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# Synthesis of Azulene-substituted Benzofurans and Isocoumarins via Intramolecular Cyclization of 1-Ethynylazulenes, and their Structural and Optical Properties

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Preparation of azulene-substituted benzofurans and isocoumarins was established by the two-types of intramolecular cyclization reaction of 1-ethynylazulenes. 2-(1-Azulenyl)- and 2,3-bis(1-azulenyl)benzofurans were prepared by the palladium-catalyzed cross-coupling reaction of 1-iodoazulenes with 2-ethynylphenol and that of 1-ethynylazulenes with 2-iodophenol under Sonogashira–Hagihara reaction conditions following the intramolecular nucleophilic addition of the oxygen nucleophile to the presumed 1-arylethynylazulenes. In contrast, 1-(phenylethynyl)azulenes bearing o-methoxycarbonyl function on the substituted phenyl moiety exhibited intramolecular cyclization either in the presence of trifluoroacetic acid or N-iodosuccinimide (NIS) to afford azulene-substituted isocoumarins and 4-iodoisocoumarins, of which structures were clarified by single crystal X-ray analysis. Optical properties of these compounds were also investigated by UV/Vis spectroscopy and theoretical calculations.

## Introduction

Oxygen-containing heterocyclic compounds, such as benzofurans[1] and isocoumarins[2], are found in many natural products as their partial structures, and their application to pharmaceuticals and organic materials are expected in recent years, so that a large number of synthetic methods have been developed to date.[3]

Azulene is one of the non-alternating 10π electron aromatic compounds, and fascinates many researchers for a long time because of its unique reactivity and properties.[4] Since the discovery of efficient synthetic methods for the azulene derivatives by Ziegler-Hafner[5] and Nozoe *et al*.[6] in the 1950's, preparation and characterization of various derivatives have been investigated to date. Azulene derivatives having aryl and heteroaryl substituent have also been prepared for the purpose of application to material sciences utilizing their unique properties.[7] In most cases, the azulene derivatives with aryl or heteroaryl substituent have been prepared by a transition-metal catalyzed cross-coupling reaction of azulenyl-metal reagents with aryl halides[8] or haloazulenes with organometallic reagents.[9,10] However, the azulenyl-metal reagents are unstable in most cases. In addition, their precursors, 2- and 6-haloazulenes, are difficult to prepare, because their synthesis requires multistep processes, normally. In addition, 1-bromo- and 1-iodoazulenes are readily available by electrophilic substitution reaction with *N*-halosuccinimides, but these derivatives without an electron-withdrawing group at their 3-position show remarkable instability.[9e,11] To avoid the difficulty in the synthesis, we have developed an efficient synthetic procedure for 1-,[12] 2-,[13] and 5-heteroarylazulenes[14] *via* electrophilic substitution reactions of azulene derivatives with triflate of *N*-containing heterocycles. Despite the fact that these procedures made it possible to access to azulene-substituted N-containing heterocycles with a short step in high product yields from readily available starting materials, however, the procedure could not be applicable to other heterocyclic compounds without nitrogen atom.

To date heterocycle synthesis by intramolecular nucleophilic addition of heteroatom nucleophile to alkyne derivatives becomes the focus of attention, in particular, in the preparation of oxygen-containing heterocycles,[15] because of the efficiency in the preparation to afford the desired product within a short step and in high yields. We have also established the preparation of various π-conjugated molecules by cycloaddition reaction using 1-ethynylazulenes as a starting material and have also clarified their unique properties. Although 1-ethynylazulenes are stable and readily available compounds that could be a useful precursor for the azulene derivatives having heteroaryl substituent, there are few examples for their application to the synthesis by utilizing

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Electronic Supplementary Information (ESI) available: Experimental details, $^{1}$H, $^{13}$C NMR, COSY, HRMS and frontier Kohn–Sham orbitals of reported compounds. See DOI: 10.1039/x0xx00000x

intramolecular nucleophilic addition of heteroatom nucleophile to their alkyne moiety.[16] From the context, we commenced the synthesis of novel azulene-substituted *O*-containing heterocycles by the intramolecular cyclization of 1-ethynylazulenes.

In this paper, we described the synthesis of azulene-substituted *O*-containing heterocycles, i.e., benzofurans and isocoumarins, by the intramolecular cyclization of 1-ethynylazulenes. In the synthesis of benzofuran derivatives, we found the two-types of azulene-substituted benzofurans were obtained in one-pot under Sonogashira–Hagihara reaction conditions depending on the aryl halides and arylalkynes employed. In contrast, isocoumarin derivatives were produced by the treatment of 1-ethynylazulenes having a methyl benzoate moiety at the alkyne terminus with either Brønsted acid or a source of electrophilic iodine. The optical properties of the new azulene derivatives obtained by the reaction were investigated by the UV/Vis spectroscopy and computational chemistry using TD–DFT method. Molecular structure of the several products was revealed by single crystal X-ray structural analysis.

