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Regioselective coupling reaction of azulene with α,β-unsaturated ketones by Mg-promoted reduction

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ABSTRACT

Mg-Promoted reductive coupling of azulene with various α,β-unsaturated ketones in the presence of chlorotrimethylsilane in 1-methyl-2-pyrrolidinone brought about regioselective formation of the corresponding 6-substituted dihydroazulenes, which were easily oxidized to the corresponding 6-substituted azulenes by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in good yields. This new regioselective method enabled us to synthesize various 6-substituted azulenes from azulene in only two steps.

Azulene, an isomer of naphthalene is well-known as a blue-coloured non-benzenoid aromatic compound and many scientists have been concentrating much attention in view of physical organic and pharmaceutical chemistry.[1] Guaiazulene easily derived from a natural compound has been studied for a long time[2] and its derivative is used as a potent pharmaceutical drug.[3] Furthermore, azulene derivatives have been recently also focused as photoreactive materials.[4–6]

In spite of such characteristics and much importance[7,8] of azulene derivatives, synthetic chemistry of azulenes has not been wide-spread sufficiently because of much difficulty in regioselective synthesis. Although in general, electrophiles may exclusively attack the five-membered ring, and nucleophilic attack may take place selectively to the seven-membered ring due to the polarity of azulene ring,[1] their detailed positional regioselectivity on both of nucleo- and electro-substitutions has been rather poor.

For example, electrophiles react at C1- or C3-position of azulene ring and Vilsmeier–Haack formylation of azulene brought about formation of 1-formylazulene.[9–12] On the other hand, alkyllithium reagents add to C4- or C8-position of azulene ring. A reaction of azulene with methyllithium followed by oxidation afforded 4-methylazulene as a single product.[13] Addition of lithium acetylide to azulene with an electron-withdrawing group in the five-membered ring led to a mixture of 4- and 6-ethynylazulenes.[14–16]

Namely, ring attacked by a reagent depends on the nature of the reagent, and regiochemistry is also controlled by resonance and conjugation of azulene ring. Therefore, it has been an important theme to control positional regioselectivity and direction of nucleophilic or electrophilic attack. Recently, Sugihara and co-workers reported the regioselective synthesis of 6-azulenethiocarboxylic acid derivatives through addition of tris(methylthio)methyllithium to azulene, which was one of the few examples of selective synthesis of 6-substituted azulenes in several steps from azulene.[17,18] Introduction of a hydroxyl group was also explored to give 6-hydroxyazulene derivatives by Makosza et al.[19] Reductive carboxylation of azulene by sodium was already reported,[20] which suggested reductive coupling would be possible. However, 1-azulenecarboxylic acid was obtained in low yield by this carboxylation.

We have already reported coupling reactions of α,β-unsaturated carbonyl compounds, anthracene, and stilbenes with carbonyl compounds by electron transfer, in which Mg turnings for Grignard reaction in the presence of chlorotrimethylsilane was found to be a superior electron transfer agent for those coupling reactions because of high reactivity, easy handling, low toxicity and easy availability with no pre-treatment.[21–23]

In this study, we have developed the regioselective coupling of azulene with α,β-unsaturated ketones through umpolung by magnesium metal followed by oxidation to establish regioselective formation of 6-substituted azulenes in good yields.

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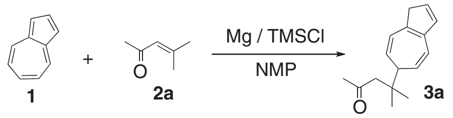
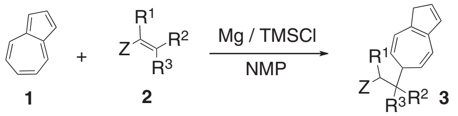
Table 1
Mg-Promoted coupling reaction of azulene (**1**) and mesityl oxide (**2a**)

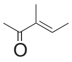
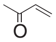
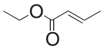
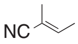
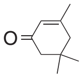
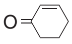
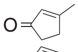
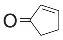


Entry	Mg (equiv)	TMSCl (equiv)	**2a** (equiv)	Temperature (°C)	GC Yield (%)
1	2	6	8	−15	46
2	3	6	8	−15	64
3	4	6	8	−15	45
4	3	3	8	−15	43
5	3	5	8	−15	44
6	3	7	8	−15	48
7	3	6	4	−15	60
8	3	6	12	−15	56
9	4	6	8	−5	25
10	4	6	8	−10	35

Reaction conditions: azulene (3.9 mmol), NMP (25 mL), under N_2 atmosphere.

