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Synthesis of heteroarylazulenes: transition metal free coupling strategy of azulene with heterocycles

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Abstract—Azulene reacts with highly electrophilic trifluoromethanesulfonates of N-containing heterocycles to give 1-dihydroheteroaryl and 1,3-bis(dihydroheteroaryl)azulene derivatives in a good yield. Treatment of the dihydroheteroarylazulene derivatives with KOH or *tert*-BuOK afforded 1-heteroaryl and 1,3-bis(heteroaryl)azulenes in a good yield.
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Heterocycles containing a nitrogen atom are found in numerous natural products and many biologically active pharmaceuticals comprise such heterocycles.[1] Therefore, it is important to develop general methods to synthesize or modify such compounds. Recently, many transition metal-catalyzed aryl–aryl cross-coupling reactions such as the Stille-,[2] Suzuki-,[3] and Ullmann-type reactions,[4] which require a relatively high temperature, are reported in the literature. Previously, we have reported a palladium-catalyzed synthesis of 2- and 6-heteroarylazulenes.[5] However, palladium-catalyzed aryl–azulenyl coupling is not effective at the 1- or 1,3-positions of azulene rings, because these positions have highly electron-donating properties. Therefore, we report herein a facile azulenyl–heteroaryl coupling reaction of heterocycles containing a nitrogen atom at the 1 or 1,3-positions of azulene via dihydroheteroarylazulene derivatives under mild conditions without a transition metal catalyst.
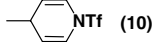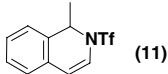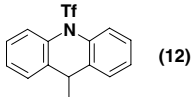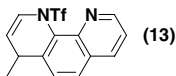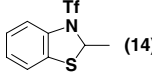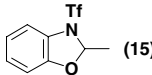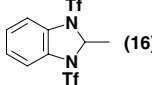
We have recently demonstrated a reaction of azulene (**1**) with trifluoromethanesulfonylpyridinium trifluoromethanesulfonate (TPT). In this case, the reaction of **1** with TPT, which is prepared from an equivalent of trifluoromethanesulfonic anhydride (Tf$_2$O) with pyridine (**2**), gave 6-(1-azulenyl)-1-trifluoromethanesulfonyl-1-azahexa-1,3,5-triene as the main product, which comes from an attack of **1** to the 2-position of TPT. However, the reaction of **1** with TPT in the presence of a large amount of **2** gave 1,3-bis(4-dihydropyridyl)azulene derivatives (**10b**), which comes from an attack of **1** to the 4-position of TPT.[6] Therefore, excess pyridine is needed to obtain the dihydropyridylazulene derivatives in a good yield. Actually, the selective synthesis of 1-(4-dihydropyridyl)azulene (**10a**) and 1,3-bis(4-dihydropyridyl)azulene derivative (**10b**) was easily controlled by the amount of Tf$_2$O under excess **2**. We extended this procedure to several N-containing heterocycles such as isoquinoline (**3**), acridine (**4**), 1,10-phenanthroline (**5**), benzothiazole (**6**), benzoxazole (**7**), benzimidazole (**8**), and quinoline (**9**). The general procedure is shown in Refs. 15 and 16. The proportion of the amounts of azulene, Tf$_2$O, and heterocycles is very important to determine the products distribution. The results are summarized in Table 1. Similarly to the reaction of pyridine (**2**), nitrogen-containing heterocycles **3**–**8** reacted with azulene (**1**) at room temperature in the presence of Tf$_2$O to give the corresponding 1-dihydroheteroarylazulene derivatives **10a**–**16a** and 1,3-bis(dihydroheteroaryl)azulene derivatives **10b**–**16b** in a good yield. In the case of the reaction of acridine (**4**), Corey and Tian have reported that electron-rich aniline derivatives do not react with **4** in the presence of Tf$_2$O,[7] whereas azulene (**1**),

