HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 463 - 474. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 28th June, 2013, Accepted, 25th July, 2013, Published online, 14th August, 2013
DOI: 10.3987/COM-13-S(S)59

SYNTHESIS OF NOVEL BENZOFURAN FUSED 1-AZAAZULENE DERIVATIVE BY TANDEM INTERMOLECULAR SUZUKI COUPLING/INTRAMOLECULAR BUCHWALD-HARTWIG TYPE COUPLING†

Hiroyuki Fujii,*[a] Kazuya Sanada,[b] Yu Kawai,[c] Reiko Ikeda,[c] Takeo Konakahara,[c] and Noritaka Abe[d]

[a]Science Research Center, Yamaguchi University, Yamaguchi 753-8512, Japan; [b]Graduate School of Science and Engineering, Yamaguchi University, Yamaguchi 753-8512, Japan; [c]Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, Noda, Chiba 278-8510, Japan; [d]Yamaguchi Study Center, The Open University of Japan, Yamaguchi 753-8512, Japan: E-mail fujii@yamaguchi-u.ac.jp

Abstract – Synthesis of benzofuran fused 1-azaazulene derivative (cyclohepta[*d*]benzo[4,5]furano[2,3-*b*]pyrrole) (**4**) was achieved successfully by tandem intermolecular Suzuki coupling/intramolecular Buchwald-Hartwig type coupling of 2-chloro-3-iodo-1-azaazulene with 2-hydroxyphenylboronic acid pinacolate in the presence of Pd catalyst. The compound **4** was also obtained by the reaction of 2-chloro-1-azaazulene with 2-iodophenol in the presence of Pd catalyst in one pot. It was considered that the obtained tetra-cyclic heterocycles would consist 18π peripheral conjugated system by the studies of UV/Vis spectra and ^{1}H NMR spectra, together with DFT calculation.

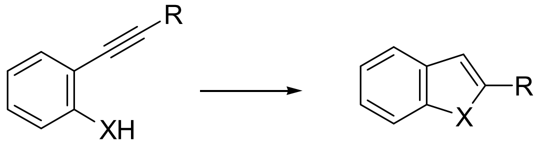
INTRODUCTION

The chemistry of 1-azaazulenes, a non-alternant heterocyclic system, was attracted attention for their interesting chemical and structural characteristics, as well as pharmaceutical properties.[1] Recently, we reported that poly-cyclic heterocycles having 1-azaazulene moiety showed several bioactivities and some interesting functionalities.[2]

---

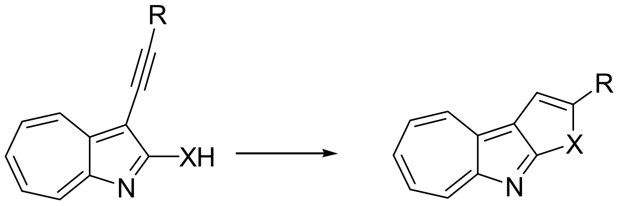
† Dedicated to Prof. Victor Snieckus on his 77th Birthday.

Benzofurans are well known fused heterocycles and also attracted attention for their biological properties such as anticancer activity.[3] Recently, extensive useful synthetic methods for benzo-heterocycles, such as benzofurans,[4] benzopyrroles,[5] and benzothiophenes,[6] have been developed, where intramolecular cyclization reactions of ortho-ethynyl substituted phenols, anilines, and thiophenols were adopted.



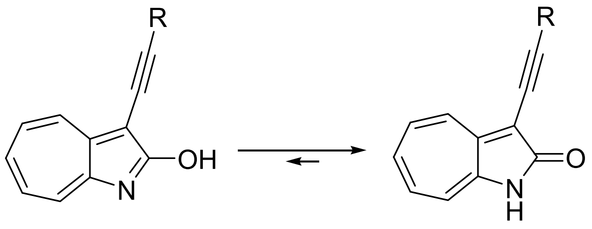
X = O, NH, S

Hitherto, we have reported about the synthesis of pyrrole[7] or thiophene[8] fused 1-azaazulenes by intramolecular cyclization of 2-amino-3-ethynyl-1-azaazulene or 3-ethynyl-2-mercapto-1-azaazulene, respectively. In a similar manner, we tried to synthesize furan fused 1-azaazulenes. But we could not obtain the target molecule by ordinal treatments.



X = NMs, S

As a reason that the intramolecular cyclization did not occur, we considered that the tautomerization between the enol form (**A**) and the keto form (**B**) exists, and the existence of **B** is extremely predominant than that of **A**. Therefore the attack of hydroxyl group to the ethynyl group did not launch.



