New Two-Step Synthesis of Azulene-1-carboxylic Esters Using Lithium Trimethylsilyldiazomethane

Yoshiyuki Hari, Shunkichi Tanaka, Yasuta Takuma, Toyohiko Aoyama*

Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya 467-8603, Japan
Fax +81(52)8363439; E-mail: aoyama@phar.nagoya-cu.ac.jp

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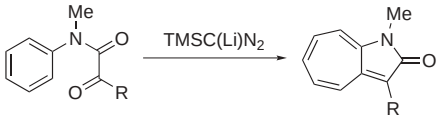
Abstract: Lithium trimethylsilyldiazomethane successfully reacted with various ethyl or *tert*-butyl 4-aryl-2-oxobutanoates to yield 2,3-dihydroazulene-1-carboxylic esters via alkylidene carbene intermediates, and the resulting 2,3-dihydroazulenes were easily converted to the corresponding azulene-1-carboxylic esters by oxidation with chemical manganese dioxide.

Key words: alkylidene carbenes, azulenes, chemical manganese dioxide, diazo compounds, lithium trimethylsilyldizaomethane

Azulenes are the most representative nonbenzenoid aromatic compounds and have not only beautiful colors but also attractive features such as pharmacological activities and electronic properties.[1] Therefore, many methods for the synthesis of azulenes have been developed to date;[2] however, few synthetic methods of azulenes via expansion of an aromatic ring have been reported.[3]

We have already demonstrated that the lithium salt of trimethylsilyldiazomethane [TMSC(Li)N_2], prepared from TMSCHN_2 with LDA or *n*-BuLi, is quite useful as a reagent for generating alkylidene carbenes from carbonyl compounds.[4] For instance, TMSC(Li)N_2 smoothly reacts with *N*-methylanilides of α-keto acids to give cyclohepta[*b*]pyrrol-2-ones via alkylidene carbene intermediates in good yields (Scheme 1).[5] We considered that this reaction involving the construction of a seven-membered ring by expansion of the benzene rings would be applicable to the synthesis of 2,3-dihydroazulenes bearing substitutents on the seven-membered ring if 4-aryl-2-oxobutanoic esters were used as substrates.[3] We here describe a two-step synthesis of azulene-1-carboxylic esters by the reaction of various 4-aryl-2-oxobutanoic esters with TMSC(Li)N_2 followed by oxidation of the resulting 2,3-dihydroazulenes with chemical manganese dioxide (CMD).[6]

First, we investigated the reaction of TMSC(Li)N_2 with commercially available ethyl 4-phenyl-2-oxobutanoate (**1a**) and found that TMSC(Li)N_2 reacted with **1a** in Et_2O to give the desired ethyl 2,3-dihydroazulene-1-carboxylate (**2a**) in 42% yield as a labile oil (entry 1 in Table 1).[7] In this reaction, LDA as a base was more effective than *n*-BuLi (entries 1 and 3). Et_2O was found to be the solvent of choice though THF could be used (entries 1 and 2).[8] Two equivalents of TMSC(Li)N_2 were required to smoothly conduct the reaction (entries 1 and 4).[9] In this reaction, there is the possibility that the reaction of TMSC(Li)N_2 with an ester moiety of **1a** competes with that with a ketone moiety. Therefore, the ethyl ester of **1a** was replaced by the more bulky *tert*-butyl ester.[10] As a result, *tert*-butyl ester **1b** successfully gave the desired dihydroazulene **2b** in 60% yield though prolonged reaction time was required (entry 5). Unfortunately, the reaction with a methyl ketone or 2-oxoamide, such as 4-phenyl-2-oxobutane or *N*,*N*-dimethyl-4-phenyl-2-oxobutanamide,[11] gave a complex mixture and the corresponding dihydroazulenes could not be detected. These results indicate that an ester group in **1** is essential in this reaction.



