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Direct synthesis of 2-arylazulenes by [8 + 2] cycloaddition of 2*H*-cyclohepta[*b*]furan-2-ones with silyl enol ethers

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We have developed the procedure for the direct synthesis of 2-arylazulenes, which were obtained in moderate to excellent yields by [8 + 2] cycloaddition of 2*H*-cyclohepta[*b*]furan-2-ones with aryl-substituted silyl enol ethers. The structure of some 2-arylazulenes was clarified by single-crystal X-ray analysis. The 2-phenylazulene derivatives obtained by this study showed noticeable fluorescence in acidic-media.

Azulene is one of the non-alternant aromatic compounds and fascinates many researchers owing to its unusual reactivity and properties derived from its polarization structure, as well as its beautiful blue color. Functionalized azulene derivatives have been mainly employed in medicinal chemistry.[1] In recent years, azulene derivatives have also prospects for the application to organic electronics, such as n-type semiconductors,[2] solar cells,[3] non-linear optics,[4] and so on.[5]

For all of the above cases, the development of the method for the functionalization of the azulene ring by an effective procedure is extremely important. However, the characteristic electronic properties of azulene derivatives sometimes prevent their selective functionalization. The reactivity of azulene at the odd-positions, i.e., 1-, 3-, 5- and 7-positions, has been extensively studied because of their high reactivity toward the aromatic electrophilic substitution reactions.[6] Whereas, the introduction of functional groups to the even-numbered positions of azulene, that is, 2-, 4-, 6- and 8-positions, is mostly established by the cross-coupling reaction.[7] Indeed, the cross-coupling reaction has enabled to access highly functionalized azulenes. However, these approaches are suffered from a serious disadvantage for the preparation of haloazulene precursors, especially 2-haloazulenes[8] and their pseudo halides[9], is usually not straightforward. Recently, Murafuji *et al*. reported the effective synthetic method for 2-iodoazulenes from several azulenes via borylation at the 2-position, followed by the treatment with CuI. This two-step procedure enables to give 2-iodoazulenes, but the use of an expensive iridium-catalyst is essential to the borylation step at the 2-position of the azulene ring.[10]

In 1979, Yasunami and Takase et al. have reported the efficient synthesis of azulenes by [8 + 2] cycloaddition (CA) reaction of 2*H*-cyclohepta[*b*]furan-2-ones with enamines, that currently becomes one of the efficient methods for azulene synthesis.[11] This procedure is very effective for the preparation of 2-alkylazulene derivatives, but it is unsuitable for the synthesis of 2-arylazulenes from the viewpoint of their product yields. Furthermore, the synthesis of 2-arylazulenes by the reaction with enamines was adapted only for the synthesis of 2-phenylazulenes. Therefore, the development of the general synthetic method for 2-arylazulenes that is not employed by the cross-coupling reaction is one of the important tasks left in azulene chemistry. From these backgrounds, we have investigated the applicability of the [8 + 2] CA reaction of 2*H*-cyclohepta[*b*]furan-2-ones with various aryl-substituted silyl enol ethers, which show a similar reactivity to the enamines, in an attempt to find a state-of-the-art method in the synthesis of 2-arylazulenes.

The silyl enol ether method was adopted for the 2-arylazulene synthesis by using 3 equiv. of phenyl-substituted silyl enol ethers under the solvent-free conditions to deliver the products **2a**–**2d** in good to excellent yields (75–92%) from **1a**–**1d** (Table 1, entries 1–4). The use of 3 equiv. reagents was essential to the CA reaction since the employment of less amount of the silyl enol ether reagents led to significant decomposition of the starting materials with a small amount of recovery (see the ESI). In most cases, unlike the cross-coupling reactions,[7] the gram-scale synthesis of 2-phenylazulene derivatives was possible under the reaction condition. The yield of **2a**–**2d** hardly depended on the substituent position of the alkyl group on the seven-membered ring. 1,2-

