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First synthesis of 1-(indol-2-yl)azulenes by the Vilsmeier–Haack type arylation with triflic anhydride as an activating reagent

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ABSTRACT

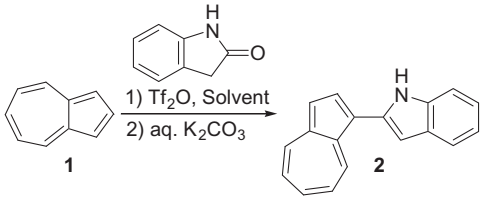
Azulene derivatives reacted with 2-indolinones in the presence of triflic anhydride (Tf_2O) to afford 1-(indol-2-yl)azulenes in good yields. In the cases of the reaction of 6-*tert*-butyl-1-(methylthio)azulene (**11**) and 1-(1,4-dihydropyridin-4-yl)azulene **14**, 1,1′-biazulene derivative **24** and 1-(indol-2-yl)azulene (**2**) were obtained under the similar reaction conditions, respectively, instead of the presumed electrophilic substitution products.

Indole derivatives are found in numerous natural products and a number of biologically active pharmaceuticals. Therefore, it is important to develop general methods to synthesize or modify such compounds.[1] Transition metal-catalyzed cross-coupling reaction is frequently utilized for the synthesis of arylindole derivatives. However, the methods for the preparation of these substances using more readily available reagents are more advantageous. Recently, Shibata et al. have reported electrophilic homocoupling reaction of indole derivatives with the triflic anhydride (Tf_2O) and 2,4,6-tri-*tert*-butylpyridine as activating reagents.[2] From a view point of electrophilic cross-coupling reaction, Black and Rezaie have reported the Tf_2O-activated Vilsmeier–Haack (V–H) type arylation of 2-indolinones with 4,6-dimethoxybenzofuran to give 2-indolylbenzofurans in good yields.[3] The electrophilic cross-coupling reactions should have a great potential to provide a facile and an efficient synthetic route for the functionalization of indole derivatives because the reactions do not require any expensive transition metal catalyst, aryl halide and a metallic coupling reagents such as boranes and stannanes.

Azulene ($C_{10}H_8$) has attracted the interest of many research groups owing to its unusual properties as well as its beautiful blue color.[4] We have recently reported the synthesis of several arylazulene derivatives by the transition-metal catalyzed cross-coupling reactions.[5] More recently, we have also demonstrated a new and two-step strategy for the heteroarylation of azulenes at the 1-, 1,3-, 5-, and 5,7-positions by the reaction with the triflate of N-containing heterocycles.[6] Although many aryl- and heteroarylazulenes have been synthesized as described in the literatures, the carbon–carbon bond formation between azulene and indole derivatives has never been reported so far.[7] If the Tf_2O-activated V–H type arylation of 2-indolinones proceeds with azulene derivatives at the 1-position, a new and facile synthetic route to 1-(indol-2-yl)azulene derivatives will be established. Moreover, success of the one-step synthesis of 1-(indol-2-yl)azulenes would provide a novel possibility for the directive heteroarylation methodology of azulene derivatives using the electrophilic substitution reaction.

We report herein the first synthesis of 1-(indol-2-yl)azulenes by the Tf_2O-activated V–H type arylation of 2-indolinones with azulene derivatives.

As a preliminary experiment for the synthesis of 1-(indol-2-yl)azulenes, the Tf_2O-activated V–H type arylation of 2-indolinone with azulene (**1**) was examined in five different organic solvents (Scheme 1). As summarized in Table 1, yields of the product were significantly dependent on the solvent employed. The reaction of **1** with 2-indolinone in dichloromethane in the presence of Tf_2O gave



Scheme 1. Reaction of azulene (**1**) with 2-indolinone.