Scheme 1

Under optimized reaction conditions (entry 5 in Table 1), various *tert*-butyl 4-aryl-2-oxobutanoates (**1c**–**f**) also gave the corresponding *tert*-butyl 2,3-dihydroazulene-1-carboxylates (**2c**–**f**) in good to moderate yields. It is worthy of comment that the reaction was considerably affected by substituents on the benzene ring of **1**. Thus, when R^2 groups were electron-donating groups such as methyl (**1c**) and methoxy groups (**1d**), the reaction smoothly proceeded to give the corresponding **2c** (72%) and **2d** (76%), respectively (entries 6 and 7). On the contrary, substitutions of electron-withdrawing groups such as chloro and trifluoromethyl groups decreased the yields (34% for **2e** and 19% for **2f**, entries 8 and 9). These phenomena may be explained as follows: an alkylidene carbene intermediate, which is generated in situ by the reaction of TMSC(Li)N_2 and **1**, is an electron deficient species; therefore, the addition of an alkylidene carbene to a benzene ring with high electron density smoothly proceeds to give **2** in good yields (Scheme 2).

It is well known that alkylidene carbenes undergo the intramolecular 1,5-C-H insertion reaction giving cyclopentene derivatives.[12,13] Therefore, the competitive reaction of *tert*-butyl 4-phenyl-2-oxopentanoate **1g**[14] via the 1,5-C-H insertion and the addition to a benzene ring was examined (Scheme 3). Interestingly, the reaction preferentially gave the 2,3-dihydroazulene analogue **2g** (47%) as

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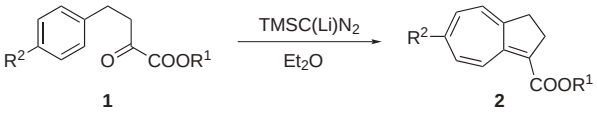
Table 1 Synthesis of 2,3-Dihydroazulene by Reaction of TMSC(Li)N_2 with Ethyl- or *tert*-Butyl 4-Aryl-2-oxobutanoates

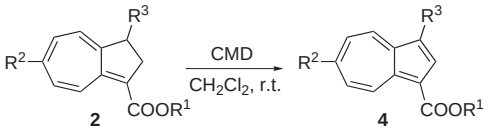


1 2

Entry	Substrate	TMSC(Li)N_2 (equiv)[b]	Conditions	Yield (%)
1	R^1 = Et, R^2 = H (**1a**)	1.2	–78 °C, 2 h → reflux, 2 h	42 (**2a**)
2[a]	**1a**	1.2	–78 °C, 2 h → reflux, 2 h	38 (**2a**)
3	**1a**	1.2[c]	–78 °C, 2 h → reflux, 2 h	32 (**2a**)
4	**1a**	2.0	–78 °C, 2 h → reflux, 2 h	49 (**2a**)
5	R^1 = *t*-Bu, R^2 = H (**1b**)	2.0	–78 °C, 3 h → reflux, 7 h	60 (**2b**)
6	R^1 = *t*-Bu, R^2 = Me (**1c**)	2.0	–78 °C, 3 h → reflux, 7 h	72 (**2c**)
7	R^1 = *t*-Bu, R^2 = OMe (**1d**)	2.0	–78 °C, 3 h → reflux, 7 h	76 (**2d**)
8	R^1 = *t*-Bu, R^2 = Cl (**1e**)	2.0	–78 °C, 3 h → reflux, 7 h	34 (**2e**)
9	R^1 = *t*-Bu, R^2 = CF_3 (**1f**)	2.0	–78 °C, 3 h → reflux, 7 h	19 (**2f**)

[a] THF was used as a solvent.
[b] TMSC(Li)N_2 was prepared from LDA and $TMSCHN_2$ (1:1)
[c] TMSC(Li)N_2 was prepared from *n*-BuLi and $TMSCHN_2$ (1:1).

