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Peri-Selective Cycloaddition Reactions of 3-Methoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one with 6,6-Dimethylfulvene[1]

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The cycloaddition reaction of 3-methoxycabonyl-2*H*-cyclohepta[*b*]furan-2-one with 6,6-dimethylfulvene was carried out under refluxing in ethanol, benzene, or xylene. The [4+2] cycloadduct was formed as a major product in ethanol or benzene together with the minor [8+2] cycloadduct. On the other hand, the [8+2] cycloadduct was formed as a single product in xylene. The [4+2] cycloadduct was completely changed to the [8+2] cycloadduct under refluxing in xylene by a retro-Diels–Alder reaction, a re-cycloaddition reaction followed by spontaneous decarboxylation. The structure of the [8+2] cycloadduct was clearly confirmed by chemical transformation to methyl 3-isopropyl-1*H*-cyclopent[*a*]azulene-9-carboxylate which was obtained by the hydride reduction of methyl 3-isopropylidene-3*H*-cyclopent[*a*]azulene-9-carboxylate.

Previously, we reported the synthetic method of azulenes in excellent yields under mild conditions by the reaction of 2*H*-cyclohepta[*b*]furan-2-one (**1a**) with enamines.[2] Subsequently, this method was developed into a useful procedure for the synthesis of alkylazulenes by the reaction of 3-methoxycabonyl-2*H*-cyclohepta[*b*]furan-2-one (**1b**) with in situ generated enamines.[3]

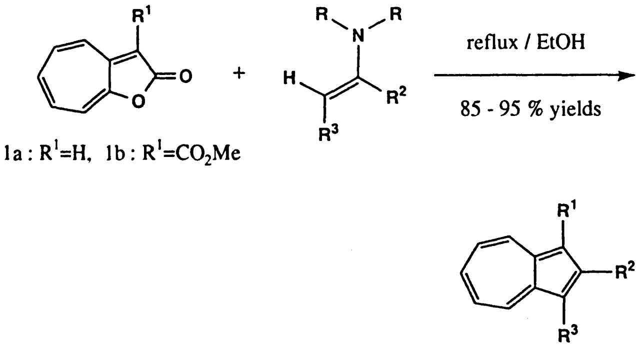


Chart 1.

After that, the cycloaddition reactions of **1b** with alkoxyethylenes were reported to give azulenes,[4] and the kinetically controlled cycloaddition reactions of **1a** with some dienophiles which were in accord with MO calculations were also reported.[5] Recently, it was found that the reaction of **1b** with silyl enol ethers derived from cycloalkanones and aryl methyl ketones also gave azulene derivatives in good yields.[6] In this paper, we would like to report the peri- and regio-selective cycloaddition reaction of **1b** with 6,6-dimethylfulvene (**2**).[1]

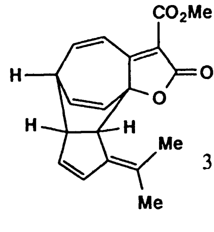
Results and Discussion

The cycloaddition reaction of **1b** with **2** was carried out in refluxing ethanol, benzene, or xylene (Scheme 1). The results are summarized in Table 1. The [4+2] cycloadduct (**3**) was formed as the major product in benzene or ethanol together with the [8+2] cycloadduct (**4**). On the other hand, the [8+2] cycloadduct (**4**) was formed as a single product in xylene.

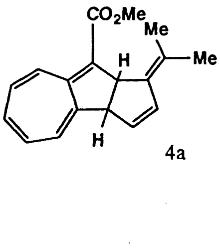
The structure of the [4+2] cycloadduct (**3**) was confirmed by spectral inspection, especially by the observation of NOE on ^{1}H NMR between H-6 and Me′ which ruled out an isomeric structure (**3a**). The molecular ion mass spectrum of **4** suggested that the product was formed by the [8+2] cycloaddition reaction of **1b** with **2** followed by spontaneous decarboxylation. The observation of NOE on ^{1}H NMR of **4** between H-4 and Me′ indicated that the structure of **4** was not a regio-isomer (**4a**). The structure of **4** was confirmed by chemical methods as follows. The treatment of **4** with 100% phosphoric acid gave methyl 3-isopropyl-1*H*-cyclopent[*a*]azulene-9-carboxylate (**5**) (Scheme 2). Compound **5** was also obtained by sodium borohydride reduction of methyl 3-isopropylidene-3*H*-cyclopent[*a*]azulene-9-carboxylate (**6**) which was synthesized by the base-catalyzed condensation reaction of methyl 3*H*-cyclopent[*a*]azulene-9-carboxylate with acetone.[7] Thus,

Table 1. Yields of **3** and **4** on the Reaction of **1b** and **2**

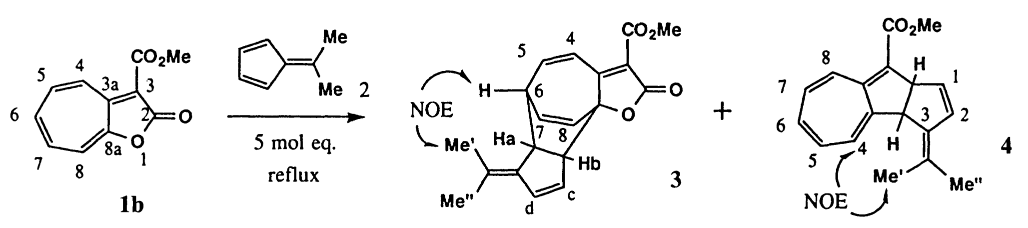
Solvent	Reaction time (h)	Product yield (%)		Recovd. (%)
		3	**4**	**1b**
Xylene	25.5		35.0	—
Benzene	24.0	28.0	21.0	38.0
Ethanol	27.0	44.1	16.5	35.8