A **B**

tautomerization

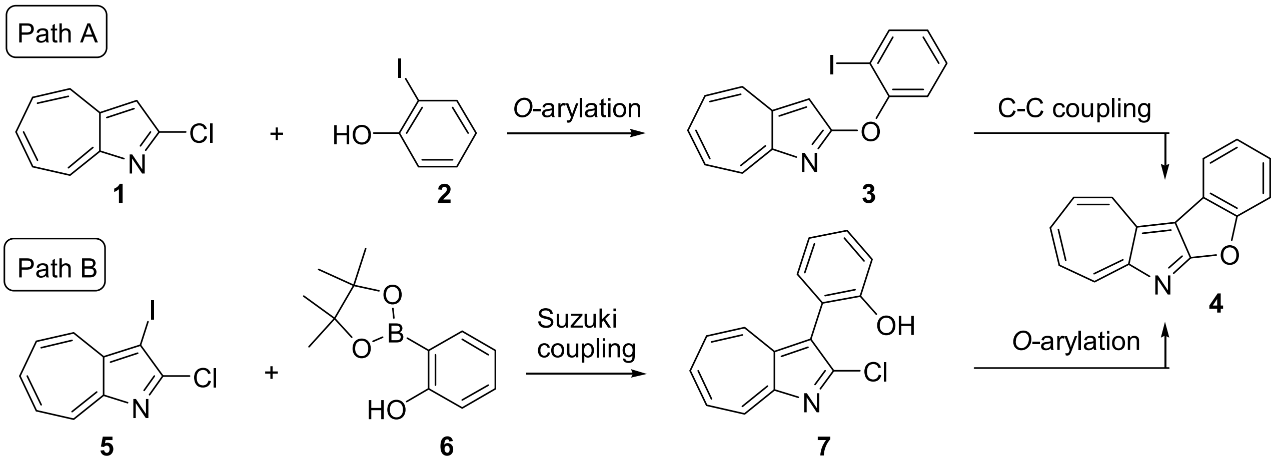
Recently the synthesis of benzofurans by cyclization of *o*-ethynylanisol was reported.[9] Therefore we considered that the furan moiety could be constructed from 3-ethynyl-2-alkoxy-1-azaazulene, by adopting the method. 2-Alkoxy-1-azaazulenes were easily synthesized and the introduction of ethynyl group to

2-alkoxy-1-azaazulenes by Sonogashira coupling was succeeded. But the intramolecular cyclization in this manner did not occur, and the target molecule was not obtained.

Therefore, we next examined another method for introducing furan moiety into fused azaazulenes. Exploiting synthetic methods of the alkoxy-1-azaazulenes, we examined the reaction of introduction of phenoxy group onto 1-azaazulene ring and successive annulation to benzofuran fused 1-azaazulene by using the characteristics of 1-azaazulenes.

RESULTS AND DISCUSSION

Halogen at C-2 of 1-azaazulenes could easily replace to alkoxy or amino group by the treatment with alcohol[10] or amine[11] under basic conditions (in the presence of alkoxide ion or aminide ion) or suffer heteroarylation[12] (Buchwald-Hartwig type reaction). Therefore, we designed two approaches (Path A and Path B) for synthesis of the target molecule (**4**).



synthetic route of Path A and Path B

In Path A, phenoxy group is introduced to C-2 of 1-azaazulene at first, and successive C-C coupling at 3-position undergoes to give furan ring. In Path B, 2-hydroxyphenyl group is introduced to C-3 of 1-azaazulene at first, and successive attack by hydroxyl group at C-2 of 1-azaazulene ring, attended substitution of chloride, gives benzofuran fused 1-azaazulene.

At the beginning, we synthesized 2-(2-iodophenoxy)-1-azaazulene (**3**) in 64% yield by the reaction of 2-chloro-1-azaazulene (**1**) with 2-iodophenoxide, prepared from 2-iodophenol (**2**) and NaH, for 48 h at 110 °C in 1,4-dioxane.

Next, we examined the cyclization of **3**. Reaction of **3** was performed in the presence of $Pd_2(dba)_3$ and Xantphos for 48 h at 110 °C in dioxane, and the desired cyclized product (**4**) was obtained in 32% yield together with 2-phenoxy-1-azaazulene (**8**), being deiodonated under the conditions, in 25%.

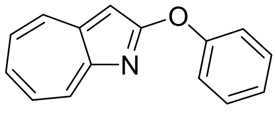
The fact that the cyclization of **3** achieved under the conditions of Buchwald-Hartwig type heteroarylation strung us to desire domino coupling of 2-chloro-1-azaazulene with 2-iodophenol in the presence of Pd catalyst. Thus we examined the reactions of 2-chloro-1-azaazulene (**1**) with 2-iodophenol (**2**) in the presence of $Pd_2(dba)_3$ and Xantphos in 1,4-dioxane at 80 °C for 24 h. As our aims, cyclized product (**4**) was obtained in 22% yield together with recovered **3** (43%). To optimize the reaction, we checked up on the conditions (temperature and reaction time). The results were summarized in Table 1. Both the yields of **4** and **3** had increased at 110 °C, but both the yields **4** and **3** had decreased at 130 °C. Therefore we prolonged the reaction time at 110 °C, and the yield of **4** was improved. In the case of 144 h, the yield of **4** was enhanced up to 72% yield.