## Results and discussion

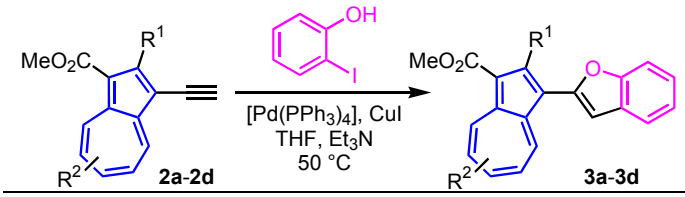
### Synthesis of azulene-substituted benzofurans

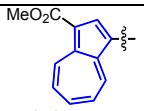
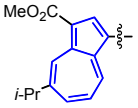
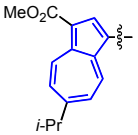
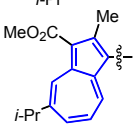
Benzofuran derivatives have attracted much attention not only as bioactive substances[3] but also as a component of organic electronic materials, such as light-emitting diodes, semiconductors, solar cells, and hole-transport materials.[17] Therefore, a number of efficient synthetic methods for the π-conjugated compounds including benzofuran moiety have been developed so far. As a classical method, benzofuran can be prepared starting from saccharic acid[18] or salicylaldehyde[19] within few steps including cyclization reaction. In recent years, the synthesis of benzofuran derivatives have been achieved by intramolecular cyclization of 2-ethynylphenols with either bases[20] or transition-metal catalysts.[16f, 21] Particularly, cyclization employing a palladium catalyst, so called oxypalladation, is an excellent method, because construction of benzofuran derivatives and functionalization at their 3-position are achieved under one-pot conditions.[22]

Recently, we have reported that 2-(1-azulenyl)benzofuran **3b** is obtained in one-pot by Sonogashira–Hagihara reaction of 1-ethynylazulene **2b** with 2-iodophenol.[16a] Although various synthetic procedures for heteroarylazulenes have been reported in literature, this is the first example for the synthesis of benzofuran derivative substituted by an azulenyl group. In order to investigate the effect of the substituent on the azulene ring toward the procedure, the similar reaction was investigated employing several 1-ethynylazulenes, since the scope and limitation of the substrates have not yet been examined. In all cases, the same reaction conditions were adopted as in the preparation of **3a**, **3c** and **3d**. The structure of the azulene moiety and the product yield are summarized in Table 1. Similar to the synthesis of **3b**, 1-ethynylazulenes **2a**,[23] **2c** and **2d**, which could be prepared from the corresponding 1-iodoazulenes **1a**,[24] **1c**[17] and **1d**[15b], reacted with 2-iodophenol to give the corresponding benzofuran derivatives bearing an azulene substituent under the Sonogashira–Hagihara reaction conditions.

Indeed, the reaction of compound **2a** with 2-iodophenol in the presence of catalytic amount of $[Pd(PPh_3)_4]$ and CuI afforded 2-(1-azulenyl)benzofuran **3a** in 65% yield, after chromatographic purification on silica gel. Benzofuran derivative **3c** was obtained in 72% yield by the reaction of compound **2c** with 2-iodophenol under the Sonogashira–Hagihara conditions. Likewise the results described above, compound **2d** reacted with 2-iodophenol to give the presumed benzofuran derivative **3d**, but in low yield (31%) in this case. The low yield is attributable to the decomposition of the product under the reaction conditions. In fact, extending the reaction time led to a decrease in the yield of the product.

**Table 1** Synthesis of 2-(1-azulenyl)benzofurans **3a**–**3d**




| Entry | Azulene | Product | Yield [%][a] |
|---|---|---|---|
| 1 |  | **3a** | 65 |
| 2 |  | **3b** | 55[16a] |
| 3 |  | **3c** | 72 |
| 4 |  | **3d** | 31 |

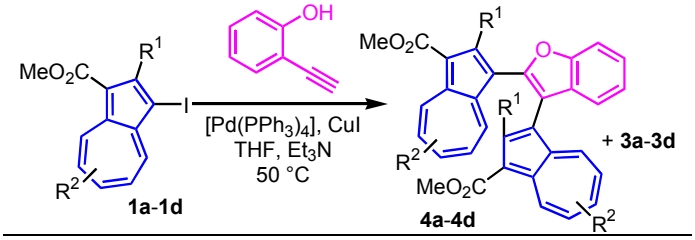
[a] Isolated yield

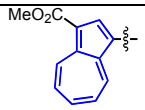
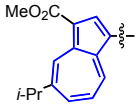
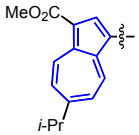
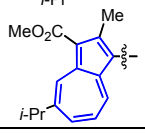
Unlike the reaction of 1-ethynylazulenes **2a–2d** with 2-iodophenol, the reaction of 1-iodoazulenes **1a–1d** with 2-ethynylphenol[25] gave 2,3-bis(1-azulenyl)benzofurans **4a–4d**, unexpectedly, along with the 2-(1-azulenyl)benzofurans **3a–3d** under the Sonogashira–Hagihara conditions. The structure of the azulene moiety and the product yield are summarized in Table 2. Thus, the reaction of 1-iodoazulene **1a** with 2-ethynylphenol yielded 2,3-bis(1-azulenyl)benzofuran **4a** and 2-(1-azulenyl)benzofuran **3a** in 19% and 10% yields, respectively. The reaction of **1b** and **1c** having an isopropyl group on the 7-membered ring of azulene moiety with 2-ethynylphenol