Table 1. Synthesis of dihydroheteroarylazulene derivatives

Heterocycle	R	Proportion	Yields (%)	
		1:Tf$_2$O:Heterocycle	a	b
Pyridine, **2**	(10)	1:1.2:5	72	10
		1:2.4:10	0	89
Isoquinoline, **3**	(11)	1:1.2:5	92	6
		1:2.4:10	0	97
Acridine, **4**	(12)	1:1.2:5	80	19
		1:2.4:10	0	99
1,10-Phen,[a] **5**	(13)	1:1.2:5	87	5
		1:2.4:10	0	94
Benzothiazole, **6**	(14)	1:1.2:5	82	14
		1:2.4:10	0	97
Benzoxazole, **7**	(15)	1:1.2:5	70	3
		1:2.4:10	0	76
Benzimidazole, **8**	(16)	1:3:1.5	84	0
		1:6:3	26	48

[a] 1,10-Phenanthroline.
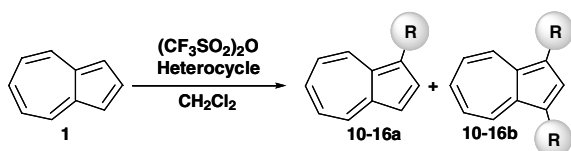
Scheme 1.

which is a highly reactive compound toward the electrophilic reaction, reacts with **4** in the presence of Tf$_2$O to afford the presumed dihydroacridylazulene derivatives **12a** and **12b**. Furthermore, the selective synthesis of the 1-dihydroheteroarylazulene derivatives and 1,3-bis(dihydroheteroaryl)azulene derivatives is easily performed by varying the amounts of heterocycles and Tf$_2$O added (Scheme 1, Table 1).

For the purpose of transformation to the heteroarylazulenes, we examined base-induced aromatization of the dihydroheteroarylazulene derivatives. Previously, Katritzky et al. reported the aromatization of dihydropyridine derivatives with *tert*-BuOK and also reported that the use of other bases was not effective for the aromatization.[8] We investigated the two bases for the reaction. The results and the reaction conditions are summarized in Table 2. 1-(4-Dihydropyridyl)azulene derivative **10a** reacted with KOH in EtOH and *tert*-BuOK in DMSO at room temperature to afford 1-(4-pyridyl)azulene (**17a**)[9] in 99% and 94% yields, respectively (entries 1 and 2), while **10a** did not react with an organic base such as Et$_2$NH, Et$_3$N, and DBU (Scheme 2).

Table 2. Reaction conditions and yields of aromatization

Entry	Substrate	Heterocycle	Conditions	Yield[a] (%)
1	**10a**	Pyridine	A	**17a**, 94
2	**10a**	Pyridine	B	**17a**, 99
3	**10b**	Pyridine	A	**17b**, 87
4	**10b**	Pyridine	B	**17b**, 99
5	**11a**	Isoquinoline	A	**18a**, 81
6	**11a**	Isoquinoline	B	—
7	**11b**	Isoquinoline	A	**18b**, 79
8	**11b**	Isoquinoline	B	—
9	**12a**	Acridine	A	—
10	**12a**	Acridine	B	**19a**, 99
11	**12b**	Acridine	A	—
12	**12b**	Acridine	B	**19b**, 98
13	**13a**	1,10-Phen[b]	B	**20a**, 99
14	**13b**	1,10-Phen[b]	B	**20b**, 97

Condition A: *t*-BuOK (3 equiv), in DMSO, for 10 min, room temperature. Condition B: KOH (3 equiv), in EtOH, for 2 h, room temperature.
[a] Isolated yield.
[b] 1,10-Phenanthroline.
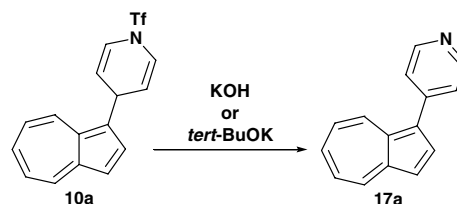
Scheme 2.

