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Tetrahedron Letters 45 (2004) 2891–2894

Tetrahedron Letters

Preparation of azulenyllithium and magnesium reagents utilizing halogen–metal exchange reaction of several iodoazulenes with organolithium or magnesium ate complex

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Received 14 January 2004; revised 10 February 2004; accepted 13 February 2004

Abstract—Preparation of several azulenyllithium and magnesium reagents was achieved by the halogen–metal exchange reaction of iodoazulenes with *n*-butyllithium or lithium tri(*n*-butyl)magnesate at low temperature and the synthetic application of the reagents was explored.

Organolithium and magnesium reagents are of great importance as synthetic tools. There are numerous reports for the preparation of various organolithium[1] and magnesium reagents[2] in the literature. However, little attention has been paid to the development of such reagents in the chemistry of azulene,[3] although the reagents tolerate the reaction with a wide range of electrophiles. Recently, the direct deprotonation and iodine–metal exchange reaction of 1,3-dihalo- and 2-iodo-1,3-dihaloazulenes has been reported to generate the corresponding 2-azulenyllithium and magnesium reagents with 1,3-dihalo substituents.[4]

However, the halogen–metal exchange reaction with a metallic reagent is still unexplored in azulene itself. With the aim of developing a new facile method for the functionalization of azulene, we investigated the iodine–metal exchange reaction of iodoazulenes using *n*-butyllithium (^{n}BuLi) and lithium tri(*n*-butyl)magnesate ($^n\mathrm{Bu_3MgLi}$), which has been recently reported to induce a facile halogen–magnesium exchange reaction with various aryl halides.[5] Herein, we report the preparation of several azulenyllithium and magnesium reagents, which should be of great importance as synthetic tools for the functionalization of azulene.

Preparation of 6-iodoazulene (**3**) was achieved by the halogen–halogen exchange reaction of diethyl 6-bromoazulene-1,3-dicarboxylate (**1**) followed by decarboxylation via diethyl 6-iodoazulene-1,3-dicarboxylate (**2**).[6] Initially, **3** was treated with ^{n}BuLi in ether at −100 °C and the subsequent addition of DMF to the reaction mixture afforded 6-azulenecarbaldehyde (**5a**)[7] in 32% yield as the sole product (Scheme 1) (Table 1, entry 1). The reaction showed neither recovery of the starting **3** nor the formation of parent azulene. The reaction of azulene derivatives with organolithium or magnesium reagents exhibits facile carbometalation reaction to produce 4- or 6-substituted 4*H*- or 6*H*-dihydroazulenides.[3] Thus, the relatively low yield of the expected **5a** should be attributed to the result on the iodine–lithium exchange reaction following the intermolecular carbolithiation reaction of the expected 6-azulenyllithium intermediate (**4a**) to exhibit the decomposition of the reagent under the reaction conditions.[8] In contrast, the magnesate reagent exhibited a

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Keywords: Azulene; Organolithium; Organomagesium ate complex; Halogen–metal exchange reaction; Nucleophilic reaction.

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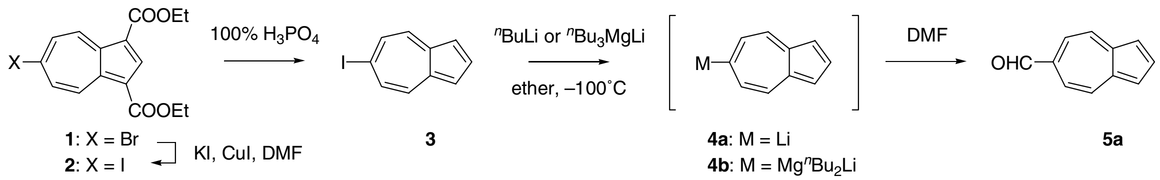
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.02.059



Scheme 1.