afforded the corresponding 2,3-bis(1-azulenyl)benzofurans **4b** (30%) and **4c** (27%), accompanied by **3b** (30%) and **3c** (13%). 1-Iodoazulene **1d** having two alkyl groups (i.e., both methyl and isopropyl groups) on the azulene ring also reacted under the same reaction conditions to afford 2,3-bis(1-azulenyl)benzofuran **4d** (33%) and mono-substituted product **3d** (23%), after the purification using silica gel chromatography.

This is the first example of the synthesis of benzofuran derivatives bearing two azulene substituents, although the preparation of benzofuran derivatives having one azulene ring have already been reported by us.[15]

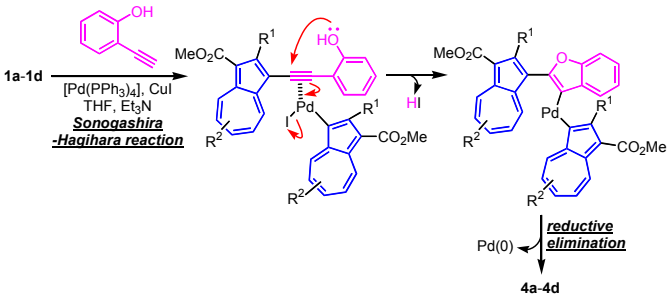
**Table 2** Synthesis of 2,3-bis(1-azulenyl)benzofurans **4a–4d**




| Entry | Azulene | Yield of 4 [%]a | Yield of **3** [%][a] |
|---|---|---|---|
| 1 |  | **4a**, 19 | **3a**, 10 |
| 2 |  | **4b**, 30 | **3b**, 30 |
| 3 |  | **4c**, 27 | **3c**, 13 |
| 4 |  | **4d**, 33 | **3d**, 23 |

[a] Isolated yield

Previously, Arcadi *et al*. reported the reaction of 2-ethynylphenol with various aryl halides or triflates under the Sonogashira–Hagihara conditions to afford 2,3-diarylbenzofurans.[21a] In the literature, they proposed oxypalladation mechanism to generate the 2,3-diarylbenzofuran derivatives. As shown in Scheme 1, formation of 2,3-bis(1-azulenyl)benzofurans **4a–4d** by the reaction of 1-iodoazulenes **1a–1d** with 2-ethynylphenol should be in accordance with the reaction mechanism proposed by Arcadi *et al.*; initially, the usual cross-coupling reaction of 1-iodoazulenes with 2-ethynylphenol proceeded to form 1-ethynylazulene intermediates having phenol substituent at the alkyne terminus, which gave the arylpalladium species by the coordination to their alkyne moiety, then the intramolecular nucleophilic addition of the oxygen nucleophile occurred to afford the 2,3- bis(1-azulenyl)benzofuran derivatives.




**Scheme 1** Plausible reaction mechanism for the formation of 2,3-bis(1-azulenyl)benzofurans **4a–4d**; ligands on palladium catalyst are omitted for the clarity.

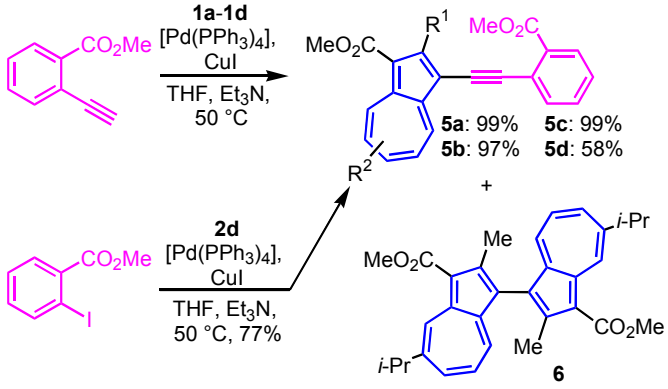
### Synthesis of azulene-substituted isocoumarins

Isocoumarin derivatives are important heterocyclic compounds that show a wide range of biological activities. For example, capillarin,[26] artemidin,[27] oosponol,[28] oospolactone[22] and cercophorin A[29] have antifungal activity. Thunberginol A and B are known to exhibit anti-allergic and immunoregulatory activities.[30] Cytogenin is also recognized as an immunomodulatory and antiarthritic agent.[31] Reticulol and NM-3,[32] which have been investigated in clinical trials, show highly effective antitumor activity.