Table 1. The reactions of **1** and **2** in the presense of $Pd_2(dba)_3$-Xantphos catalysts.[a]

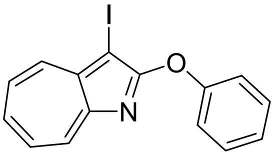
	conditions		product (%)[b]		
entry	temp. (°C)	time (h)	**4**	**3**	**1**[c]
1	80	24	22	43	18
2	110	24	29	54	0
3	130	24	26	48	0
4	80	53	28	47	11
5	110	65	32	45	0
6	110	90	58	24	0
7	110	144	72	12	0

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Pd catalyst (3 mol%), ligand (4 mol%), and base (1.5 equiv.) were dissolved in 1,4-dioxane (5 mL) and the mixture was heated under Ar atmosphere. [b] Yields were determined by ^1H NMR spectra. [c] Recovery of **1**.

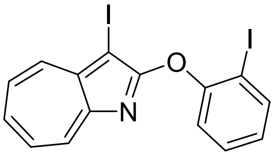
In the reaction, deiodonated compound (**8**) was not detected. It is considered that the palladation of the iodine on the phenol and successive hydrogenation gave **8**. As a yield of **3** decreased and a yield of **4** increased under prolonged reaction time, it seems that the heteroarylation at C-2 of 1-azaazulene occurred at first, and then the successive coupling reaction at C-3 of 1-azaazulene occurred and the annulations was achieved.



8



9



10

To confirm the consideration, we examined the reaction of 3-iodo-2-phenoxy-1-azaazulene (**9**) or 3-iodo-2-(2-iodophenoxy)-1-azaazulene (**10**) under the conditions of Buchwald-Hartwig type heteroarylation. At first, we treated **8** with NIS in $CHCl_3$ and obtained **9** in 81% yield. Similar treatment of **3** with NIS gave **10** in 83% yield. Treatment of **9** in the presence of $Pd_2(dba)_3$ and Xantphos in 1,4-dioxane at 110 °C for 24 h gave **4** in 23% yield together with **9** (11%) and **8** (11%). Under similar conditions, the reaction of **10** gave **4** in only 2% yield together with **10** (55%) and **8** (1%). These results consisted with the consideration.

Suzuki coupling of halo-1-azaazulenes was known.[13] For synthesis of **4**, we next examined the synthesis of 2-chloro-3-(2-hydroxyphenyl)-1-azaazulene (**7**) by Suzuki coupling and successive cyclization (Path B).

The reaction of 2-chloro-3-iodo-1-azaazulene (**5**) with 2-hydroxyphenylboronic acid pinacolate (**6**) in the presence of $PdCl_2(PPh_3)_2$ and K_2CO_3 was carried out at 110 °C for 24 h in toluene, but only recovered **5** (54%) was isolated and the desired product was not obtained. When the reaction was examined in THF, the coupling product **7** was not isolated, instead further cyclization proceeded and benzofuran fused 1-azaazulene (**4**) was isolated in 22% yield. To improve the reaction, the reaction time was prolonged to 48 h at 110 °C. As the results, the yield of **4** was improved up to 60% yield (Table 2).

Thus we could achieve tandem intermolecular Suzuki coupling/intramolecular Buchwald-Hartwig type coupling of 2-chloro-1-azaazulene with 2-iodophenol.

Table 2. The reactions of **5** and **6** in the presense of $PdCl_2(PPh_3)_4$.[a]

	conditions			product[b]	
entry	solvent	base	time (h)	**4**	**5**[c]
1	toluene	K_2CO_3	24	0	54
2	THF	Cs_2CO_3	24	22	8
3	THF	Cs_2CO_3	48	60	0

[a]Reaction conditions: **5** (0.5 mmol), **6** (0.75 mmol), Pd catalyst (4 mol%), and base (3 equiv.) were dissolved in solvent (5 mL) and the mixture was heated under Ar atomsphere. [b]Yeilds were determined by ^1H NMR spectra. [c]Recovery of **5**.

UV/Vis spectra of the compounds (**8**, **3**, and **4**) in MeCN were shown in Figure 1. The longest wavelength absorption bands of **3** and **8** were appeared at around 450 nm and the corresponding absorption of **4** appeared at around 500 nm. Characteristically, whereas the absorptions of **3** and **8** appeared at around 330 nm, the corresponding absorption of **4** appeared at around 390 nm attended with red-shift and bathochromic-shift. The results suggested that the *π*-conjugation of **4** would be expanded.