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Table 1
Synthesis of 1-(indol-2-yl)azulene (**2**)

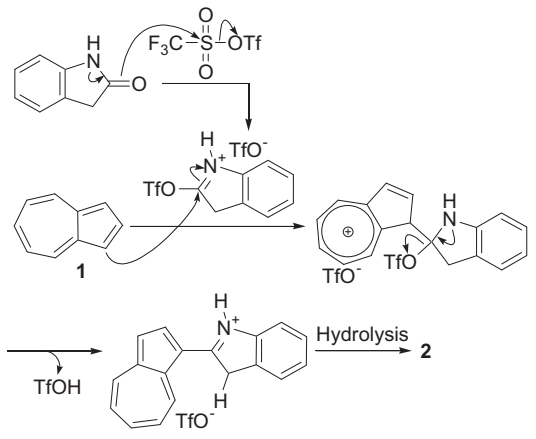
Entry	Solvent	Yield of **2** (%)
1	Dichloromethane	89
2	1,2-Dichroloethane	76
3	Toluene	75
4	Acetonitrile	59
5	Chloroform	33

the desired 1-(indol-2-yl)azulene (**2**) in an 89% yield (entry 1).[8] When 1,2-dichroloethane and toluene were used as a solvent, compound **2** was obtained in 76% and 75% yields, respectively (entries 2 and 3). Despite the fact that the highly polar solvent, acetonitrile, was a successful solvent in the Tf_2O-activated Reissert–Henze type electrophilic heteroarylation of azulenes,[9] the yield of the reaction to give **2** was moderate with acetonitrile as the solvent (59%, entry 4). The reaction in chloroform was also revealed to be insufficient due to the low product yield (33%, entry 5), because of the significant decomposition of the product under the reaction conditions. Among the solvents tested, dichloromethane was found to be the best with respect to the yield of the product (89%).

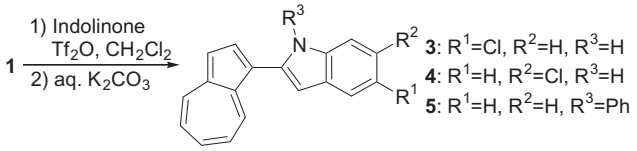
Presumed reaction mechanism of this reaction is illustrated in Scheme 2. Namely, the reaction of Tf_2O with 2-indolinone forms a Vilsmeier salt analogue, which is attacked by **1** at the most reactive site 1-position, to give 1-(indol-2-yl)azulene (**2**).

To examine the generality of the reaction of 2-indolinones, we investigated the reaction of **1** with three commercially available indolinone derivatives under the optimized reaction conditions (Scheme 3 and Table 2). 5-Chloro-2-indolinone and 6-chloro-2-indolinone were reacted with **1** in the presence of Tf_2O to give the corresponding 1-(5- and 6-chloroindol-2-yl)azulenes (**3** and **4**) in 91% and 89% yields, respectively (entries 1 and 2). The reaction of **1** with 1-phenyl-2-indolinone gave the presumed substitution product **5** in 27% yield (entry 3). Low yield of the product **5** might be ascribed to the steric effect of the phenyl moiety on the nitrogen atom to the electrophilic reaction. These results show the generality of the V–H type reaction of azulene (**1**) with 2-indolinone derivatives, although the N-phenyl substituent of 2-indolinone was directly affected toward the product yield.

A series of azulene derivatives were subjected to this V–H type reaction under the optimized reaction conditions to explore the scope of this reaction (Scheme 4). Examined compounds and yield of the products are summarized in Table 3. The by-products of reaction are also shown in the Figure 1.

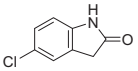
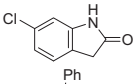
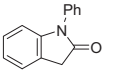


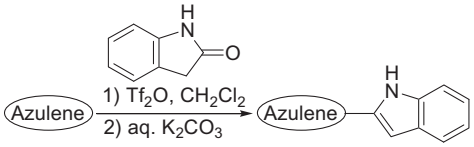
Scheme 2. Presumed reaction mechanism.



Scheme 3. Reaction of azulene (**1**) with 2-indolinone derivatives.