To prepare the bioactive compounds as described above, a number of synthetic procedures for the isocoumarin derivatives have been developed so far. Modern synthetic methods for isocoumarin derivatives have focused on the transition-metal catalysed reaction by using expensive transition-metal such as palladium,[33] rhodium,[34] ruthenium[35] and gold[36] catalysts. Preparation of isocoumarins using iron[37], bismuth[38] and copper catalyst[39] has also been developed to avoid the use of expensive catalysts as described above. Although the isocoumarin synthesis using a metal catalyst is an excellent method, the Brønsted-acid-mediated cyclization reaction of *o*-ethynylated benzoic acid esters afforded the products in high yield with high functional group tolerance.[40] In addition, the most of the Brønsted acids are cheaper and less toxic compared to the transition-metal catalysts. Thus, we commenced the Brønsted-acid-mediated synthesis of azulene-substituted isocoumarin derivatives for the development of an efficient synthetic procedure for the heterocyclic compounds based on 1-ethynylazulenes.

The azulene derivatives bearing a methyl *o*-ethynylbenzoate moiety **5a–5c**, which become the precursors of 1-azulenylisocoumarins, were prepared in excellent yields (97%–99%) by the Sonogashira–Hagihara reaction of 1-iodoazulenes with methyl *o*-ethynylbenzoate. A similar reaction was also adopted to the reaction of compound **1d**, but the yield of **5d** was relatively low (58%) owing to the formation of 1,1'-biazulene **6** (17%) as a by-product. The generation of 1,1'-biazulene **6** might indicate that transmetalation process of copper acetylide is a rate-determining step in the reaction of **1d**. Therefore, alkyne **5d** was prepared by the reaction of **2d** with methyl *o*-

iodobenzoate in good yield (77%), without the formation of **6**, as shown in Scheme 2.



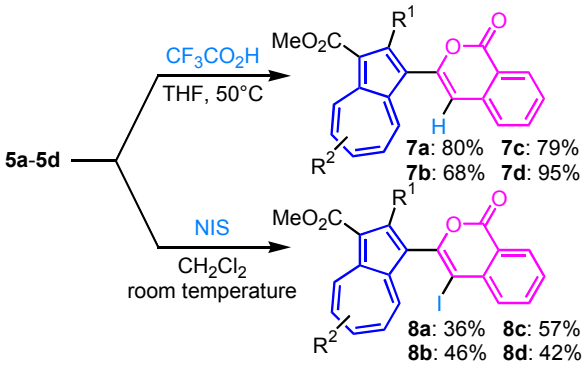

**Scheme 2** Preparation of o-ethynylated benzoic acid esters **5a–5d** with an azulene substituent.

Intramolecular cyclization of alkynes **5a–5d** in the presence of trifluoroacetic acid produced the corresponding 1-azulenylisocoumarin derivatives **7a–7d** in good to excellent yields (Scheme 3). Thus, the acid-mediated reaction of **5a** gave 1-azulenylisocoumarin **7a** in 80% yield. Similar to the formation of **7a**, isocoumarin derivatives **7b** and **7c** were obtained in 68% and 79% yields, respectively, by the intramolecular cyclization of 1-ethynylazulenes **5b** and **5c** having an isopropyl group on the 7-membered ring of azulene moiety. Compound **5d** with a methyl substituent at the 2-position of azulene ring produced isocoumarin derivative **7d** in excellent yield (95%) by the acid-mediated cyclization reaction. This indicates that the steric hindrance by the methyl group at the 2-position of the azulene ring has little effect toward the product yield in this case.

Larock *et al*. have been extensively studied the synthesis of polyaromatic hydrocarbons[14d,41] and heterocyclic compounds, such as thiophene,[42] furan[14c] and indoles,[14f] by iodocyclization reaction. In 2003, they also reported the iodination of 2-ethynylbenzoate derivatives using ICl or $I_2$ as the iodine source.[14a] This is one of the effective methods to obtain 4-iodoisocoumarins in excellent yields, which are difficult to access directly by the iodination of isocoumarins.

Despite the fact that iodocyclization reaction of alkyne with electrophilic iodine source is an effective method for the preparation of the iodine-substituted heterocyclic compounds, there are no reports on the reaction for azulene derivatives. If the method can be applied to azulene derivatives, the new synthetic route to azulene derivatives bearing iodine-substituted heterocyclic compounds should be established. Thus, for the purpose of establishing the synthetic methodology, synthesis of azulene-substituted 4-iodoisocoumarin derivatives was investigated by the iodocyclization reaction of **5a–5d** with N-iodosuccinimide (NIS), which is easy iodine source to handle.

Although NIS has not been used for the synthesis of 4-iodoisocoumarins by the iodocyclization reaction, the reaction of **5a** was completed within 1.5 h to afford azulene-substituted 4-iodoisocoumarin **8a** in 36% yield. The reaction of **1b** and **1c** bearing an isopropyl group on the 7-membered ring of azulene moiety also reacted with NIS to give the corresponding cyclization products in 46% and 57% yields, respectively. Similarly, the iodocyclization reaction of **5d** with NIS produced 4-iodoisocoumarin **8d** in 42% yield. The iodo function at the 4-position of isocoumarin moiety is a useful substituent because further molecular transformation is expected by the transition-metal catalyzed cross-coupling reaction, as reported by Larock *et al*.