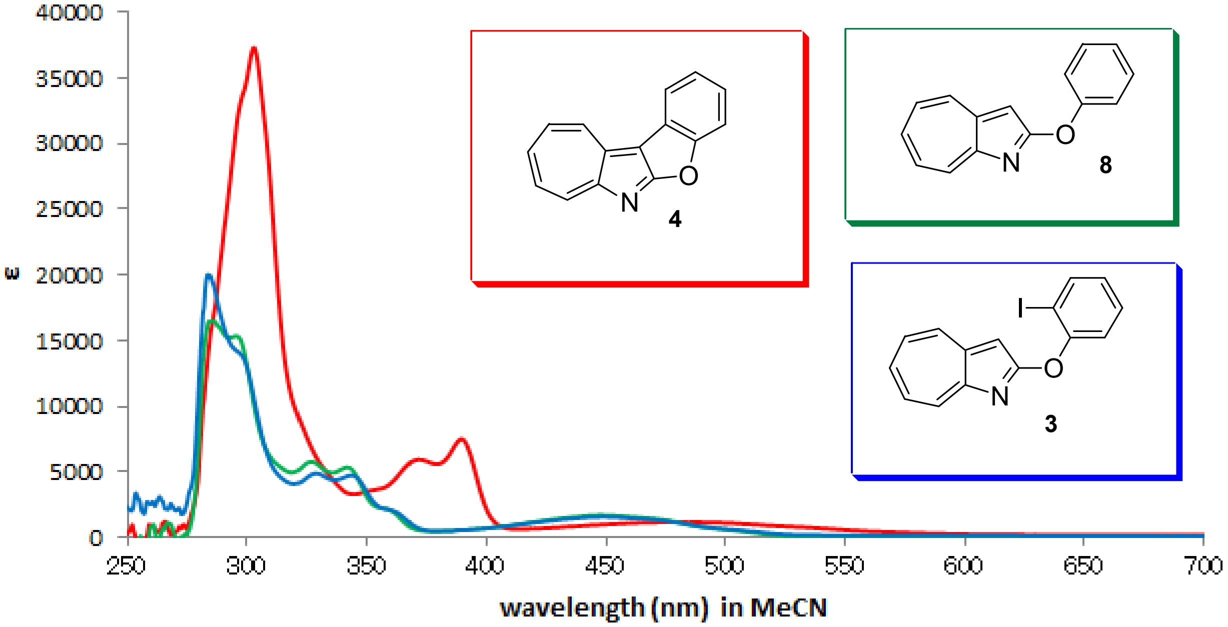
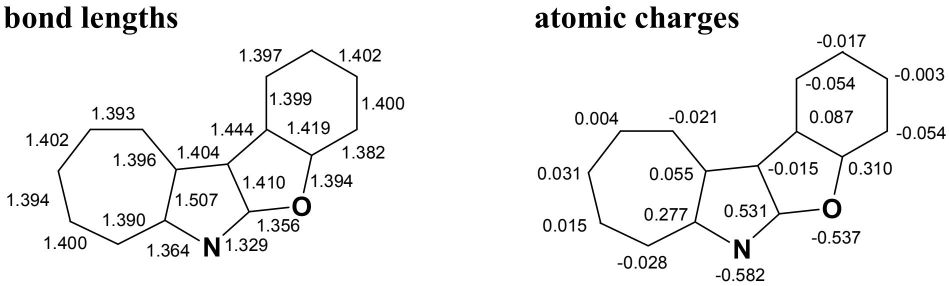


Figure 1. UV/Vis specta of compounds **3**, **4**, and **8**.

Ab initio calculation using Gaussian 03 (B3LYP/6-31G∗) was performed for certification of a molecular structure of **4** (Figure 2). From the results of calculation of bond lengths, it is shown that the bond–alternation exists. But the divergence of the bond lengths of seven-membered ring was small (Δ 0.012~0.009 Å), and this suggests that the bond-alternation is small. The C-O bonds and C-C bonds (1.410 and 1.419 Å), corresponding C(2)-C(3) and C(4)-C(5) of furan moiety of **4** are slightly longer than those of ordinary furan ring. From the results of the calculation of atomic charges of **4**, it is shown that the deviation of electron densities was slightly small and the *π*–electrons would be delocalized over the molecule. These results suggested that the compound **4** has 18*π* peripheral conjugated structure. The ^{1}H NMR spectrum of **4** shows slightly lower field resonated signals (*δ* 7.4~8.8) than the signals of ordinal 1-azaazulenes (*δ* 7.7~8.6) and benzofuran (*δ* 7.2~7.8 for benzene ring). It is known that the coupling constants of the seven-membered ring protons of 1-azaazulenes were generally about 10 Hz.[14] The coupling constants of seven-membered ring moiety of **4** were *J* = 9.0~10.2 Hz and the divergences were small, in comparison with those of fused 1-azaazulenes having heptafulvene form (*J* = 8.0~12.5 Hz).[2a,14] The results showed that the bond-alternation of **4** was small, and consisted with the calculation results. The *J* value of protons on C(10)-C(11) (9.2 Hz) of **4** is smaller than the corresponding *J* value of protons on C(4) and C(5) (10.2 Hz) of **3**. All above phenomena would be caused to generation of bond-alternation attended by cyclization of **3** to **4**. These results consist with the consideration.



Bond lengths are given in Å.

Atomic charges with hydrogens summed into heavy atoms.
Sum of Mulliken charges = 0.000.