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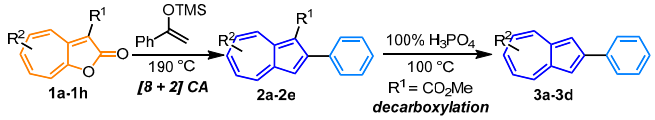
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Diphenylazulene **2e** was also similarly obtained from **1e** in 70% yield. The reaction of **1f**, **1g**, and **1h** without ester function also afforded the corresponding products **3a** (66%), **3b** (63%) and **3c** (71%), but the product yields were a bit low compared with those of the cases of **1a**–**1d** (Table 1, entries 6 and 7). This fact that the product yields of **1a**–**1d** were higher than those of **1e**–**1h** implies that the electron-withdrawing group on 2*H*-cyclohepta[*b*]furan-2-ones enhances the reactivity toward the [8 + 2] CA reaction with the silyl enol ethers. Removal of the ester function from **2a**–**2d** was also accomplished by the treatment with 100% H_3PO_4 to afford **3a**–**3d** in excellent yields (75–96%). As described above, 1,3-positions of the azulene ring are the most reactive sites toward electrophiles,[6] so that further functionalization of **3a**–**3d** could be established by the electrophilic substitution.

Table 1. Reaction of 2*H*-cyclohepta[*b*]furan-2-ones **1a**–**1h** with a phenyl-substituted silyl enol ether.[a]



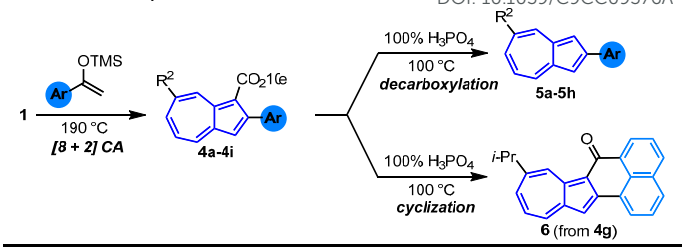
Entry	Substrate	R^1	R^2	[8 + 2] CA Product, Yield [%][b]	decarboxylation Product, Yield [%][b]
1	**1a**	CO_2Me	H	**2a**, 92	**3a**, 95
2	**1b**	CO_2Me	6-*i*-Pr	**2b**, 85	**3b**, 96
3	**1c**	CO_2Me	7-*i*-Pr	**2c**, 84	**3c**, 89
4	**1d**	CO_2Me	6-Me	**2d**, 75	**3d**, 75
5	**1e**	Ph	H	**2e**, 70	–
6	**1f**	H	H	**3a**, 66	–
7	**1g**	H	6-*i*-Pr	**3b**, 63	–
8	**1h**	H	5-*i*-Pr	**3c**, 71	–

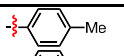
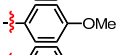
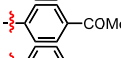
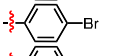
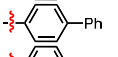
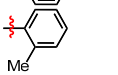
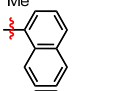
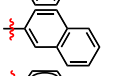
[a] 3 equiv. of silyl enol ether was employed. [b] Isolated yield.

As shown in Table 2, we also examined the substituent effect on the benzene ring of the silyl enol ethers toward the product yields by using the reaction of **1a** and **1b**. As a result, we found that the yield of the products was greatly influenced by the electronic nature of the substituent on the benzene ring. For instance, silyl enol ethers having an electron-donating group at the *para*-position on the benzene ring produced the target products in higher yields, compared with those of ones possessing an electron-withdrawing group (entries 1–5). This result means that the electron-withdrawing group at the *para*-position decreases the reactivity of the silyl enol ethers.

The introduction of the substituent at the *ortho*-position led to the decrement for the reactivity of the silyl enol ethers toward the [8 + 2] CA process (entry 6). The naphthalene-substituted silyl enol ethers reacted with **1a** and **1b** to give the corresponding 2-naphthylazulene derivatives **4g** and **4h**, but the yields differed greatly by the substitution positions (entries 7 and 8). Ferrocene-substituted azulene derivative **4i**, which could not be prepared by the palladium-catalyzed cross-coupling reaction,[12] was also obtained by this method in good yield (entry 9).