Similarly, 1,3-bis(4-dihydropyridyl)azulene derivative **10b** reacted with KOH in EtOH and *tert*-BuOK in DMSO to give 1,3-bis(4-pyridyl)azulene in 99% and 87% yields, respectively (entries 3 and 4).[11] Treatment of 1-(1-dihydroisoquinolyl)azulene derivative **11a** and 1,3-bis(1-dihydroisoquinolyl)azulene derivative **11b** with KOH did not afford the presumed products. However, **11a** and **11b** reacted with *tert*-BuOK in DMSO to give 1-(1-isoquinolyl)azulene (**18a**) and 1,3-bis(1-isoquin-olyl)azulene (**18b**) in 81% and 79% yields, respectively (Scheme 3, entries 5–8).

In contrast, the reaction of 1-(9-dihydroacridyl)azulene derivative **12a** and 1,3-bis(9-dihydroacridyl)azulene derivative **12b** with *tert*-BuOK in DMSO leads to decomposition. However, treatment of **12a** and **12b** with KOH in EtOH afforded 1-(9-acridyl)azulene (**19a**) and 1,3-bis(9-acridyl)azulene (**19b**) in 99% and 98%, respectively (Scheme 4, entries 9–12).

Similarly, treatment of **13a** and **13b** with KOH afforded 1-(1,10-phenanthrolin-4-yl)azulene (**20a**) and 1,3-bis(1,10-phenanthrolin-4-yl)azulene (**20b**) in 99% and 97% yield, respectively (Scheme 5, entries 13 and 14).

Suitable single crystals of **13a** for X-ray crystallographic analysis were obtained by the recrystallization from CH_2Cl_2.[10] The structure of **13a** was established as shown
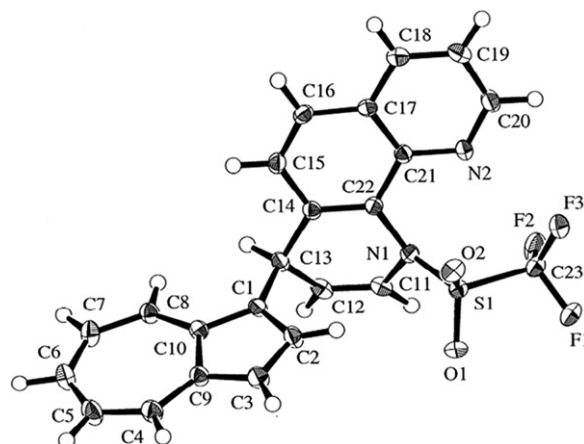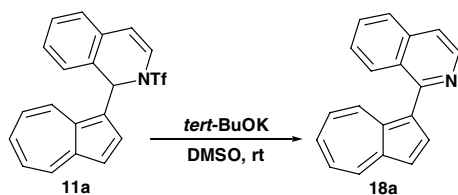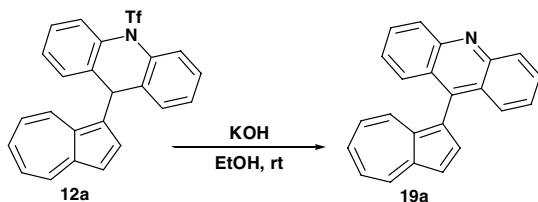

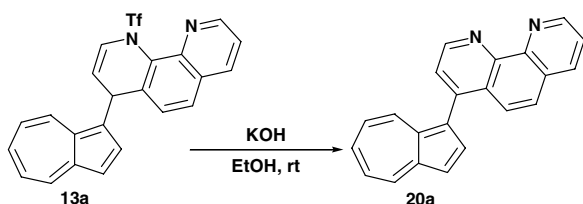**Figure 1.** ORTEP drawing of **13a**.

in Figure 1.[11] The boat conformation of the dihydro-pyridine moiety in **13a** was similar to that of the 1-tri-flyl-1,4-dihydropyridines previously reported.[12]

The advantageous feature of this synthetic methodology is that these reactions do not require an expensive transition metal catalyst, aryl halide, and a coupling reagent such as borane and stannane. Thus, these procedures would be widely applicable for the synthesis of heteroarylazulenes.