Table 1. Iodine–metal exchange reaction of iodoazulenes and the reaction with DMF[a]

Entry	Substrate	Reagent[b]	Temperature (°C)	R	Product	Yield (%)[c]	Reference
1	**3**	^{n}BuLi	−100	CHO	**5a**	32	7
2	**3**	^{n}Bu$_3$MgLi	−100	CHO	**5a**	90	
3	**6**	^{n}BuLi	−100	CHO	**8a**	89	11
4	**6**	^{n}Bu$_3$MgLi	−80	CHO	**8a**	99	
5	**10**	^{n}BuLi	−80	CHO	**12a**	82	12
6	**10**	^{n}Bu$_3$MgLi	−60	CHO	**12a**	95	

[a] The reaction of **3** (1 mmol), **6** (1 mmol), and **10** (1 mmol) with ^{n}BuLi (1.2 mmol) or ^{n}Bu$_3$MgLi (1.2 mmol) was carried out in ether (20 mL) for 30 min. The reaction was quenched by adding DMF (0.4–1 mL).

[b] Magnesium reagent was prepared by mixing ^{n}BuMgCl (0.84 or 0.90 M solution in THF) and ^{n}BuLi (1.6 M solution in hexane) in a 1:2 ratio in ether (10 mL) at 0 °C.

[c] All yields are isolated yields.

clean iodine–magnesium exchange reaction to afford 6-azulenylmagnesium reagent (**4b**), which reacted with DMF to give **5a** in high yield (entry 2).[†] The slow carbometalation characteristic of the magnesium reagents should be considered to be important for success of the halogen–metal exchange reaction of **3**.[9]

In contrast to the results on the reaction of **3**, satisfactory results were obtained when the metalation of 2-iodoazulene (**6**)[10] with ^{n}BuLi was conducted in ether at −100 °C. Subsequent reaction with DMF at the same temperature, followed by warming the mixture to room temperature, gave 2-azulenecarbaldehyde (**8a**)[11] in 89% yield as the sole product (Scheme 2) (entry 3). The iodine–magnesium exchange reaction of **6** utilizing ^{n}Bu$_3$MgLi is also efficient for the preparation of 2-azulenylmetal reagent (**7b**) (entry 4). Treatment of the reagent **7b** with DMF also afforded the expected **8a** in 99% yield.

1-Iodoazulene **10** prepared by the iodination of **9** was also tolerated in the halogen–metal exchange reaction with both ^{n}BuLi and ^{n}Bu$_3$MgLi, and the intermediary 1-azulenylmetal reagents **11a** and **11b** reacted with DMF to give 1-azulenecarbaldehyde **12a**[12] in high yields (Scheme 3) (entries 5 and 6).

The synthetic application to the functionalization of azulene was explored utilizing the azulenylmagnesium reagents (**4b**, **7b**, and **11b**) due to the clean conversion of the metalation step in all three substrates. The results on the reaction with several electrophiles are summarized in Table 2. The reaction of **4b**, **7b**, and **11b** with deuterium oxide gave 6-, 2-, and 1-dueterioazulenes (**5b**,[13] **8b**,[14] and **12b**) in 90—98% yields with high deuteration ratio (Table 2, entries 1–3), which provides the criterion of the high efficiency of the iodine–magnesium exchange reaction in iodoazulenes with ^{n}Bu$_3$MgLi. Under similar conditions, the reaction of **4b** and **7b** with chlorodiphenylphosphine also afforded the desired coupling product **5c** and **8c** in high yields (entries 4 and 5). The relatively low yield of the reaction of **11b** with chlorodiphenylphosphine to afford 1-azulenylphosphine **12c** should be attributed to the instability of the product with electron-rich phosphine owing to the substitution with the 1-azulenyl group (entry 6) (Schemes 4–6).