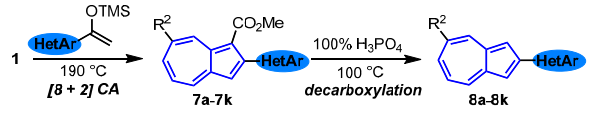
Table 2. Reaction of 2*H*-cyclohepta[*b*]furan-2-ones with aryl-substituted silyl enol ethers.



Entry	Ar	R^2	[8 + 2] CA Product, Yield [%][a]	decarboxylation Product, Yield [%][a]
1		H	**4a**, 85	**5a**, 98
2		H	**4b**, 88	**5b**, 94
3		H	**4c**, 43	**5c**, 96
4		H	**4d**, 56	**5d**, 99
5		*i*-Pr	**4e**, 74	**5e**, 95
6		*i*-Pr	**4f**, 13	**5f**, 93
7		*i*-Pr	**4g**, 29	**5g**, 14 **6**, 61
8		H	**4h**, 86	**5h**, 93
9		*i*-Pr	**4i**, 59	Decomp.

[a] Isolated yield.

Table 3. Reaction of 2*H*-cyclohepta[*b*]furan-2-ones with heteroaryl-substituted silyl enol ethers.



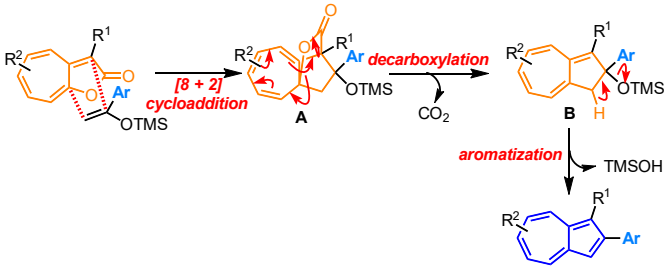
Entry	Ar	R^2	[8 + 2] CA Product, Yield [%][a]	decarboxylation Product, Yield [%][a]
1		H	**7a**, 22	**8a**, 94
2		H	**7b**, 10	**8b**, 84
3		H	**7c**, 75	**8c**, 99
4		*i*-Pr	**7d**, 79	**8d**, 95
5		*i*-Pr	**7e**, 72	**8e**, 51[b]
6		H	**7f**, 73	**8f**, 56
7		*i*-Pr	**7g**, 73	**8g**, 35
8		H	**7h**, 23	**8h**, 44
9		H	**7i**, 46	**8i**, 51
10		H	**7j**, 30	Decomp.
11		H	**7k**, 21	**8k**, 85

[a] Isolated yield. [b] Debrominated product **8d** was also obtained in 39% yield.

The reaction of **1a** and **1b** with the silyl enol ethers having a heteroaryl group have also investigated to produce 2-

heteroarylazulenes **7a**–**7k** with an ester function (Table 3). Although the product yield of the reaction of the silyl enol ethers substituted by electron-deficient heterocycles (such as pyridines and thiazole) was rather low (entries 1, 2 and 10), thiophene- and furan-substituted ones gave 2-heteroarylazulene derivatives **7c**–**7g** in good yields (entries 3–7). These results also equate nicely that the electron-deficient heterocycles decrease the reactivity of the silyl enol ethers toward **1a** and **1b**, as was the case of the reaction with the silyl enol ethers having an electron-withdrawing substituent on the benzene ring. Although the pyrrole ring is an electron-rich heterocycle, the yields of the reaction of **1a** with the silyl enol ethers to afford the corresponding 2-pyrrolylazulene derivatives were rather low (Table 3, entries 8–10); the low yields are due to the instability of **7h**–**7j** under the reaction conditions. Indeed, even though **7a**–**7g** and **7k** showed considerable stability under the ambient conditions, **7h**–**7j** gradually decomposed under the same conditions.

The plausible reaction mechanism for the formation of 2-arylazulenes is shown in Scheme 1. Namely, the intermediate **A** is given by [8 + 2] CA reaction of 2*H*-cyclohepta[*b*]furan-2-ones with the silyl enol ethers, as similar to the reaction with enamines. Since silyl enol ether is less reactive than enamine, the higher reaction temperature may be required to proceed the cycloaddition reaction. Then, intermediate **A** is transformed into dihydroazulene intermediate **B** by decarboxylation. Eventually, 2-arylazulene is formed *via* aromatization of **B** accompanied by the desilication.



