 5.45.

2,2"-Diamino-1,1",3,3"-tetrakisethoxycarbonyl-6,1':3',6"-terazulene (15)

Yield: 46%; reddish brown powder; mp 235–238 °C.

IR: 1673 (CO) cm⁻¹.

¹H NMR: δ = 1.51 (12 H, t, *J* = 7.1 Hz), 4.50 (8 H, q, *J* = 7.1 Hz), 7.29 (2 H, t, *J* = 10.0 Hz), 7.72 (1 H, t, *J* = 8.8 Hz), 7.80 (4 H, s), 7.92 (4 H, d, *J* = 11.4 Hz), 8.29 (1 H, s), 8.62 (2 H, d, *J* = 9.6 Hz), 9.24 (4 H, d, *J* = 11.4 Hz).

 ^{13}C NMR: δ = 14.73, 59.86, 100.02, 125.46, 130.77, 133.11, 134.93, 136.80, 137.87, 138.25, 140.10, 142.04, 144.55, 162.23, 166.61.

UV/VIS (dioxane): λ_{max} (ϵ) = 249 (66160), 280 (31010), 345 (67410), 469 (49510), 620 (sh) (500).

Anal. Calcd for $C_{42}H_{38}N_2O_8$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.43; H, 5.64; N, 3.40.

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