**Scheme 3** Synthesis of azulene-substituted isocoumarins **7a–7d** and iodoisocoumarins **8a**–**8d**.

### Spectroscopic properties

Azulene-substituted benzofurans **3a–3d** and **4a–4d**, and isocoumarin derivatives **7a–7d** and **8a–8d** were fully characterized based on their spectral data, as summarized in the Experimental Section. The signal assignment of $^1$H NMR was accomplished by COSY experiment. High resolution mass spectra ionized by FAB or EI methods showed the presumed molecular ion peaks of the products. These results prove the correctness of the structure of the novel compounds. Since the single crystals were obtained from the slow evaporation of the solvent, the molecular structure of **3b**, **3d**, **7c**, **8a**, **8c** and **8d** was clarified by the single crystal X-ray structure analysis.[43] The X-ray structural analysis revealed that the substituents on both azulene and heterocycle moieties affected the planarity of the compounds.

The compound **3b** shows almost a planar structure about the azulene and benzofuran connectivity, in which the dihedral angle was 7.5(5)° (Figure 1). On the other hand, X-ray crystal structure analysis of **3d** revealed the twisted structure between the azulene and benzofuran moieties by 37.8(8)° (see the Supporting Information, Figure S103). The low planarity of compound **3d** is ascribed to the steric repulsion between the methyl group at the 2-position of azulene ring and the benzofuran moiety.

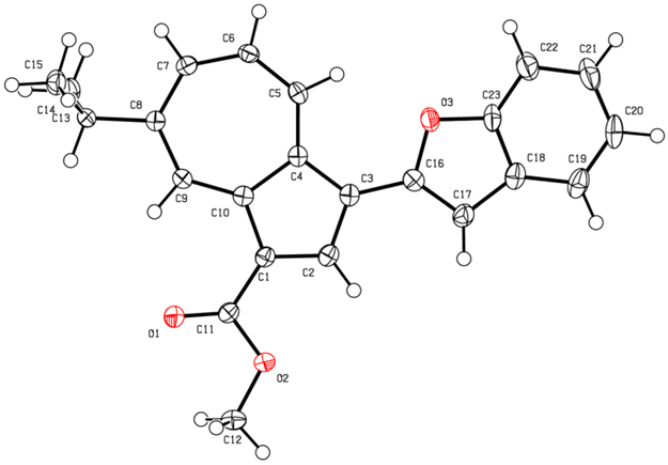



**Fig. 1** ORTEP drawing of **3b**; ellipsoids are drawn at the 50% probability level.

The X-ray crystal structure analysis denoted that isocoumarin **7c** was almost planar molecule with a dihedral angle of 0.9(1)° between the azulene and isocoumarin moieties (Figure 2). Whereas, 4-iodoisocoumarin **8c** evinced the structure in which the azulene and isocoumarin moieties were twisted by 48.9(7)° (Figure 3). These results suggest that the steric repulsion between the iodine substituent introduced at the 4-position of isocoumarin and azulene ring lowers the planarity of the molecule. These variations in planarity were also reflected on the difference in the longest wavelength absorption maxima in their UV/Vis spectra described later.