Boronate reagents represent an important class of synthetic intermediates for the transition-metal catalyzed cross-coupling reaction.[15] Recently, preparation of 2-azulenylboronate (**8d**) has been reported by the Pd-catalyzed cross-coupling reaction of **6** and the Ir-catalyzed direct introduction reaction of azulene with bis(pinacolato)diboron in 42% and 70% yields, respectively.[16] The iodine–magnesium exchange of **6** with ^{n}Bu$_3$MgLi followed by an addition of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane also furnished the desired boronate **8d** (entry 8). 6-Azulenylboronate

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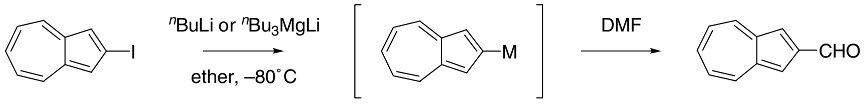
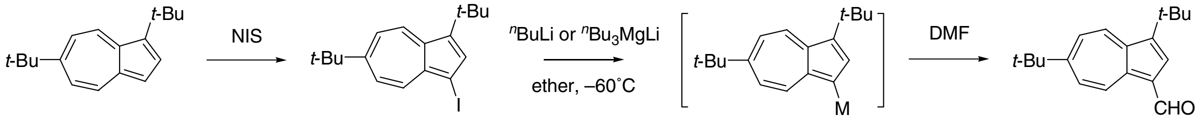
[†] A typical example: To a solution of ^{n}BuMgCl (1.3 mL, 0.90 M solution in THF) in ether (10 mL) was added ^{n}BuLi (1.5 mL, 1.6 M solution in hexane) at 0 °C, and the mixture was stirred for 10 min. After the mixture was cooled at −100 °C, a solution of 6-iodoazulene (**3**) (252 mg, 0.993 mmol) in ether (20 mL) was added dropwise. The mixture was allowed to react at the temperature for 30 min. To the cooled mixture was added dropwise DMF (0.35 mL, 4.5 mmol). The mixture was allowed to warm to room temperature to react for 1.5 h. The reaction was quenched with water, washed with NH$_4$Cl solution, and dried with MgSO$_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel with CH$_2$Cl$_2$ to afford **5a** (140 mg, 90%) as green prisms. Mp 58.0–58.5 °C (methanol) [lit.[7] mp 56 °C].



6 **7a**: M = Li **7b**: M = MgⁿBu$_2$Li **8a**

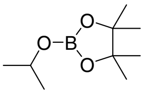
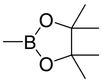
Scheme 2.



9 **10** **11a**: M = Li **11b**: M = MgⁿBu$_2$Li **12a**

Scheme 3.

Table 2. Reaction of azulenymagnesium reagents with electrophiles[a]

Entry	Substrate	Electrophile	R	Product	Yield (%)[b]	Reference
1	**3**	D_2O	D	**5b**	91 (99)[c]	13
2	**6**	D_2O	D	**8b**	90 (90)[c]	14
3	**10**	D_2O	D	**12b**	98 (100)[c]	
4	**3**	Ph_2PCl	PPh_2	**5c**	83	
5	**6**	Ph_2PCl	PPh_2	**8c**	81	
6	**10**	Ph_2PCl	PPh_2	**12c**	52[d]	
7	**3**			**5d**	55[e]	
8	**6**			**8d**	53	16
9	**10**			**12d**	90	
10	**3**	Bu_3SnCl	$SnBu_3$	**5e**	82	17
11	**6**	Bu_3SnCl	$SnBu_3$	**8e**	91	17
12	**3**	Allyl bromide	Allyl	**5f**	54[f]	
13	**6**	Allyl bromide	Allyl	**8f**	57[g]	
14	**10**	Allyl bromide	Allyl	**12e**	83	

[a] The reaction of **3** (1 mmol), **6** (1 mmol), and **10** (1 mmol) with ⁿBu_3MgLi (1.2–1.5 mmol) was carried out in ether (20 mL) for 30 min. The reaction was quenched by adding D_2O (0.1–1 mL) or other electrophiles (4.5 mmol) in ether (5 mL).

