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Synthesis of 5-heteroarylazulenes: first selective electrophilic substitution at the 5-position of azulene

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Abstract—1,3-Di-*tert*-butylazulene reacted with highly electrophilic trifluoromethanesulfonate of N-containing heterocycles to give 5-(dihydroheteroaryl)azulene derivatives in good yield and treatment of the 5-(dihydroheteroaryl)azulene derivatives with KOH afforded 5-(heteroaryl)azulenes in excellent yield.

Electrophilic substitutions are a very important and general methodology for the functionalization of aromatic compounds. In azulene derivatives, there are numerous reports for electrophilic substitutions at the 1- and 3-positions of the azulene ring.[1] However, functionalization of the seven-membered ring of azulene using electrophilic substitution has been relatively difficult so far. In 1962, Hafner reported that 1,3-dialkyl-substituted azulene derivatives underwent electrophilic substitution such as Friedel–Crafts acylation and Vilsmeier formylation at the 5-position, but in very low selectivity compared with *ipso*-substitution at the 1-position.[3]

There are no reports for the synthesis of 5-arylazulene derivatives by arylation of the azulene ring. The multistep synthesis of 5-phenylazulene from bicyclo[5.3.0]-decan-5-one was the only example for the synthesis of 5-arylazulenes.[4] Morita and co-workers recently reported efficient arylation using Grignard reagents, but at the 4-position of the azulene ring.[2] Recently, we have reported the transition metal-catalyzed synthesis of arylazulenes.[5] However, the application of the transition metal-catalyzed aryl–aryl coupling at the 5-position might be difficult because of the limited availability of 5-haloazulenes.[6] More recently, we have demonstrated that the reaction of azulene with the triflate of N-containing heterocycles, which are readily available from the reaction of N-containing heterocycles with trifluoromethanesulfonic anhydride (Tf_2O), gives 1-(dihydroheteroaryl)- and 1,3-bis(dihydroheteroaryl)azulene derivatives.[7] The transformation from the dihydroarylazulene derivatives to 1-hetroaryl- and 1,3-bisheteroarylazulene derivatives opened a new two-step strategy for the heteroarylation of azulene.[8] If the triflates exhibit electrophilic substitution with azulene derivatives at the 5-position, new and facile synthetic route to the 5-heteroarylazulene derivatives will be established. We report herein the reaction of 1,3-di-*tert*-butylazulene (**1**) with triflate of N-containing heterocycles and the transformation to the 5-heteroarylazulenes via electrophilic dihydroheteroarylation.

For the functionalization at the 5-position of the azulene, 1,3-di-*tert*-butylazulene (**1**), which is prepared by Friedel–Crafts alkylation of azulene with *tert*-butyl chloride/$AlCl_3$, was applied for the electrophilic substitution with the triflates of several N-containing heterocycles.[9] The *tert*-butyl substituents at the 1- and 3-positions would suppress the most reactive site for the azulene ring and also the substituents might be subjected to further functionalization by Hafner's electrophilic *ipso*-substitution reaction.[3] As expected, the reaction

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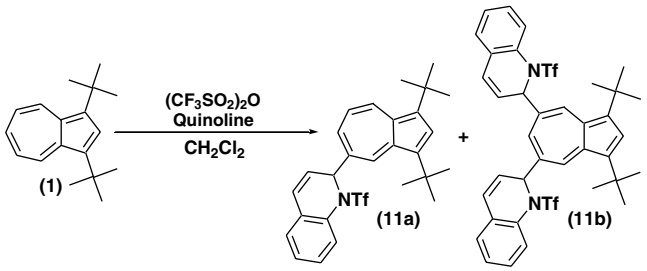


Scheme 1.

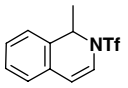
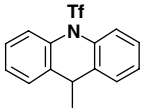
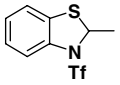
of **1** with quinoline (**2**) in the presence of 1.5 equiv of Tf_2O and excess **2** provided 5-(dihydroquinolyl)azulene derivative **11a** as the sole product (entry 3). Similarly, the reaction with 3.0 equiv of Tf_2O and excess **2** afforded 5,7-bis(dihydroquinolyl)azulene derivative **11b** as a major product (entry 5). However, when an equimolar amount of Tf_2O and **2** was used, yields of both products became relatively low probably due to the decomposition of the azulene derivatives by the generated acid (entries 2 and 4). Therefore, these results suggest that basic conditions are necessary to obtain good product yields (Scheme 1, Table 1).