Dihydrobenzoazole derivatives **14a**–**16a** and **14b**–**16b** reacted with KOH in EtOH to give 1-formyl and 1,3-diformylazulenes, respectively.[13] In these cases, the base attacks the sulfur atom of the trifuloromethylsulfonyl group and the generated imine intermediate is easily hydrolyzed to 1-formyl- (**6a**, 94%; **7a**, 92%; **8a**, 89%) and 1,3-diformylazulenes (**6b**, 82%. **7b**, 84%. **8b**, 79%.). Especially, **15a** and **15b** were readily hydrolyzed on silica gel to afford formylazulenes.

In the reaction of azulene (**1**), the addition of 1.2 equiv of Tf_2O with 5 equiv of quinoline (**9**) (v.s. azulene) generates unisolatable products. Therefore, azulene (**1**) is reacted with 2.4 equiv of Tf_2O with 10 equiv of quinoline (**9**), the crude product is treated with *tert*-BuOK in DMSO without isolation, and then subjected to reversed-phase chromatography (ODS with 70% aq MeOH) and preparative GPC with $CHCl_3$ to afford 1,3-bis(quinolyl)azulenes **21a**, **21b**, and **21c** in 27%, 29%, and 32% yield, respectively (Scheme 6).

Table 3 shows the selected ^{1}H NMR chemical shifts of **1**[14] and **18a** and **18b**, **21a**–**c**. The H-8 proton of **21b** and H-4 and H-8 protons of **21c** exhibited remarkable low-field shift as compared with those of the parent azulene (**1**). However, in the case of **18a** and **18b**, the remarkable low-field shift is not observed. It should be attributable to anisotropy and also the intramolecular interaction of the nitrogen atom of the quinoline ring and the H-4 and/or H-8 proton of azulene. Therefore, it is considered that the azulene ring and the quinoline ring in **21b** and **21c** are coplanar.

Scheme 3.
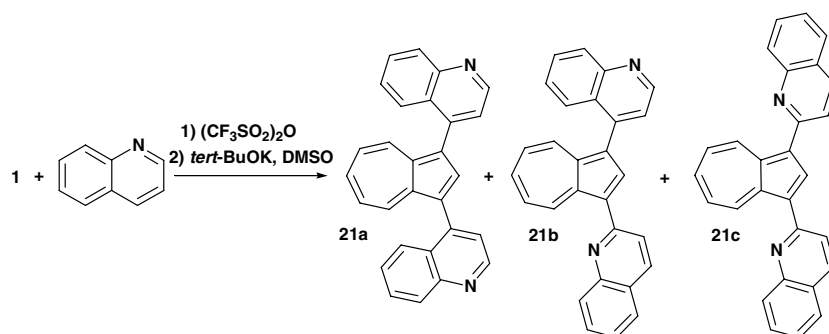
Scheme 4.

Scheme 5.

Scheme 6. Synthesis of 1,3-bis(quinolyl)azulenes **21a–c**.

Table 3. Chemical shifts of **1**, **18a**, **18b**, **21a**, **21b**, and **21c** at 2, 4, and 8-H protons

Compound	Chemical shift (ppm)		
	H-2	H-4	H-8
1	7.81	8.23	8.23
18a	8.21	8.41	8.64
18b	8.52	8.79	8.79
21a	7.73	8.33	8.33
21b	8.52	8.22	10.07
21c	8.86	10.01	10.01

To evaluate this methodology, we also attempted the introduction of different heterocycles at the 1- and 3-positions of azulene (**1**). 1-(9-Dihydroacridyl)azulene (**12a**) reacted with TPT, which was prepared from 5 equiv of **2** and 1.2 equiv of Tf$_2$O, to afford 1-(9-dihydroacridyl)-3-(4-dihydropyridyl)azulene (**22**) in a 79% yield. Product **22** was treated with KOH in EtOH at room temperature to give 1-(9-acridyl)-3-(4-pyridyl)azulene (**23**) in a 98% yield (Scheme 7).