Table 2 Oxidation of 2,3-Dihydroazulene-1-carboxylic Esters by CMD



2 4

Entry	Substrate	CMD (equiv)	Time (h)	Yield (%)
1	R^1 = Et, R^2 = R^3 = H (**2a**)	20	21	81 (**4a**)
2	R^1 = *t*-Bu, R^2 = R^3 = H (**2b**)	20	21	40 (**4b**)
3	**2b**	40	6	52 (**4b**)
4	R^1 = *t*-Bu, R^2 = Me, R^3 = H (**2c**)	40	6	64 (**4c**)
5	R^1 = *t*-Bu, R^2 = OMe, R^3 = H (**2d**)	40	6	71 (**4d**)
6	R^1 = *t*-Bu, R^2 = Cl, R^3 = H (**2e**)	40	6	68 (**4e**)
7	R^1 = *t*-Bu, R^2 = CF_3, R^3 = H (**2f**)	40	6	49 (**4f**)
8	R^1 = *t*-Bu, R^2 = H, R^3 = Me (**2g**)	40	0.2	74 (**4g**)

the sole isolable product and the cyclopentene **3** could not be detected.

Finally, oxidation of the resulting dihydroazulenes **2** to azulenes **4** by CMD was examined.[15,16] As shown in Table 2, the ethyl ester **2a** was easily converted to the desired azulene-1-carboxylic ester **4a** in 81% yield (entry 1). Under the same reaction conditions, the *tert*-butyl ester **2b** also gave **4d**, though the yield was low. However, the use of large excess of CMD led to significant improvement of the yield (52%) with shortened reaction time (entries 2 and 3). Analogously, CMD oxidation of the other substrates **2c**–**g** also gave the corresponding azulenes **4c**–**g** in good to moderate yields (entries 4–8).

In conclusion, the two-step synthesis of azulene-1-carboxylic esters from 4-aryl-2-oxobutanoic esters by using TMSC(Li)N_2 was achieved. This route allowed us to synthesize azulene analogues bearing substituents on both the seven- and five-membered rings, and will provide added flexibility in the azulene synthesis.

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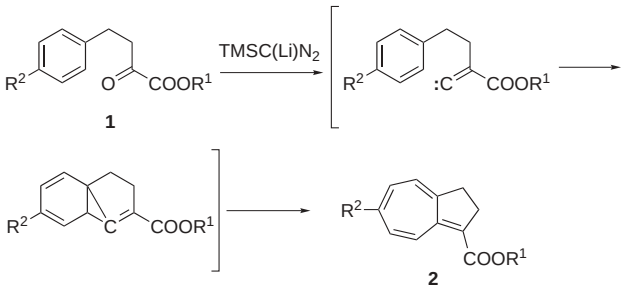
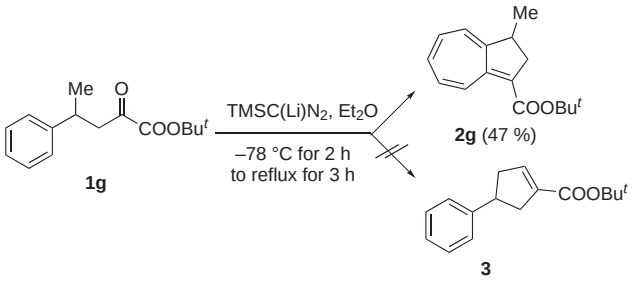


