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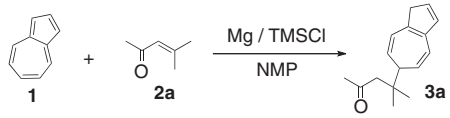
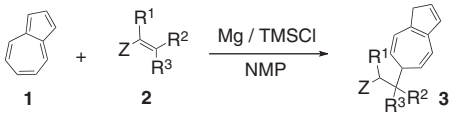
Table 1
Mg-Promoted coupling reaction of azulene (**1**) and mesityl oxide (**2a**)

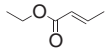


Entry	Mg (equiv)	TMSCl (equiv)	**2a** (equiv)	Temperature (°C)	GC Yield (%)
1	2	6	8	−15	46
2	3	6	8	−15	64
3	4	6	8	−15	45
4	3	3	8	−15	43
5	3	5	8	−15	44
6	3	7	8	−15	48
7	3	6	4	−15	60
8	3	6	12	−15	56
9	4	6	8	−5	25
10	4	6	8	−10	35

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**



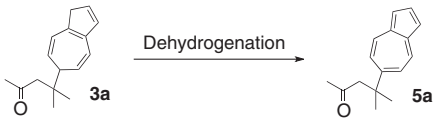
Entry	**2**		Isolated yield **3**[a] (%)	
1	**2b**		**3b**	43[b]
2				0
3				0
4				0
5	**2c**		**3c**	41[b]
6	**2d**		**3d**	49[b]
7	**2e**		**3e**	54[b]
8	**2f**		**3f** and **4**	21[b,c]

[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,

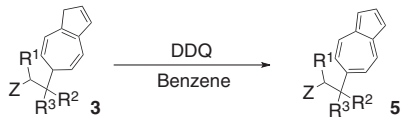
Table 3
Dehydrogenation of dihydroazulene **3a**



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



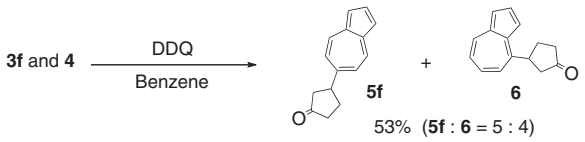
Entry	R^1	R^2	R^3	*Z*	Isolated yield **5** (%)	
1	H	CH_3	CH_3	CH_3CO	**5a**	70
2	CH_3	H	CH_3	CH_3CO	**5b**	41[a]
3	H	CH_3	$-CH_2C(CH3)_2CH_2CO-$		**5c**	52
4	H	H	$-CH_2CH_2CH_2CO-$		**5d**	78
5	H	CH_3	$-CH_2CH_2CO-$		**5e**	82

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

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).

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.

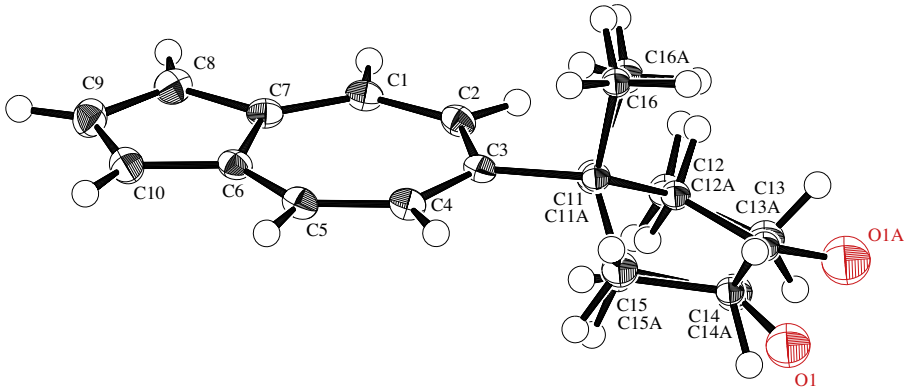
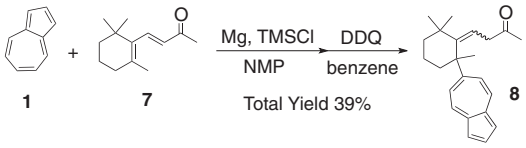
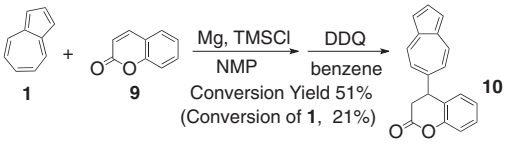


Figure 1. Chemical structure of **5e** by X-ray crystalline analysis.



Scheme 2.



Scheme 3.

The NMR spectra clearly supported symmetrical structure of those obtained azulene derivatives **5a**–**f**, which suggested regioselective synthesis of 2- or 6-substituted azulene. Finally, the structure of azulene racemate **5e** was confirmed by X-ray crystalline analysis, as shown in Figure 1.

Similarly, the coupling reaction of β-ionone, α,β,γ,δ-conjugated dienone (**7**), with azulene also regioselectively proceeded at the δ-carbon atom towards the carbonyl group among the three possible carbon atoms of **7**. Regioselective addition of conjugated dienone **7** to the C6-position of the azulene ring, followed by oxidation, also occurred to give a single product **8** (Scheme 2). In this case, isolation of dihydroazulene was quite difficult and the dihydroazulene was oxidized to the corresponding azulene promptly.

Furthermore, a coupling compound **10** was obtained in the similar reaction of **1** with coumarin (**9**), a typical aromatic α,β-unsaturated ester, while the conversion of **1** was quite low, compared with the reactions of aliphatic α,β-unsaturated compound (Scheme 3). The yield of **10** was calculated on the basis of the converted amount of **1**. It may be interesting to obtain different results between aliphatic α,β-unsaturated ester and aromatic one in the coupling with **1**.