Figure 2. Calculated structure of **4**

Biological evaluation

It is known that azaazulene derivatives showed some kinds of bioactivities.[1] In our research about 1-azaazulenes, we found that some heteroaryl-substituted 1-azaazulenes and fused 1-azaazulenes showed strong cytotoxic activity against HeLa S-3 cells.[2a-c,12a,15] In the line of our research, we evaluated the cytotoxic activity of compound **4** against HeLa S-3 cells. Unfortunately, the IC_{50} value of **4** was >100 μM and **4** would be inactive against HeLa S-3 cells.

CONCLUSION

We successfully synthesized benzofuran fused 1-azaazulene derivatives (cyclohepta[*d*]benzo[4,5]-furano[2,3-*b*]pyrrole) (**4**) by tandem intermolecular Suzuki coupling/intramolecular Buchwald-Hartwig type coupling of 2-chloro-3-iodo-1-azaazulene with 2-hydroxyphenylboronic acid pinacolate in the presence of Pd catalyst. Compound **4** was also obtained by the reaction of 2-chloro-1-azaazulene with 2-iodophenol in the presence of Pd catalyst in one pot. Compound **4** has a characteristic conjugated tetracyclic system, in which the bond-alternation was small, and it is suggested that **4** has 18π peripheral conjugated system.

EXPERIMENTAL

Mps are measured using a Yanagimoto micro-melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400S (400 MHz) and ^{13}C NMR were recorded on a Bruker AVANCE 400S (100.6 MHz) using deuteriochloroform as a solvent and tetramethylsilane as an internal standard; *J* values are recorded in Hz. IR spectra were recorded for KBr pellets on a Nicolet FT-IR Impact 410 otherwise stated. Electronic spectra were recorded with Shimadzu UV-1600PC spectrophotometer. Mass spectra (ESI-MS) were taken with JEOL JMS-T100CS. GC-Mass spectra were taken with Shimadzu GC-MS QP2010 Plus. Elemental analyses were taken with a Perkin Elmer 2400II. Kieselgel 60 was used for column chromatography and Kieselgel 60G was used for thin-layer chromatography.

Synthesis of 2-(2-iodophenoxy)-1-azaazulene (3)

Under argon atmosphere, a mixture of 2-iodophenol (**2**) (262 mg, 1.191 mmol) and 60 wt% sodium hydride (61 mg, 1.525 mmol) in 1,4-dioxane (4 mL) was stirred for 15 min at rt. To the mixture, 2-chloro-1-azaazulene (**1**) (88 mg, 0.538 mmol) in 1,4-dioxane (1 mL) was added, and the mixture was stirred for 48 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue gave **3** (119 mg, 64%) and the recovery of substrate **1** (27 mg, 31%).

3: Yellow oil; δ_H 6.61 (s, 1H), 7.04 (ddm, *J* 8.0, 7.9 , 1H), 7.39 (ddm, *J* 8.4, 7.9, 1H), 7.43 (dm, *J* 8.4 , 1H), 7.52-7.57 (m, 1H), 7.63-7.69 (m, 2H), 7.92 (dm, *J* 8.0, 1H), 8.24 (d, *J* 10.2, 1H), and 8.36-8.42 (m, 1H); δ_C 89.8, 98.1, 122.2, 127.1, 129.4, 129.8, 130.1, 132.2, 132.7, 134.4, 140.0, 147.8, 154.8, 155.4, and 173.6; ν_{max}/cm^{-1} 1214 (-O-); λ_{max} (MeCN) nm (log ε) 286 (4.22), 327 (3.76), 342 (3.73), and 448 (3.23); *m/z* (rel intensity) 347 (M^+, 72), 220 (M^+-I, 100). Picrate of **3**: Yellow powders (from EtOH), mp 217-222 ℃: *Anal.* Calcd for $C_{15}H_{10}INO \cdot C_6H_3N_3O_7$: C, 43.77; H, 2.27; N, 9.72. Found: C, 43.88; H, 2.00; N, 10.25.

Synthesis of cyclohepta[*d*]benzo[4,5]furano[2,3-*b*]pyrrole (4)

Under argon atmosphere, a mixture of $Pd_2(dba)_3$ (7 mg, 0.008 mmol), Xantphos (8 mg, 0.014 mmol), Cs_2CO_3 (76 mg, 0.233 mmol), and **3** (44 mg, 0.127 mmol) in 1,4-dioxane (4 mL) was stirred for 48 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue gave **4** (9 mg, 32%) and **8** (7 mg, 25%).