Table 2
Mg-promoted regioselective coupling of azulene (**1**) and α,β-unsaturated carbonyl compounds **2**



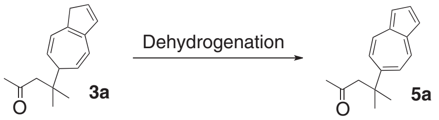
Entry		**2**		Isolated yield **3**[a] (%)
1	**2b**		**3b**	43[b]
2				0
3				0
4				0
5	**2c**		**3c**	41[b]
6	**2d**		**3d**	49[b]
7	**2e**		**3e**	54[b]
8	**2f**		**3f** and **4**	21[b,c]

[a] Neither significant regioisomer nor by-product was detected except entry 8. Olefinic position could not be examined in detail.
[b] A mixture of diastereomers.
[c] A mixture of 4- and 6- regioisomers. (**4** and **3f**, respectively).

Thus, Mg-promoted reduction of azulene (**1**) in the presence of 8 equiv of mesityl oxide (**2a**) and 6 equiv of chlorotrimethylsilane in 1-methyl-2-pyrrolidinone at −15 °C gave a single cross-coupling compound **3a** at the C6-position of **1** as shown in Table 1. The results of reductive coupling of **1** with various kinds of α,β-unsaturated carbonyl compounds under the similar reaction conditions are summarized in Table 2.

The structure of **3a** was determined by ^1H and ^{13}C NMR spectra. Coupling pattern and chemical shift of the signals of **3a** are quite similar to those of dihydroazulene given by Birch reduction of azulene.[24,25] Existence of alkyl group at the β-carbon atom towards the carbonyl carbon atom is essential to proceed this coupling reaction, and this reaction is not applicable to aliphatic esters or nitriles instead of ketones because of easy polymerization of the starting materials (entries 2–4). Cyclic ketones also reacted with azulene to give the corresponding 6-substituted dihydroazulenes in spite of steric hinderance (entries 5–7). Interestingly, only the reaction of 2-cyclopenten-1-one (**2f**) afforded a mixture of 4- and 6-regioisomers probably because three-dimensionally small size of **2f** minimized the steric effect between **2f** and hydrogen atom at C1-position of the azulene ring (entry 8).

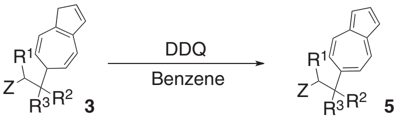
Table 3
Dehydrogenation of dihydroazulene **3a**



Entry	Method	Isolated Yield **5a** (%)
1[a]	DDQ/CH_2Cl_2	21
2[b]	DDQ/benzene	70
3[c]	*p*-Chloranil/Et_2O	20
4[d]	Air oxidation(bubbling)/benzene	-
5[e]	Pd/C/toluene(reflux)	-

[a] 0 °C to rt, 1 day.
[b] Substrate 0.88 mmol, DDQ 1.2 equiv, benzene 50 ml, 7 °C, 20 min.
[c] 0 °C to rt, 1 day.
[d] rt, 1 day.
[e] rt, 12 h.

Table 4
Synthesis of azulene **5** by dehydrogenation

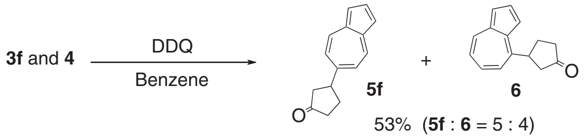


Entry	R^1	R^2	R^3	*Z*	Isolated yield **5** (%)	
1	H	CH_3	CH_3	CH_3CO	**5a**	70
2	CH_3	H	CH_3	CH_3CO	**5b**	41[a]
3	H	CH_3	$-CH_2C(CH3)_2CH_2CO-$		**5c**	52
4	H	H	$-CH_2CH_2CH_2CO-$		**5d**	78
5	H	CH_3	$-CH_2CH_2CO-$		**5e**	82

[a] A mixture of diastereomers (9:1).

Oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene turned out to be an efficient route to azulene **5a** from **3a** while neither air oxidation nor dehydrogenation by palladium–carbon afforded the corresponding azulene (Table 3). The results of dehydrogenation of **3a**–**e** are summarized in Table 4 and most of the dihydroazulenes were transformed into the corresponding azulenes in good to moderate yields.

The mixture of isomers **3f** and **4** was also oxidized under the similar reaction conditions to give the corresponding mixture of regioisomers **5f** and **6** in 53% yield. The 6-substituted isomer **5f** turned out to be a predominant product by isolation and analysis of the products (Scheme 1).



Scheme 1.