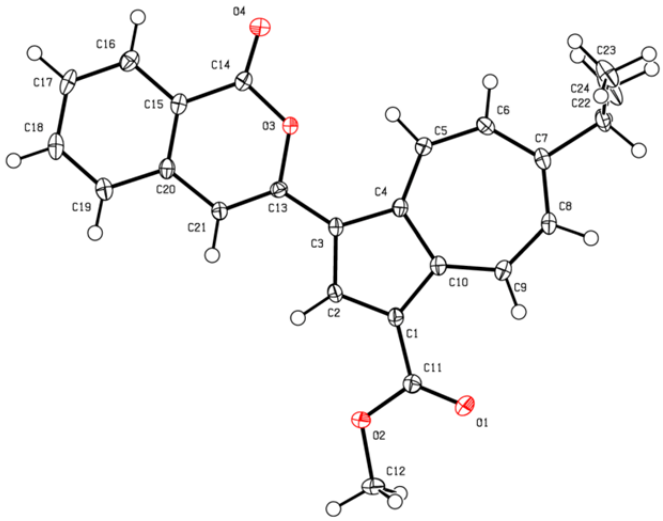



**Fig. 2** ORTEP drawing of **7c**; ellipsoids are drawn at the 50% probability level.

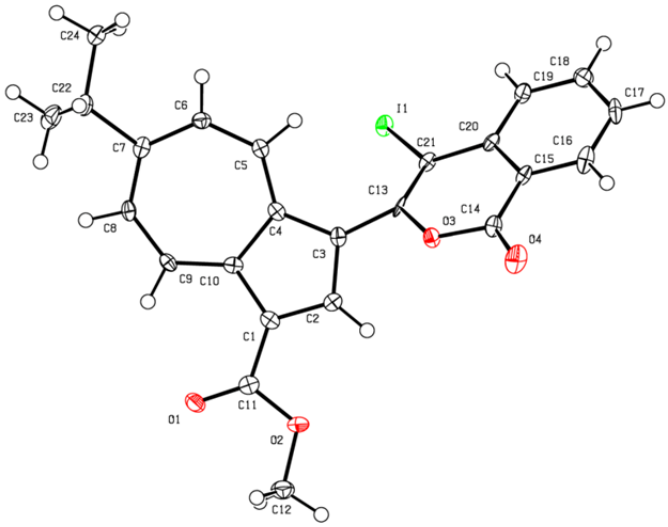



**Fig. 3** ORTEP drawing of **8c**; ellipsoids are drawn at the 50% probability level.

The UV/Vis spectra of the benzofuran derivatives **3a–3d** in $CH_2Cl_2$ showed a weak absorption band in the visible region, but their absorption maxima were varied each other (Figure 4). Compound **3a** showed the longest wavelength absorption maximum at $\lambda_{max}$ = 579 nm in the UV/Vis spectrum. The longest wavelength absorption maximum of compound **3b** ($\lambda_{max}$ = 582 nm) with isopropyl group at the 5-position of azulene ring exhibited a slight bathochromic shift compared to that of **3a**. However, the longest wavelength absorption band of compound **3c** ($\lambda_{max}$ = 564 nm) having an isopropyl group at the 6-position of the azulene ring displayed hypsochromic shift compared with that of **3a** and **3b**. Compound **3d** ($\lambda_{max}$ = 546 nm) showed the longest wavelength absorption at the shortest wavelength region among that of 2-(1-azulenyl)benzofurans **3a–3d**. Since the longest wavelength absorption maxima of **3a–3d** exhibited the bathochromic shift compared to that of the azulene subunits **9a–9d** (Figure 5),[23] the substituted benzofuran should contribute to expansion of the π-conjugated system. The relatively strong absorption at around 400 nm observed in compounds **3a–3d** might be originated from the intramolecular charge transfer (ICT) between the benzofuran and substituted azulene rings, because such absorption band cannot be observed in the UV/Vis spectrum of **9a–9d**.

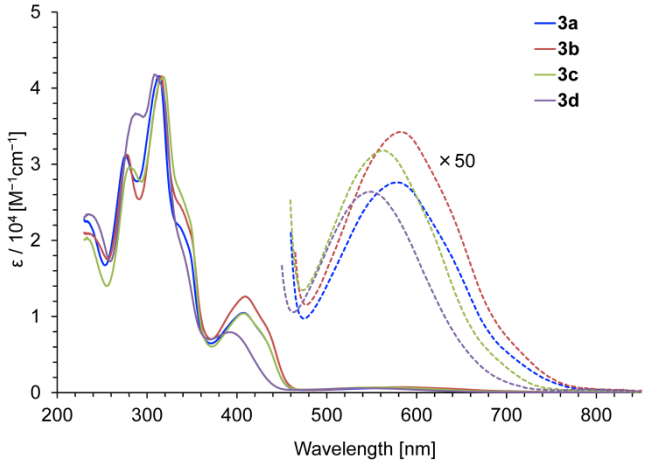



**Fig. 4** The UV/Vis spectra of **3a** (blue line), **3b** (red line), and **3c** (light green line) and **3d** (purple line) in $CH_2Cl_2$; the dotted lines represent those of 50 magnifications.

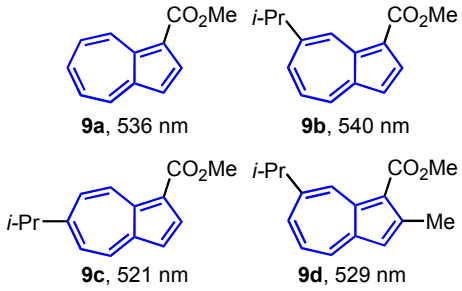



**Fig. 5** Structure of azulene derivatives **9a–9d** and their longest wavelength absorption maxima.

In the early years of azulene chemistry, Plattner *et al*. had systematically examined the absorption spectrum of azulene and its derivatives and found a rule of thumb, so called Plattner's rule, in the longest wavelength absorption.[44] According to the rule, when the alkyl group is substituted at the odd-numbered positions of the azulene ring (i.e., 1-, 3-, 5-, and 7-positions), the absorption maximum shows red-shift on the UV/Vis spectrum. Conversely, blue-shift can be observed by the substitution of alkyl groups at the even-numbered positions (such as 2-, 4-, 6-, and 8-positions) of the azulene ring. Therefore, the order in the absorption maxima of **3a–3d** can be clearly explained in accordance to the Plattner's rule described above. The spectrum of compound **3d** shifted to the shortest-wavelength side among that of the benzofuran derivatives **3a–3d**, which should be ascribed to the synergistic effect of both the substitution of the methyl group at the 2-position and the low planarity between the benzofuran and azulene rings as observed by the X-ray crystal structure analysis.