Scheme 1. The plausible reaction mechanism for the formation of 2-arylazulenes.

The decarboxylation reaction of **4a**–**4j** with 100% H_3PO_4 gave the corresponding decarboxylated derivatives in high yields (Table 2, entries 1–6 and 8). While the reaction of **4g** produced cyclization product **6**, which should be produced by intramolecular Friedel-Crafts type reaction, in 61% yield, along with the decarboxylated derivative **5h** (Table 2, entry 7). Whereas, treatment of **4j** with 100% H_3PO_4 under the same conditions led to the decomposition of the compound (Table 2, entry 9). The reaction of 2-heteroarylazulenes **7a**–**7k** with 100% H_3PO_4 was also afforded the decarboxylated derivatives **8a**–**8k**, except for **7j** (Table 3, entries 1–11). The yield of the target products **8f**–**8i** by the reaction of compounds **7f**–**7i** was a bit low (Table 3, entries 6–9), and the case of the reaction of **7j** resulted in the complete decomposition (Table 3, entry 10).

All compounds were characterized by NMR and HRMS experiments as summarized in the ESI. Since the suitable single crystals for X-ray structure analysis were obtained in **4e**, **4f**, **8i**, and **8k,** their crystal structures were clarified as summarized in Figure 1. Although **8i** and **8k** showed high planarity between the azulene ring and the substituted heterocycle, **4e** and **4f** indicated the twisted structure due to the steric hindrance between the ester group on the azulene and benzene ring connected.

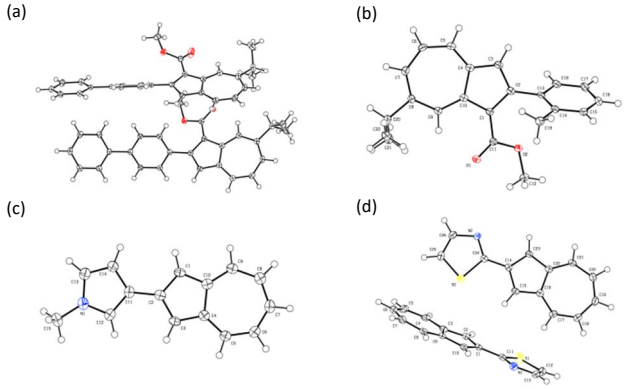


Fig. 1 ORTEP drawing of (a) **4e** (CCDC 1883650), (b) **4f** (CCDC 1883651), (c) **8i** (CCDC 1883652) and (d) **8k** (CCDC 1883653).

Azulene derivative is one of the compounds exhibiting the fluorescence from S_2 to S_0 states against Kasha's rule, but the emission intensity is generally weak.[13] In recent years, some researchers, including our group, have reported that several azulene derivatives exhibit relatively strong fluorescence under acidic conditions due to the formation of a tropylium ion substructure by the protonation.[7b,7c,14] We found that 2-phenylazulene derivatives **3a**–**3c** and **5a**–**5h** in an acidic solution displayed fluorescence, whose emission maxima depended on the electronic properties of the substituent at the *para*-position of the benzene ring (Table 2 and Fig. 2). On the whole, **3a**–**3c** and **5a**–**5h** showed longer emission maxima and higher fluorescence quantum yield than those of parent azulene, except for **5b**. Among the **3a**–**3c**, the isopropyl derivatives showed a slight short-wavelength shift of λ_{fl}. The compounds having an electron-donating substituent at the *para*-position on the benzene ring, such as **5a**, **5b**, and **5e**, were proved to show longer wavelength shifts in the emission along with lowering the quantum yields. Whereas, **5c** having an electron-withdrawing group exhibited the opposite effect (Fig. 2 and 3).

Table 2. Absorption maxima (λ_{max}) and fluorescence properties of **3a**–**3c** and **5a**–**5h** in 30% CF_3CO_2H/CH_2Cl_2.