4: Red plates (from acetone), mp 165-167 ℃; δ_H 7.40-7.44 (m, 2H), 7.65-7.68 (m, 1H), 7.81 (ddm, *J* 10.0, 9.0, 1H), 7.88 (ddm, *J* 10.2, 9.2, 1H), 7.93 (ddm, *J* 10.2, 9.0, 2H), 7.99-8.01 (m, 1H), 8.74 (dm, *J* 9.2, 1H), and 8.80 (dm, *J* 10.0, 1H); δ_C 110.3, 112.6, 120.8, 122.8, 123.9, 125.5, 129.2, 130.1, 132.0, 134.9, 135.5, 136.3, 159.9, 160.9, and 178.6; ν_{max}/cm^{-1} 1181 (-O-); λ_{max} (MeCN) nm (log ε) 303 (4.57), 372 (3.77), 390 (3.88), and 478 (3.07); *m/z* (rel intensity) 219 (M^+, 100). HRMS (ESI^+): Calcd for

$C_{15}H_9NNaO$: 242.0582; Found: *m/z* 242.0514. *Anal.* Calcd for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39. Found: C, 81.80; H, 3.91; N, 6.40.

Synthesis of 2-phenoxy-1-azaazulene (8)

Under argon atmosphere, a mixture of phenol (100 mg, 1.06 mmol) and NaH (39 mg, 0.98 mmol) in 1,4-dioxane (4 mL) was stirred for 15 min at rt. To the solution, 2-chloro-1-azaazulene (**1**) (85 mg, 0.52 mmol) in 1,4-dioxane (1 mL) was added, and the mixture was stirred for 24 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt/hexane = 1/1) of the residue gave **8** (104 mg, 91%).

8: Yellow oil; δ_H 6.61 (s, 1H), 7.28 (t, *J* 7.2, 1H), 7.35 (dd, *J* 8.4, 1.0, 2H), 7.46 (dd, *J* 8.4, 7.2, 2H), 7.53 (dd, *J* 10.2, 10.0, 1H), 7.60-7.69 (m, 2H), 8.20 (d, *J* 10.0, 1H), and 8.37 (dm, *J* 10.2, 1H); δ_C 97.6, 120.6, 125.1, 129.2, 129.6, 129.9, 131.7, 132.0, 133.9, 147.5, 154.7, 155.3, and 174.3; ν_{max}/cm^{-1} 1203 (-O-); λ_{max} (MeCN) nm (log ε) 284 (4.30), 329 (3.69), 344 (3.68), and 449 (3.20); *m/z* (rel intensity) 221 (M^+, 71), 220 (M^+-H, 100). *Anal.* Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.40; H, 4.93; N, 6.32.

Synthesis of 3-iodo-2-phenoxy-1-azaazulene (9)

Under argon atmosphere, a mixture of **8** (123 mg, 0.556 mmol), NIS (148 mg, 0.658 mmol), and benzoyl peroxide (2 cups of spatulas) in $CHCl_3$ (8 mL) was stirred for 1 h at rt. The reaction mixture was poured into saturated $NaHSO_3$ solution (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, $CHCl_3$) of the residue gave **9** (156 mg, 81%).

9: Orange needles (from acetone), mp 108-110 ℃; δ_H 7.27 (t, *J* 7.2, 1H), 7.46 (dd, *J* 8.2, 7.2, 2H), 7.40 (d, J 8.2, 2H), 7.60-7.67 (m, 3H), 8.22 (dd, *J* 10.6, 1.2, 1H), and 8.23 (dd, *J* 8.4, 1.6, 1H); δ_C 58.2, 120.8, 125.3, 129.6, 130.2, 130.6, 132.0, 133.2, 134.7, 147.7, 154.5, 155.8, and 172.1; ν_{max}/cm^{-1} 1204 (-O-); *m/z* (rel intensity) 347 (M^+, 87), 220 (M^+-I, 100), 127 (3), 77 (13). *Anal.* Calcd for $C_{15}H_{10}INO$: C, 51.90; H, 2.90; N, 4.03. Found: C, 51.63; H, 2.77; N, 3.95.

Synthesis of 3-iodo-2-(2-iodophenoxy)-1-azaazulene (10)

Under argon atmosphere, a mixture of **3** (44 mg, 0.127 mmol), NIS (38 mg, 0.169 mmol), and benzoyl peroxide (a cups of spatulas) in $CHCl_3$ (3 mL) was stirred for 1 h at rt. The reaction mixture was poured into saturated $NaHSO_3$ solution (50 mL), and extracted with $CHCl_3$. The organic layer was dried over

Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, $CHCl_3$) of the residue gave **10** (50 mg, 83%).

10: Brown oil; δ_H 7.03 (ddd, *J* 8.0, 5.8, 3.0, 1H), 7.46 (dd, *J* 5.8, 1.0, 1H), 7.47 (d, *J* 8.0, 1H), 7.62-7.73 (m, 3H), 7.90 (dm, *J* 8.0, 1H), 8.22 (dd, *J* 8.8, 1.2, 1H), and 8.26 (dd, *J* 11.6, 1.2, 1H); δ_C 58.0, 89.7, 122.4, 127.2, 129.6, 130.2, 130.6, 132.4, 133.5, 135.0, 139.8, 147.8, 154.4, 155.7, and 171.4; ν_{max}/cm^{-1} 1210 (-O-) *m/z* (rel intensity) 346 (M^+-I, 100), 219 (M^+-2I, 44), 127 (3), 76 (14). Picrate of **10**: Brown powders (from EtOH), mp 158-161 °C: *Anal.* Calcd for $C_{15}H_9I_2NO \cdot C_6H_3N_3O_7 \cdot 1/2C_2H_5OH$: C, 36.48; H, 1.94; N, 7.72. Found: C, 36.92; H, 1.59; N, 8.02.