2,3-Bis(1-azulenyl)benzofurans **4a–4d** also exhibited an absorption band depending on the substitution position of the alkyl group according to the Plattner's rule, similar to those of **3a–3d** (Figure 6). Although the molar extinction coefficient of compounds **4a–4d** showed about twice as large as those of **3a–3d** due to the substitution of the two azulene rings, the absorption maximum of **4a–4d** exhibited slight bathochromic shift, compared with that of **3a–3d**. These phenomena indicate that the low planarity of **4a–4d**, arose from the steric repulsion between the azulene rings substituted at the 2- and 3-positions of the benzofuran moiety, inhibited the effective extension of π-conjugated system.

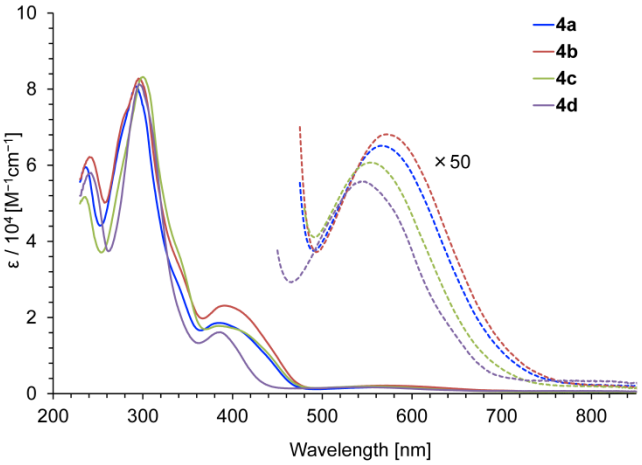



**Fig. 6** The UV/Vis spectra of **4a** (blue line), **4b** (red line), and **4c** (light green line) and **4d** (purple line) in $CH_2Cl_2$; the dotted lines represent those of 50 magnifications.

In order to investigate the theoretical aspect of the spectroscopic properties of 2-(1-azulenyl)benzofurans **3a–3d**, molecular orbital calculations were carried out using time-dependent density functional theory (TD–DFT) at B3LYP/6-31G** level. The frontier Kohn–Sham orbitals of 3a–3d are shown in the Supporting Information.

The absorption maxima of **3a–3d** derived by the calculations obeyed the Plattner's rule. The calculations revealed that the longest wavelength absorption band of compounds **3a–3d** is a transition from HOMO, located on both benzofuran and azulene, to LUMO, located on the azulene moiety. The bathochromic shift of the longest wavelength absorption band of **3a–3d**, compared to that of **9a–9d**, was attributed to their smaller gap of HOMO–LUMO derived from the extension of the π-conjugation by the substitution of the benzofuran.

Calculated energy levels for HOMO and LUMO of **3b** (HOMO, −4.97 eV; LUMO, −2.17 eV) and **3c** (HOMO, −4.99 eV; LUMO, −2.11 eV) showed higher values than those of **3a** (HOMO, −5.07 eV; LUMO, −2.22 eV), that is, the isopropyl group on the 7-membered ring of azulene rises the energy levels both in HOMO and LUMO. The energy level of LUMO between **3b** and **3c** showed a slight difference compared with that of HOMO. Thus, the isopropyl group at the 6-position of azulene increases the LUMO-level more efficiently, rather than that at the 5-position. The largest HOMO–LUMO gap was observed in compound **3d** among **3a–3d** that might be the consequence of the low planarity between the azulene and benzofuryl moieties due to the steric hindrance of methyl group at the 2-position.

The TD–DFT calculations also revealed that the absorption band at around 400 nm of **3a–3d** is attributable to the ICT from

both azulene and benzofuran to azulene (HOMO to LUMO+1 and HOMO−2 to LUMO). However, the ICT from benzofuran to azulene should mainly contribute to these absorption bands, because these absorptions did not appear in the UV/Vis spectrum of the parent derivatives **9a–9d** as described above.

**Table 3** Electronic transitions for **3a**–**3d** derived from the computed values based on the TD−DFT calculations at the B3LYP/6-31G** level and experimental results.

| Sample | Experimental | Computed values | | |
|---|---|---|---|---|
| | $\lambda_{max}$ (log ε) | $\lambda_{max}$ (strength) | Composition of band[a] (amplitude) | H − L gap [eV] |
| **3a** | 408 (3.99) | 395 (0.2100) | H → L+1 (0.8634) | |
| | 432 sh (3.82) | | | |
| | 579 (2.72) | 573 (0.0071) | H → L (0.9753) | 2.85 |
| **3b** | 409 (4.10) | 397 (0.2552) | H → L+1 (0.8666) | |
| | 435 sh (3.92) | | | |
| | 582 (2.84) | 582 (0.0083) | H → L (0.9765) | 2.80 |
| **3c** | 408 (4.02) | 396 (0.2258) | H-2 → L (0.2238) | |
| | 434 sh (3.82) | | H → L+1 (0.8688) | |
| | 564 (2.80) | 565 (0.0070) | H → L (0.9767) | 2.88 |
| **3d** | 392 (3.90) | 386 (0.1387) | H → L+1 (0.8680) | |
| | 546 (2.72) | 531 (0.0078) | H → L (0.9658) | 3.04 |