Scheme 2



Scheme 3

Acknowledgment

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(7) Selected data for the synthesized azulene analogues **2a**–**g**. Compound **2a**: ^{1}H NMR ($CDCl_3$): δ = 1.27 (3 H, d, *J* = 7 Hz), 2.63 (4 H, s), 4.17 (2 H, q, *J* = 7 Hz), 5.80–6.03 (4 H, m), 7.40 (1 H, d, *J* = 12 Hz). HRMS (EI) calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0995. Compound **2b**: ^{1}H NMR ($CDCl_3$): δ = 1.48 (9 H, s), 2.58 (4 H, s), 5.74–5.97 (4 H, m), 7.33 (1 H, d, *J* = 12 Hz). HRMS (EI) calcd for $C_{15}H_{18}O_2$: 230.1307. Found: 230.1313. Compound **2c**: ^{1}H NMR (CD_2Cl_2): δ = 1.34 (9 H, s), 1.71 (3 H, s), 2.43 (4 H, s), 5.64–5.71 (2 H, m), 5.76 (1 H, d, *J* = 12 Hz), 7.18 (1 H, d, *J* = 12 Hz). HRMS (EI) calcd for $C_{16}H_{20}O_2$: 244.1463. Found: 244.1461. Compound **2d**: ^{1}H NMR (CD_2Cl_2): δ = 1.37 (9 H, s), 2.48 (4 H, s), 3.45 (3 H, s), 5.16 (1 H, d, *J* = 9 Hz), 5.71–5.81 (2 H, m), 7.36 (1 H, d, *J* = 13 Hz). HRMS (EI) calcd for $C_{16}H_{20}O_3$: 260.1410. Found: 260.1412. Compound **2e**: ^{1}H NMR (CD_2Cl_2): δ = 1.28 (9 H, s), 2.38 (4 H, s), 5.48 (1 H, d, *J* = 9 Hz), 5.76 (1 H, dd, *J* = 2, 13 Hz), 5.89 (1 H, dd, *J* = 2, 9 Hz), 7.09 (1 H, d, *J* = 13 Hz). HRMS (EI) calcd for $C_{15}H_{17}ClO_2$: 264.0917. Found: 264.0919. Compound **2f**: ^{1}H NMR (CD_2Cl_2): δ = 1.34 (9 H, s), 2.12 (1 H, t, *J* = 8 Hz), 2.59 (1 H, t, *J* = 8 Hz), 6.66 (1 H, d, *J* = 12 Hz), 7.02–7.31 (2 H, m), 11.30 (1 H, d, *J* = 12 Hz). HRMS (EI) calcd for $C_{16}H_{17}F_3O_2$: 298.1181. Found: 298.1183. Compound **2g**: ^{1}H NMR (CD_2Cl_2): δ = 1.20 (3 H, d, *J* = 7 Hz), 1.46 (9 H, s), 2.14–2.21 (1 H, m), 2.65–2.82 (2 H, m), 5.76–5.99 (4 H, m), 7.34 (1 H, d, *J* = 12 Hz). HRMS (EI) calcd for $C_{16}H_{20}O_2$: 244.1463. Found: 244.1461.

(8) When 1,2-dimethoxyethane was used as a solvent, the reaction gave a complex mixture.

(9) **Typical Procedure:** To a stirred solution of diisopropylamine (114 mg, 1.0 mmol) in Et_2O (4 mL) was added dropwise *n*-BuLi (1.56 M in hexane solution, 0.64 mL, 1.0 mmol) at –78 °C under N_2, and the mixture was stirred for 10 min. $TMSCHN_2$ (1.33 M *n*-hexane solution, 0.75 mL, 1.0 mmol) was further added dropwise, and the mixture was stirred for 20 min. A solution of **1b** (134 mg, 0.5 mmol) in Et_2O (1 mL) was added dropwise. The mixture was stirred at –78 °C for 3 h, then heated under reflux for 7 h. After being quenched with H_2O (3 mL) at 0 °C, the mixture was extracted with EtOAc (30 mL × 3). The organic extracts were washed with H_2O (80 mL) and sat. brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane:Et_2O = 20:1) to give **2b** (68 mg, 60%) as a brown wax.

(10) *tert*-Butyl 4-aryl-2-oxobutanoates **1c**–**f** were prepared by the reaction of 2-arylethylmagnesium bromides, prepared from 2-arylethyl bromides and magnesium, with di-*tert*-butyl oxalate according to the literature on the synthesis of **1b**, see: Dao D. H., Kawai Y., Hida K., Hornes S., Nakamura K., Ohno A.; *Bull. Chem. Soc. Jpn.*; **1998**, *71*: 425

(11) This compound was prepared from hydrolysis of **2a** followed by condensation with dimethylamine.

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(13) First report on the cyclopentene synthesis by the reaction of ketones with $TMSC(Li)N_2$, see: Ohira, S.; Okai, K.; Moritani, T. *Chem. Commun.* **1992**, 721.

(14) This compound was prepared by the reaction of a Grignard reagent, prepared from 2-phenyl-1-propyl bromide and magnesium, with di-*tert*-butyl oxalate.