In conclusion, we have established a synthesis of N-containing heteroarylazulenes without the use of transition metal catalyst via the corresponding dihydroheteroarylazulene derivatives, which were easily prepared by a reaction with the parent heterocycles and Tf$_2$O under mild conditions. Treatment of the dihydroheteroarylazulene derivatives with KOH in EtOH and *tert*-BuOK in DMSO afforded the corresponding heteroarylazulenes. Dihydrobenzazoles were easily hydrolyzed to afford 1-formyl- and 1,3-diformylazulenes. Pharmacological activities and physical properties of these new compounds are now under investigation in our laboratory.
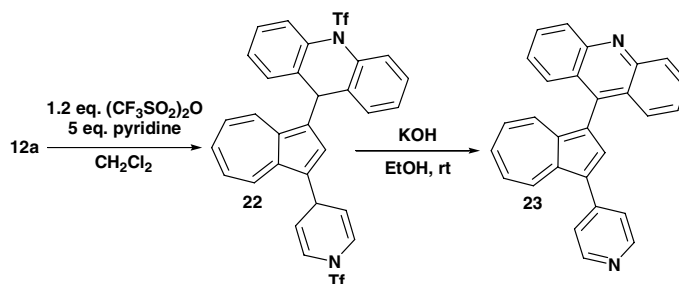
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.083.

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Scheme 7.

9. Similar compounds were previously reported. (a) Ueno, T.; Toda, H.; Yasunami, M.; Yoshifuji, M. *Chem. Lett.* **1995**, *24*, 169; (b) Ueno, T.; Toda, H.; Yasunami, M.; Yoshifuji, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1645; (c) Wang, D.; Imafuku, K. *J. Heterocycl. Chem.* **2000**, *37*, 1019.

10. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 615972 for compound **13a**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-1223-336033, e-mail: deposit@ccdc.cam. ac.uk or http://www.ccdc.cam.ac.uk).

11. Crystal data for **13a**: triclinic, $a = 9.836(5)$ Å, $b = 10.228(9)$ Å, $c = 9.742(8)$ Å, $\alpha = 91.785(4)°$, $\beta = 95.059(3)°$, $\gamma = 103.178(3)°$, $V = 949.3(1)$ Å^3, $Z = 2$, $D_{calc} = 1.541$ g cm^{-3}, μ (MoKα) = 2.24 cm^{-1}, $R = 0.124$, $Rw = 0.114$, $R_1 = 0.047$.

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15. *General procedure for the synthesis of dihydroheteroaryl-azulenes*: To a solution of azulene (1.0 mmol) and hetero-cycles (5.0 or 10 mmol) in CH$_2$Cl$_2$ (10 mL) was added dropwise a solution of Tf$_2$O (1.2 or 2.4 mmol) in CH$_2$Cl$_2$ (10 mL). The resulting solution was stirred for 30 min–2 h at room temperature and the solvent was removed in vacuo and the reaction mixture was purified by column chromatography on silica gel to give the corresponding dihydroheteroarylazulenes.

16. *General procedure for the synthesis of heteroarylazulenes*: 3 equiv of KOH or *tert*-BuOK was added to a solution of dihydroheteroarylazulenes in EtOH or DMSO. The resulting solution was stirred at room temperature for 10 min or 2 h. After a usual workup, the crude product was purified by reversed-phase chromatography (ODS/70% aq MeOH) and preparative GPC to give heteroarylazulenes.