[b] All yields are isolated yields. All the reactions reported here did not show any recovery of the starting iodoazulenes.

[c] Deuteration ratio, which was shown in the parentheses, was determined by ^1H NMR spectra.

[d] Azulene was also obtained in 7% yields.

[e] Azulene was also obtained in 8% yields.

[f] 6-Butylazulene was also obtained in 8% yields.

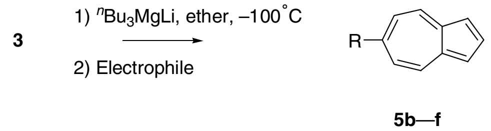
[g] 2-Butylazulene was also obtained in 6% yields.

5d was also obtained by a similar reaction of **3** (entry 7). 1-Azulenylboronate **12d** was also prepared by the reaction of **10** in high yield (entry 9).[‡]

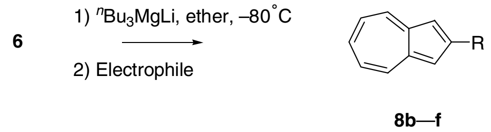
We have recently reported the preparation of 6-(tri-*n*-butylstannyl)azulene (**5e**) and its 1,3-diethoxycarbonyl derivative utilizing Pd-catalyzed direct stannylation of the corresponding 6-bromoazulenes. The reagents are applied to the Pd(0)-catalyzed Stille cross-coupling reaction with aryl, acyl, and/or azulenyl halides.[17] The extension of the methodology to the functionalization of azulene at the 2-position is hampered by the inefficiency of the preparation of 2-(tri-*n*-butylstannyl)azulene (**8e**) under the direct stannylation conditions. However, the iodine–magnesium exchange reaction of iodoazulenes **3** and **6** with ⁿBu_3MgLi followed by an addition of ⁿBu_3SnCl furnished the desired **5e** and **8e** in high yields (entries 10 and 11).[§]

[‡] Azulenylboronate **12d** showed facile hydrolysis to give **9** in 79% yield. Isolation of **12d** was achieved by using column chromatography on Bio-Beads® S-X3 with CH_2Cl_2.

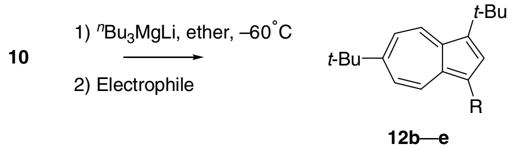
[§] Compound **8e** prepared by this reaction showed facile hydrolysis to give azulene by column chromatographic purification utilizing silica gel, although 6-(tri-*n*-butylstannyl) derivative **5e** was stable under the conditions. Isolation of **8e** was possible to use column chromatography on Al_2O_3.



Scheme 4.



Scheme 5.



Scheme 6.

Finally, we demonstrated the use of the new azulenylmagnesium reagents in the synthesis of allylazulenes. As expected, the reaction of **4b**, **7b**, and **11b** with allyl bromide afforded the expected allylazulenes **5f**, **8f**, and **12e** in good yields (entries 14–16). In the case of the reaction of **3** and **6** afforded 6- and 2-butylazulenes in 8% and 6% yields, respectively, as a side reaction.

We have demonstrated that organolithium or magnesium ate complex induces facile halogen–magnesium exchange of iodoazulenes **3**, **6**, and **10**; the only exception was the reaction of **3** with ^{n}BuLi. The high reactivity of the azulenylmagnesium reagents **4b**, **7b**, and **11b** formed by the halogen–metal exchange reaction with a variety of organic electrophiles, provided an efficient method for functionalization of azulene. The widespread use of boronate and tin reagents produced by this reaction also should provide an efficient method for functionalization of azulene in various metal-catalyzed C–C bond-forming reactions.

Acknowledgements

The present work was supported by a Grant-in-Aid for Scientific Research (No. 14540486 to S.I.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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