Table 2
Synthesis of 1-(indol-2-yl)azulene derivatives

Entry	Indolinone	Reaction time (h)	Product, yield (%)
1		3	**3**, 91
2		2.5	**4**, 89
3		17	**5**, 27

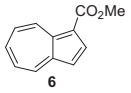
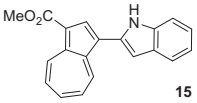
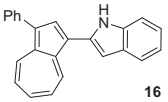
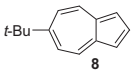
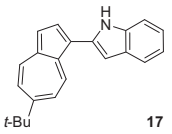
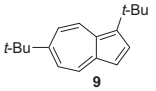
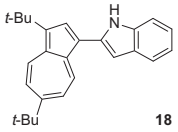
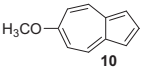
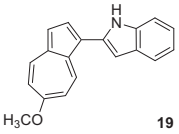
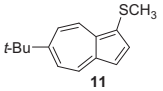
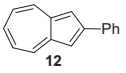
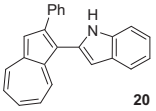
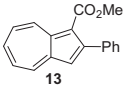
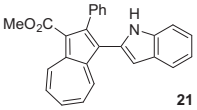
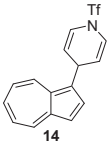


Scheme 4. Reaction of azulene derivatives (**6**–**14**) with 2-indolinone.

The reaction of **6** that possesses an electron-withdrawing substituent at the 1-position with 2-indolinone in the presence of Tf_2O in dichloromethane at room temperature gave methyl 1-(indol-2-yl)azulene-3-carboxylate (**15**) in 71% yield, along with **22** in a 22% yield (entry 1). Generation of **22** should be attributed to the condensation between the two molecules of **6** under the acidic reaction conditions. As similar with **6**, the reaction of 1-phenylazulene (**7**) with 2-indolinone under the similar reaction conditions afforded the corresponding substitution product **16** in an 88% yield (entry 2). The substrate **8** possessing an electron-donating *tert*-butyl group at the 6-position afforded the di-substituted product, 6-*tert*-butyl-1,3-di(indol-2-yl)azulene (**23**) (13%) in addition to the desired substitution product **17** (64%) (entry 3). Formation of the di-substituted product **23** indicates that *tert*-butyl group at the 6-position enhances the reactivity toward the V–H type reaction, because generation of the di-substituted product was not observed in the reaction of **1**. The reaction of more electron-rich substrates **9** and **10** resulted in decrease of the product yields (**18**: 47%, **19**: 45%) due to the decomposition of the products (entries 4 and 5) during the reaction. Furthermore, products **18** and **19** were found to be unstable under ambient condition and exhibited ready decomposition to give an unidentified complex mixture. Instead of the formation of the presumed indole derivative, 1,1′-biazulene derivative **24**[10] was obtained in a 43% yield by the reaction of **11** under the similar reaction conditions (entry 6). Recently, we have reported the formation of the 3,3′-methylthio-1,1′-biazulene derivative by the treatment of 1-methylthioazulene with pyridine N-oxide and Tf_2O.[9] Therefore, the formation of the 1,1′-biazulene derivative **24** in this reaction is attributable to the presence of Tf_2O, which should act as an oxidant for the homo-coupling reaction of **11**.

The reaction of the substrates **12** and **13** having a phenyl group at the 2-position also afforded the desired products **20** and **21**, respectively, in satisfactory yields. Substrate **12** reacted with 2-

Table 3
Synthesis of 1-(indol-2-yl)azulene derivatives

Entry	Azulene	Reaction time (h)	Product	Yield (%)
1	 **6**	2.5	 **15**	71
2	 **7**	3	 **16**	88
3	 **8**	2.5	 **17**	64
4	 **9**	3	 **18**	47
5	 **10**	2	 **19**	45
6	 **11**	3	**24**	43
7	 **12**	3	 **20**	82
8	 **13**	6	 **21**	65
9	 **14**	3	**2**	72

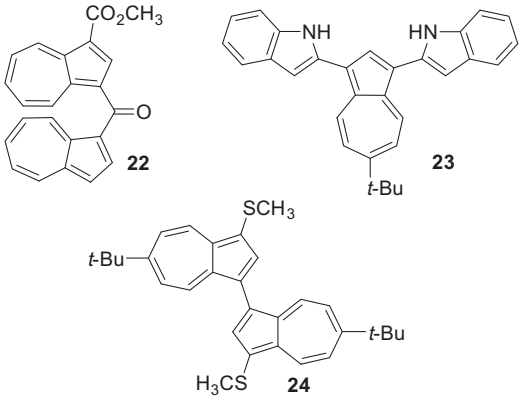


Figure 1. By-products of the Tf_2O-activated V–H type reaction.

indolinone to give 1-(indol-2-yl)-2-phenylazulene (**20**) in an 82% yield as a sole product (entry 7). From the aspect of the product yield, relatively bulky 2-phenyl substituent did not significantly affect the electrophilic substitution reaction. On the other hand, 2-phenylazulene derivative **13** bearing a methoxycarbonyl group at the 1-position was converted into indole derivative **21** in a 65% yield, along with decarboxylated product **12**[11] in a 27% yield (entry 8).