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(15) **Typical Procedure:** A mixture of **2b** (59 mg, 0.26 mmol), CMD (890 mg, 40 equiv) in CH_2Cl_2 (3 mL) was stirred for 6 h. The mixture was filtered through a pad of Celite® and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane:EtOAc = 30:1) to give **4b** (31 mg, 52%) as a violet wax.

(16) Selected data for the synthesized azulene analogues **4a**–**g**. Compound **4a**: ^{1}H NMR ($CDCl_3$): δ = 1.45 (3 H, t, *J* = 7 Hz), 4.43 (2 H, d, *J* = 7 Hz), 7.30 (1 H, d, *J* = 4 Hz), 7.44 (1 H, t, *J* = 10 Hz), 7.55 (1 H, t, *J* = 10 Hz), 7.80 (1 H, t, *J* = 10 Hz), 8.38 (1 H, d, *J* = 4 Hz), 8.46 (1 H, d, *J* = 10 Hz), 9.66 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{13}H_{12}O_2$: 200.0837. Found: 200.0837. Compound **4b**: ^{1}H NMR ($CDCl_3$): δ = 1.67 (9 H, s), 7.27 (1 H, d, *J* = 7 Hz), 7.41 (1 H, t, *J* = 10 Hz), 7.50 (1 H, t, *J* = 10 Hz), 7.76 (1 H, t, *J* = 10 Hz), 8.33 (1 H, d, *J* = 4 Hz), 8.43 (1 H, d, *J* = 10 Hz), 9.63 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{15}H_{16}O_2$: 228.1150. Found: 228.1148. Compound **4c**: ^{1}H NMR ($CDCl_3$): δ = 1.65 (9 H, s), 2.71 (3 H, s), 7.18 (1 H, d *J* = 4 Hz), 7.31 (1 H, d, *J* = 10 Hz), 7.40 (1 H, d, *J* = 10 Hz), 8.20 (1 H, d, *J* = 4 Hz), 8.28 (1 H, d, *J* = 10 Hz), 18.92 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{16}H_{18}O_2$: 242.1307. Found: 242.1316. Compound **4d**: ^{1}H NMR ($CDCl_3$): δ = 2.07 (9 H, s), 4.00 (3 H, s), 6.81–6.87 (2 H, m), 7.00–7.15 (1 H, m), 8.04 (1 H, d, *J* = 4 Hz), 8.28 (1 H, d, *J* = 11 Hz), 9.48 (1 H, d, *J* = 11 Hz). HRMS (EI) calcd for $C_{16}H_{18}O_3$: 258.1256. Found: 258.1258. Compound **4e**: ^{1}H NMR ($CDCl_3$): δ = 1.65 (9 H, s), 7.28 (1 H, d *J* = 4 Hz), 7.51 (1 H, dd, *J* = 2, 10 Hz), 7.60 (1 H, dd, *J* = 2, 11 Hz), 8.23 (1 H, d, *J* = 10 Hz), 8.28 (1 H, d, *J* = 4 Hz), 9.43 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{15}H_{15}ClO_2$: 262.0761. Found: 262.0766. Compound **4f**: ^{1}H NMR ($CDCl_3$): δ = 1.67 (9 H, s), 7.30–7.33 (1 H, m), 7.40 (1 H, d, *J* = 4 Hz), 7.67 (1 H, d, *J* = 10 Hz), 7.75 (1 H, d, *J* = 10 Hz), 8.48 (1 H, d, *J* = 4 Hz), 9.69 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{16}H_{15}F_3O_2$: 296.1024. Found: 296.1028. Compound **4g**: ^{1}H NMR ($CDCl_3$): δ = 1.65 (9 H, s), 2.62 (3 H, s), 7.34 (1 H, t, *J* = 10 Hz), 7.38 (1 H, t, *J* = 10 Hz), 7.71 (1 H, t, *J* = 10 Hz), 8.15 (1 H, s), 8.32 (1 H, d, *J* = 10 Hz), 9.53 (1 H, d, *J* = 10 Hz). HRMS (EI) calcd for $C_{16}H_{18}O_2$: 242.1307. Found: 242.1307.

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