Sample	λ_{max}	λ_{fl}	Storks shift [nm]	Φ_{fl} [%][a]	τ [ns][b]
Azulene	353	420	67	0.9	1.5
3a	446	500	54	29	5.4
3b	446	493	47	34	5.5
3c	442	488	42	35	5.7
5a	467	524	57	13	3.5
5b	499	571	72	0.4	0.24
5c	434	484	50	50	4.2
5d	455	509	54	23	3.0
5e	480	558	78	25	2.1
5f	443	495	52	37	5.3
5g	483	556	73	21	2.5
5h	492	569	77	5	1.1

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[a] Quantum yield. [b] Emission lifetime.

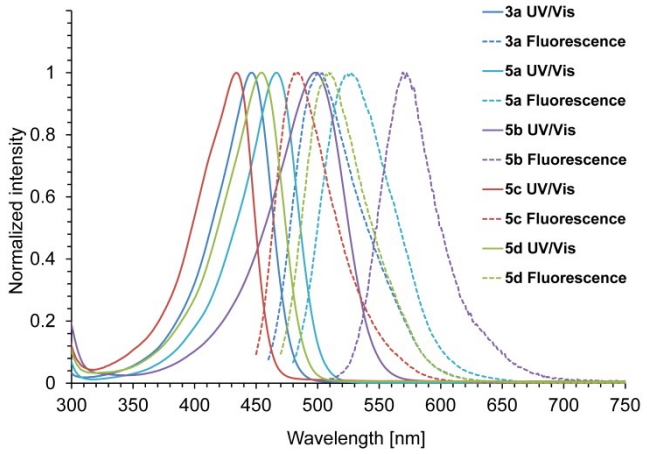

Fig. 2 UV/Vis and fluorescence spectra of **3a** and **5a**–**5d** in 30% CF_3CO_2H/CH_2Cl_2.

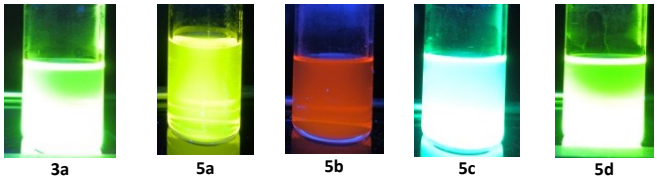

Fig. 3 Photos of **3a** and **5a**–**5d** in 30% CF_3CO_2H/CH_2Cl_2 under the irradiation of UV light (λ_{ex} = 365 nm).

In summary, we have established the direct synthesis of 2-arylazulenes by [8 + 2] CA reaction of 2*H*-cyclohepta[*b*]furan-2-one derivatives with aryl-substituted silyl enol ethers. Since the precursors are readily available, the synthetic procedure possesses significant advantages in comparison with the cross-coupling strategy by using aryl- and heteroarylmetal reagents with 2-haloazulenes and their pseudo halides, which are known to be difficult to prepare.

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Conflicts of interest

There are no conflicts to declare.

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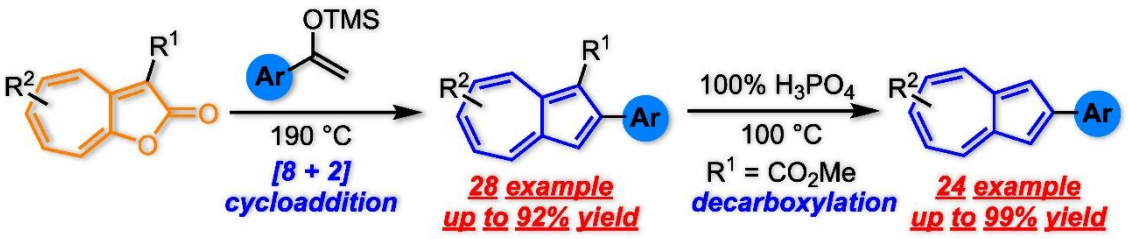

We have developed the procedure for the direct synthesis of 2-arylazulenes. The 2-arylazulenes are formed in moderate to excellent yield by [8 + 2] cycloaddition of 2*H*-cyclohepta[*b*]furan-2-one derivatives with aryl-substituted silyl enol ethers.