Synthesis of 4 by Buchwald-Hartwig type coupling of 1 with 2

Under argon atmosphere, a mixture of $Pd_2(dba)_3$ (29 mg, 0.032 mmol), Xantphos (18 mg, 0.031 mmol), 2-iodophenol (275 mg, 1.25 mmol), Cs_2CO_3 (369 mg, 1.13 mmol), and 2-chloro-1-azaazulene (**1**) (160 mg, 0.978 mmol) in 1,4-dioxane (10 mL) was stirred for 144 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt) of the residue gave **4** (154 mg, 72%) and **3** (41 mg, 12%).

Synthesis of 4 by Suzuki coupling of 5 with 6

Under argon atmosphere, a mixture of 2-chloro-3-iodo-1-azaazulene (144 mg, 0.497 mmol), 2-hydroxyphenylboronic acid pinacolate (0.16 mL, 0.763 mmol), Cs_2CO_3 (510 mg, 1.57 mmol), and $PdCl_2(PPh_3)_2$ (14 mg, 0.020 mmol) in THF (5 mL) was stirred for 24 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt/$CHCl_3$ = 1/1) of the residue gave **4** (65 mg, 60%).

Synthesis of 4 by cyclization of 9

Under argon atmosphere, a mixture of $Pd_2(dba)_3$ (8 mg, 0.009 mmol), Xantphos (6 mg, 0.010 mmol), Cs_2CO_3 (103 mg, 0.316 mmol), and **9** (88 mg, 0.253 mmol) in 1,4-dioxane (3 mL) was stirred for 24 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, $CHCl_3$) of the residue gave **4** (13 mg, 23%), **8** (6 mg, 11%), and the recovery of **9** (10 mg, 11%).

Synthesis of 4 by cyclization of 10

Under argon atmosphere, a mixture of $Pd_2(dba)_3$ (10 mg, 0.011 mmol), Xantphos (8 mg, 0.014 mmol), Cs_2CO_3 (121 mg, 0.371 mmol), and **10** (141 mg, 0.298 mmol) was stirred in 1,4-dioxane (5 mL) for 24 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, $CHCl_3$) of the residue gave **4** (1 mg, 2%), **10** (77 mg, 55%) and **8** (1 mg, 2%).

Biological assay

HeLa S-3 cells were obtained from AIST and used after cultivation. The cultivated HeLa S-3 cells were cell counted and the culture fluid was prepared to the cell consistency of 2×10^4 cell/mL. The compounds were added to the medium in DMSO solutions. To the aliquot of the culture fluid, which was incubated for 3 h at 37 ℃, the test sample was added and then the culture fluid was incubated for 72 h. To the culture fluid, MTT (3-[4,5-dimethylthiazol]-2-yl-2,5-diphenyltetrazolium bromide) solution was added, and incubated for 4 h. Then the sample was centrifuged at 3000 rpm for 10 min at 4 ℃, and the solvent was evaporated. Then DMSO was added to obtained mixture. The MTT-formazan was dissolved by plate-mixing and OD540 was measured. The rate of outlive determined to refer with un-dosed control. Dose-response curve was drawn up and IC_{50} was pursued. Every experiment in the cytotoxic assay was replicated four times in order to define the IC values.

REFERENCES

1. a) N. Abe and T. Gunji, *Heterocycles*, 2010, **82**, 201; b) N. Abe, '*Recent Research Developments in Organic and Bioorganic Chemistry*', 2001, **4**, 14, Transworld Research Network; c) N. Abe, '*Trends in Heterocyclic Chemistry*', 2001, **7**, 25, Research Trends; d) T. Nishiwaki and N. Abe, *Heterocycles*, 1981, **15**, 547; e) M. Kimura, *Yuki Gousei Kagaku Kyokai Shi*, 1981, **39**, 690.
2. a) T. Ariyoshi, K. Yoshinaga, K. Koizumi, H. Fujii, R. Ikeda, T. Konakahara, and N. Abe, *Heterocycles*, 2010, **80**, 427; b) E. Yoshioka, H. Fujii, T. Murafuji, R. Ikeda, T. Konakahara, T. Gunji, and N. Abe, *Heterocycles*, 2011, **83**, 1409; c) M. Nakatani, H. Fujii, T. Murafuji, T. Gunji, R. Ikeda, T. Konakahara, and N. Abe, *Heterocycles*, 2012, **84**, 461; d) E. Yoshioka, K. Koizumi, K. Nakashima, H. Fujii, T. Murafuji, T. Gunji, and N. Abe, *Heterocycles*, 2012, **85**, 1683.
3. a) D. M. X. Donnelly and M. J. Meegan, *Comprehensive Heterocyclic Chemistry,* ed. by A. R. Katritzky and C. W. Rees, Pergamon Press: Oxford, 1984, **4**, 657; b) P. Cagniant and C. Cagniant, *Adv. Heterocycl. Chem.,* 1975, **18**, 343; c) R. S. Ward, *Nat. Prod. Rep.*, 1993, **10**, 1; d) R. S. Ward, *Nat. Prod. Rep.*, 1995, **12**, 183; e) W. Friedrichsen, *Comprehensive Heterocyclic Chemistry II,* ed. by C. W. Bird, A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon: London, 1996, Vol. 2,