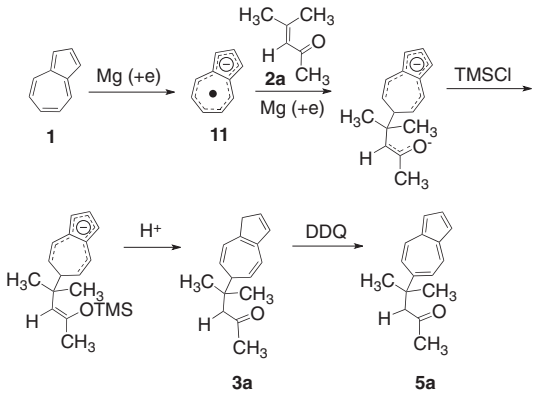
Application of guaiazulene instead of azulene to this coupling reaction with mesityl oxide gave no coupling compound probably because of the steric hindrance of alkyl groups of guaiazulene.

To clarify the reaction mechanism, reduction potential of the substrates was measured by cyclic voltammetry as shown in Table 5, indicating that azulene is much easily reduced than **2a.** Therefore, it may be reasonably postulated that the reaction between azulene and aliphatic α,β-unsaturated ketone is initiated

Table 5
Reduction potential of substrates by cyclic voltammetry

Substrate	Potential/V versus Ag/AgCl	Substrate	Potential/V versus Ag/AgCl
1	−1.58	**9**	−1.77
2a	−2.18	TMSCl	No wave (−3.0–0)

Working electrode, counter electrode: Pt, reference Electrode: Ag/AgCl, solvent: NMP, supporting electrolyte: Bu_4NClO_4, sweep rate: 100 mV/s.



Scheme 4.

by single electron transfer from magnesium to azulene. On the other hand, the difference of reduction potential between azulene **1** and coumarin **9** is not so large, and the reduction of **1** and **9** may occur competitively, therefore, the reaction is thought to proceed less selectively and ineffectively.

The plausible reaction mechanism is shown in Scheme 4. An anion radical species **11** derived from single electron transfer from magnesium to azulene attacks α,β-unsaturated ketone **2a** to give a coupling compound which is reduced by the second electron transfer from magnesium immediately. Azulene radical anion can be represented as a structure of **11** in which the negative charge is delocalized mainly in the five-membered ring and the unpaired electron is delocalized mainly in the seven-membered ring. Since the C4 or C8 position may be sterically influenced by the hydrogen

atom at the C1 or C3 position, respectively, **11** would undergo Michael addition to **2a** at C6-position in a selective manner. After silylation by chlorotrimethylsilane, followed by usual work-up, dihydroazulene **3a** was isolated and azulene **5a** was obtained through dehydrogenation by DDQ.

As a summary, Mg-promoted reduction of azulene in the presence of α,β-unsaturated ketone and chlorotrimethylsilane afforded 6-substituted dihydroazulenes in good yield[26] and the dihydroazulenes can be easily converted into the corresponding azulenes in good to moderate yields. This coupling reaction is a novel method for the regioselective synthesis of 6-substituted azulenes through electron transfer only in two steps, and also a novel carbon–carbon bond formation between electron-deficient carbon atoms at the same time. Further investigations on synthetic and mechanistic aspects of these reductive coupling reactions are now in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.080.

References and notes

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26. *General procedure for the coupling reaction of azulene and mesityl oxide.* A general procedure is as follows. Magnesium turnings (0.28 g, 11.5 mmol) for Grignard reagent with no pre-treatment in dry 1-methyl-2-pyrrolidinone (NMP) (20 ml) was placed in a 100 mL-four-necked flask and TMSCl (2.54 g, 23.4 mmol) was added dropwise. After activation of magnesium for 30 min, the mixture was cooled to −15 °C and a mixture of azulene (0.5 g, 3.9 mmol) and mesityl oxide (3.06 g, 31.2 mmol) in dry NMP (5 ml) was added dropwise and stirring was continued until azulene was consumed completely. Then the reaction mixture was poured into a mixture of water (10 ml), THF (50 ml) and *p*-toluenesulfonic acid mono-hydrate (1.2 g, 6.3 mmol) was added to the flask and the mixture was stirred for 30 minutes. The reaction mixture was extracted with ether three times. The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography to give **3a**. *4-(1,6-Dihydroazulenyl)-4-methylpentan-2-one (**3a**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.17 (6H, s), 1.38–1.41 (1H, m), 2.16 (3H, s), 2.53 (2H, s), 3.30–3.31 (2H, m), 5.17 (1H, dd, J = 6.4 Hz, 9.6 Hz), 5.28 (1H, dd, J = 6.4 Hz, 9.6 Hz), 6.38–6.40 (1H, m), 6.50–6.55 (2H, m), 6.64–6.63 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.07, 32.75, 34.54, 43.68, 48.51, 52.45, 117.37, 119.41, 122.90, 124.08, 131.95, 134.66, 143.96, 144.32, 208.85. IR (Neat): 3054, 2985, 2305, 1703, 1421, 1360, 1265, 1018, 956, 987, 735, 705 cm^{-1}. LRMS (EI) m/z: 228 [M$^+$]. HRMS (EI): Calculated for $C_{16}H_{20}O$, 228.1514, Found 228.1513.
27. Crystallographic data for the structural analyses of **5e** have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 883613). Copy of this information can be obtained free of charge via www.ccdc.cam.ac.uk.