[a] H = HOMO; L = LUMO; sh = shoulder peak

In general, isocoumarins **7a**–**7b** showed the bathochromic shifts of the longest wavelength absorption maxima compared with those of 4-iodoisocoumarin derivatives **8a**–**8d** (Figures 7 and 8). For example, the longest wavelength absorption maximum of compound **7c** was observed at $\lambda_{max}$ = 539 nm, while the corresponding iodo derivative **8c** displayed the absorption maximum at $\lambda_{max}$ = 516 nm. These results suggest that the steric repulsion between the iodine substituent of 4-iodoisocoumarin and the azulene ring in **8c** led to a more twisted structure compared to that of **7c**, that means ineffectiveness in π-conjugation, as expected from the results on the X-ray crystal structure analysis (Figures 2 and 3).

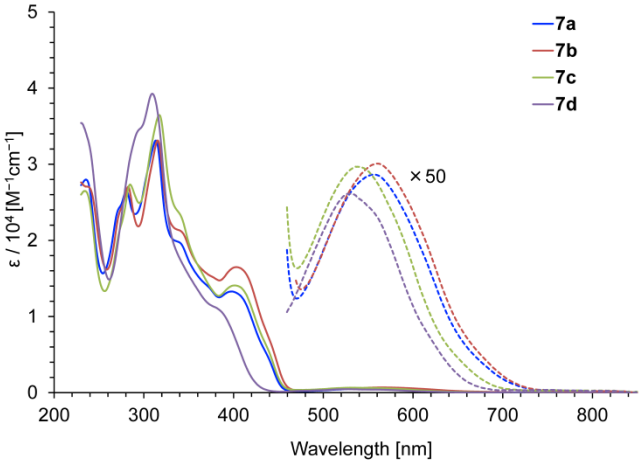



**Fig. 7** The UV/Vis spectra of **7a** (blue line), **7b** (red line), and **7c** (light green line) and **7d** (purple line) in $CH_2Cl_2$; the dotted lines represent those of 50 magnifications.

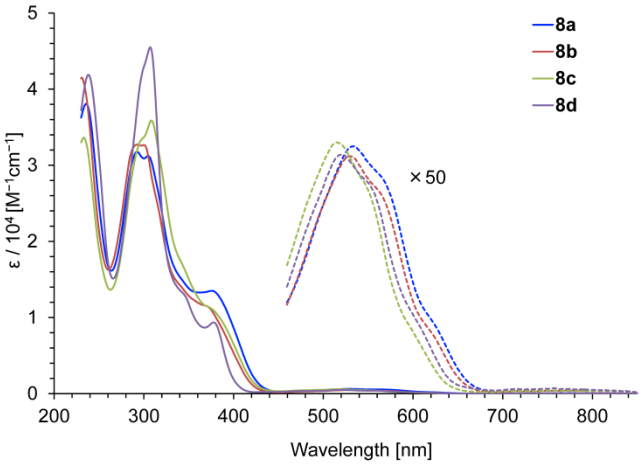



**Fig. 8** The UV/Vis spectra of **8a** (blue line), **8b** (red line), and **8c** (light green line) and **8d** (purple line) in $CH_2Cl_2$; the dotted lines represent those of 50 magnifications.

## Conclusions

In conclusion, we have established an efficient method for the preparation of azulene-substituted benzofurans and isocoumarins *via* intramolecular cyclization of 1-ethynylazulenes. 2-(1-Azulenyl)benzofuran derivatives **3a**–**3d** were obtained by the reaction of 1-ethynylazulenes with 2-iodophenol under the Sonogashira−Hagihara conditions. Whereas, the Sonogashira−Hagihara reaction of 1-iodoazulenes with 2-ethynylphenol afforded 2,3-bis(1-azulenyl)benzofurans **4a–4d**. We also applied to the two-type intramolecular cyclization for the synthesis of azulene-substituted isocoumarin derivatives. The reaction of alkynes **5a–5d** with trifluoroacetic acid produced the isocoumarins **7a–7d** in good to excellent yields. Iodocyclization of **5a–5d** with NIS also gave 4-iodoisocoumarins **8a–8d**. Although the yields of **8a–8d** were moderate, this is the first example of iodine cyclization in the azulene chemistry.

The single crystal X-ray analysis revealed that the presence of the substituent on the azulene or the heterocycle moiety affects the planarity of the molecule. The comparison between the UV/Vis spectra and X-ray crystal structure of isocoumarins **7c** and **8c** suggests that the decrease in the planarity of the molecule leads to hypsochromic shift of absorption maximum.

These results represented here should be one of the effective methods to access the heteroarylazulene derivatives which have difficulty in the preparation by the previous procedures.

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