Chapter 2.7, pp. 368-378; f) R. S. Ward, *Nat. Prod. Rep.,* 1997, **14**, 43; g) I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani, D. C. Dunber, and D. Ferreira, *J. Nat. Prod*., 2003, **66**, 804; h) *Comprehensive Heterocyclic Chemistry II*, ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press: Oxford, UK, 1996, Vol. 2, pp. 259-321.

4. a) R. N. Nair, P. J. Lee, A. L. Rheingold, and D. B. Grotjahn, *Chem. Eur. J.*, 2010, **16**, 7992; b) T. J. Barton and B. L. Groh, *J. Org. Chem.*, 1985, **50**, 158; c) A. Fuerstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024.
5. a) R. N. Nair, P. J. Lee, and D. Grotjahn, *Topics in Catalysis*, 2010, **53**, 1045; b) R. N. Nair, P. J. Lee, A. L. Rheingold, and D. B. Grotjahn, *Chem. Eur. J.*, 2010, **16**, 7992; c) V.-F. Alejandro, J. A. Varela, and C. Saa, *Synthesis*, 2012, **44**, 3285; d) V.-F. Alejandro, J. A. Varela, and C. Saa, *Adv. Synth. Catal.*, 2011, **353**, 1933; e) X. Li, J.-Y. Wang, W. Yu, and L.-M. Wu, *Tetrahedron*, 2009, **65**, 1140.
6. Z. Wang, W. Geng, H. Wang, S. Zhang, W.-X. Zhang, and Z. Xi, *Tetrahedron Lett.*, 2011, **52**, 6997.
7. H. Fujii, N. Abe, N. Umeda, and A. Kakehi, *Heterocycles*, 2002, **58**, 283.
8. N. Abe, Y. Harada, Y. Imachi, H. Fujii, A. Kakehi, and M. Shiro, *Heterocycles*, 2007, **72**, 459.
9. H.-A. Du, X.-G. Zhang, R.-Y. Tang, and J. H. Li, *J. Org. Chem.*, 2009, **74**, 7844.
10. N. Abe and T. Nishiwaki, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1277.
11. a) N. Abe, T. Nishiwaki, H. Yamamoto, and N. Kunishige, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3703; b) K. Fujimori, N. Hirako, and K. Yamane, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1247.
12. a) K. Koizumi, K. Shimabara, A. Takemoto, S. Yamazaki, N. Yamauchi, H. Fujii, M. Kurosawa, T. Konakahara, and N. Abe, *Heterocycles*, 2009, **79**, 319; b) E. Yoshioka, K. Koizumi, S. Yamazaki, H. Fujii, and N. Abe, *Heterocycles*, 2009, **78**, 3065.
13. a) M. Oda, K. Ogura, N. C. Thanh, S. Kishi, S. Kuroda, K. Fujimori, T. Noda, and N. Abe, *Tetrahedron Lett.*, 2007, **48**, 4471; b) T. Ariyoshi, T. Noda, S. Watarai, S. Tagashira, Y. Murakami, H. Fujii, and N. Abe, *Heterocycles*, 2009, **77**, 565.
14. a) N. Abe and A. Gomi, *Heterocycles*, 1987, **26**, 767; b) N. Abe, I. Osaki, S. Kojima, H. Matsuda, Y. Sugihara, and A. Kakehi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2351; c) N. Abe, K. Odagiri, and A. Kakehi, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2189; d) N. Abe, K. Odagiri, H. Fujii, and A. Kekehi, *Heterocycles*, 2000, **53**, 323; e) N. Abe, M. Nabeshima, H. Fujii, A. Kakehi, Y. Kageura, and T. Konakahara, *Heterocycles*, 2001, **54**, 329; f) N. Abe, Y. Fukumoto, H. Fujii, and A. Kakehi, *Heterocycles*, 2002, **56**, 171; g) H. Fujii, I. Kawano, K. Iwafuji, Y. Sawae, K. Nagamatsu, and N. Abe, *Heterocycles*, 2006, **70**, 207.
15. N. Yamauchi, H. Fujii, A. Kakehi, M. Shiro, M. Kurosawa, T. Konakahara, and N. Abe, *Heterocycles*, 2008, **76**, 617.