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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.

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_2O) with pyridine (**2**), gave 6-(1-azulenyl)-1-trifluoromethanesulfonyl-1-aza-hexa-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_2O 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_2O, 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_2O 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_2O,[7] whereas azulene (**1**),

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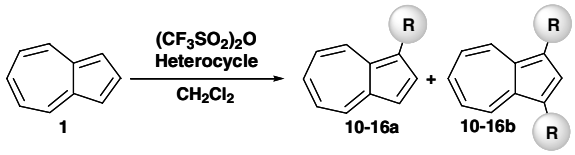
Table 1. Synthesis of dihydroheteroarylazulene derivatives

Heterocycle	R	Proportion 1:Tf_2O:Heterocycle	Yields (%) a	b
Pyridine, **2**	NTf (10)	1:1.2:5	72	10
		1:2.4:10	0	89
Isoquinoline, **3**	NTf (11)	1:1.2:5	92	6
		1:2.4:10	0	97
Acridine, **4**	Tf N (12)	1:1.2:5	80	19
		1:2.4:10	0	99
1,10-Phen,[a] **5**	NTf N (13)	1:1.2:5	87	5
		1:2.4:10	0	94
Benzothiazole, **6**	Tf N S (14)	1:1.2:5	82	14
		1:2.4:10	0	97
Benzoxazole, **7**	Tf N O (15)	1:1.2:5	70	3
		1:2.4:10	0	76
Benzimidazole, **8**	Tf N N Tf (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_2O 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_2O 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_2NH, Et_3N, and DBU (Scheme 2).

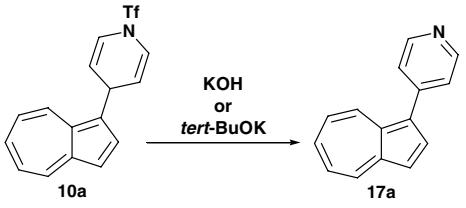
Table 2. Reaction conditions and yields of aromatization

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.