We applied the reaction to several N-containing heterocycles; that is, isoquinoline (**3**), acridine (**4**), benzothiazole (**5**), benzimidazole (**6**), *N*-methylbenzimidazole (**7**) and *N*-methylimidazole (**8**). The N-containing heterocycles **3**–**5** also reacted with **1** at room temperature in the presence of Tf_2O to afford the corresponding 5-(dihydroheteroaryl)azulene derivatives **12**–**14** in good yields as summarized in Table 2. The structures of **11**–**14** were confirmed based on their spectral data. In these reactions, *ipso*-substitution of the 1- and/or 3-positions was not observed and the electrophilic substitution proceeded at the 5-position selectively to give the corresponding 5-(dihydroheteroaryl)azulene derivatives.[10] However, triflates of **6**–**8**, which were smoothly reacted with the parent azulene at the 1- and/or 1,3-positions at room temperature, did not react with **1** even under more severe reaction conditions such as in refluxing chloroform (Scheme 2, Table 2).

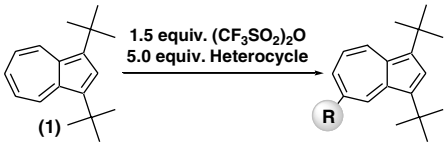
Table 1. Synthesis of 5-(dihydroheteroaryl)azulenes

Entry	Proportion	Yield, %	
	1:$(CF_3SO_2)_2O$:Quinoline	**11a**	**11b**
1	1.0:1.0:5.0	68	0
2	1.0:1.5:1.5	31	0
3	1.0:1.5:5.0	85	0
4	1.0:3.0:3.0	7	34
5	1.0:3.0:10	18	71

Table 2. Synthesis of 5-(dihydroheteroaryl)azulenes

Heterocycle	R	Product (%)
Isoquinoline (**3**)[a]		**12** (89)
Acridine (**4**)[a]		**13** (91)
Benzothiazole (**5**)[a]		**14** (87)
Benzimidazole (**6**)[b]		No reaction
N-Methylbenzimidazole (**7**)[b]		No reaction
N-Methylimidazole (**8**)[b]		No reaction

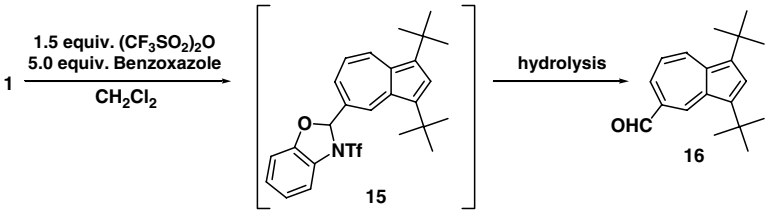
[a] In CH_2Cl_2, for 30 min, room temperature.
[b] In $CHCl_3$, for 24 h, reflux.



Scheme 2.

The formyl group is very useful for organic synthesis. Preparation of 5-formylazulene derivative **16** was established by using a similar electrophilic substitution reaction. The reaction of **1** with benzoxazole (**9**) in the presence of Tf_2O afforded 5-(dihydrobenzoxazolyl)azulene derivative **15** in 77% yield. Product **15** was easily hydrolyzed to afford **16** in quantitative yield. Although synthesis of **16** has been reported,[3] this sequence provides higher yield and high selectivity. Therefore, this sequence may be useful for the preparation of 5-formylazulene derivative (Scheme 3).[11]

For the purpose of transformation from the 5-(dihydroheteroaryl)azulenes to 5-(heteroaryl)azulenes, we investigated aromatization of products **11**–**14** using basic conditions. Treatment of **11**–**14** with 3 equiv of KOH in methanol at room temperature afforded the corresponding 5-(heteroaryl)azulenes derivatives **17**–**20** in high yield as summarized in Table 3 (Scheme 4).[11] Differing from the 1-(dihydroisoquinolyl)azulene derivative, product **12** reacted with KOH to afford 5-(isoquinolyl)azulene derivative (**18**).[8] Product **14** was also converted to the desired 5-(benzothiazolyl)azulene



Scheme 3.