Contrary to our expectations, the reaction of **14** afforded indole derivative **2** in a 72% yield, whose formation could be ascribed by the *ipso*-substitution reaction of azulene ring at the 1-position (entry 9). This represents the first example of dihydropyridine moiety acting as a leaving group during the electrophilic substitution reaction in the field of azulene chemistry. Previously, Hafner et al.[12] and our group[13] reported that 1,3-di-(isopropyl and *tert*-butyl)azulenes undergo facile electrophilic *ipso*-substitution reactions such as Friedel–Crafts acylation and Vilsmeier formylation at their 1- and/or 3-positions in good yields. Thus, the 1,4-dihydropyridyl group on **14** can be regarded as a good leaving group toward the electrophilic *ipso*-substitution reaction, likewise the isopropyl and *tert*-butyl groups.

In conclusion, the Tf_2O-activated V–H type reaction of azulene (**1**) with 2-indolinone has been disclosed. This methodology allowed us to the first synthesis of 1-(indol-2-yl)azulene (**2**).

The 1-(indol-2-yl)azulene derivatives were available by the reaction of the corresponding azulene derivatives with 2-indolinones in the presence of Tf_2O, following the hydrolysis with aq. K_2CO_3. Under the reaction conditions, we found 6-*tert*-butyl-1-(methylthio)azulene (**11**) was converted into 1,1′-biazulene derivative **24**. By the Tf_2O-activated V–H type reaction of **14**, novel *ipso*-substitution was clarified to give **2** in good yield. These results suggest dihydropyridine moiety at the 1-position behaves as a good leaving group, as well as isopropyl and *tert*-butyl groups. These results would warrant the development of new synthetic methodology for azulene derivatives.

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8. *A typical procedure:* Tf_2O (203 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) were added at room temperature to a solution of azulene (**1**) (67 mg, 0.52 mmol) and 2-indolinone (101 mg, 0.76 mmol) in CH_2Cl_2 (15 mL). The resulting solution was stirred at the same temperature for 2.5 hours. The reaction mixture was poured into a 2 M K_2CO_3 solution, extracted with AcOEt, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with hexane/AcOEt (10:1) as an eluent to give 1-(indol-2-yl)azulene (**2**) (113 mg, 89%) as green crystals. ^{1}H NMR (500 MHz, $CDCl_3$): ppm; δ_H = 8.80 (d, 1H, *J* = 9.5 Hz, 8-H), 8.33 (d, 1H, *J* = 9.5 Hz, 4-H), 8.25 (br s, 1H, NH of indole), 8.06 (d, 1H, *J* = 4.0 Hz, 2-H), 7.66 (d, 1H, *J* = 7.5 Hz, 4′-H of indole), 7.61 (t, 1H, *J* = 9.5 Hz, 6-H), 7.43 (d, 1H, *J* = 4.0 Hz, 3-H), 7.41 (d, 1H, *J* = 7.5 Hz, 8′-H of indole), 7.22–7.13 (m, 4H, 5,7-H, 5,6-H of indole), 6.79 (s, 1H, 3′-H of indole) ppm; ^{13}C NMR (125 MHz): δ_C = 142.19 (C-8a), 138.78 (C-6), 137.63 (C-4), 136.55 (C-8a′ of indole), 136.01 (C-8), 135.62 (C-3a), 135.48 (C-2), 134.76 (C-1), 129.54 (C-3a′ of indole), 123.93, 123.81, 121.73 (C-7), 120.21, 120.09 (C-4′ of indole), 117.93 (C-3), 110.61 (C-8′ of indole), 101.20 (C-3′ of indole) ppm.
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