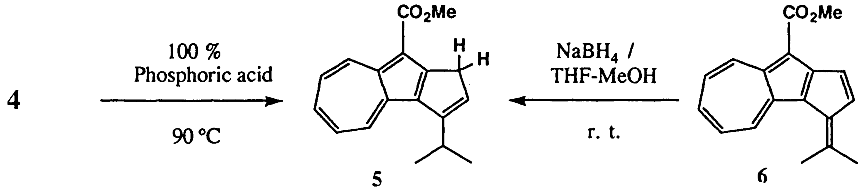
3a



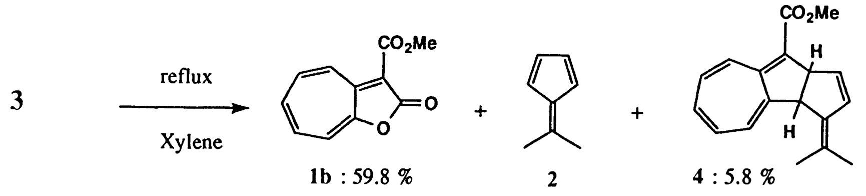
4a



Scheme 1.



Scheme 2.



Scheme 3.

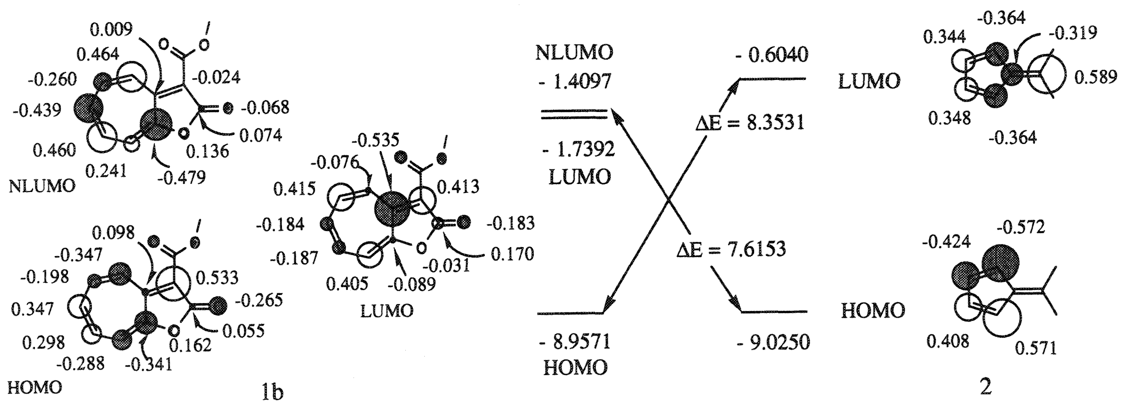


Fig. 1. Molecular orbital correlation diagrams of **1b** and **2**.

the structure of the [8+2] cycloadduct (**4**) was chemically confirmed.

Products **3** and **4** were stable in refluxing benzene or ethanol, respectively. However, the [4+2] cycloadduct (**3**) was completely changed in refluxing xylene solution to give **1b** (59.8%), **4** (5.8%), and **2**. This fact indicated that the retro-Diels–Alder reaction of **3** occurred under conditions to give **1b** and **2**, and their subsequent [8+2] re-cyclization, accompanied by irreversible decarboxylation, occurred to give **4**.

The MNDO PM3 calculations were carried out using MOPAC version 6 and the results are shown in Fig. 1.[8] In the case of the [8+2] cycloaddition reaction of **1b** with **2**, only the interaction of HOMO(**1b**) with LUMO(**2**) was symmetry allowed.

In the case of the [4+2] cycloaddition reaction, the interactions of NLUMO(**1b**)–HOMO(**2**), LUMO(**1b**)–HOMO(**2**), and HOMO(**1b**)–LUMO(**2**) were symmetry allowed. The interaction of LUMO(**1b**)–HOMO(**2**) was unimportant because of the small coefficients at the 6- and 8a-positions of LUMO(**1b**). The energy gap of NLUMO(**1b**)–HOMO(**2**) was considerably smaller than that of HOMO(**1b**)–LUMO(**2**). Therefore, the interaction of NLUMO(**1b**) with HOMO(**2**) controlled the [4+2] cycloaddition reaction to give **3**, which was a Diels–Alder reaction with inverse electron demand.

The smaller energy gap of NLUMO(**1b**)–HOMO(**2**) compared with of HOMO(**1b**)–LUMO(**2**) indicated that the [4+2] cycloaddition reaction was prior to the [8+2] cycloaddition reaction. However, the retro-Diels–Alder reaction of the cycloadduct (**3**) occurred at high temperatures such as refluxing in xylene, and then the [8+2] cycloaddition reaction was followed by irreversible decarboxylation to give **4**.

The coefficients of the molecular orbitals which controlled the cycloaddition reaction of **1b** with **2** could not clearly indicate regio-selectivity. The steric hindrance of the methyl group of **2** dominated the regio-selectivity of the cycloaddition reaction.

Experimental

General. Melting points were determined with a Yamato Model-MP21 melting point apparatus. Microanalyses were performed at the Instrumental Analysis Center of Chemistry, Faculty of Science, Tohoku University. NMR spectra were recorded on an EM-390 (^{1}H) or Varian XL-200 (^{1}H & ^{13}C), and chemical shift values are given in δ (ppm) relative to internal tetramethylsilane. Infrared, ultraviolet, and mass spectra were recorded on a Hitachi Model 260-30, a Hitachi Model 323, and a Hitachi M-50 spectrometers, respectively.

The Cycloaddition Reactions of 3-Methoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one with 6,6-Dimethylfulvene in Various Solvents. a) Reaction in Ethanol. 6,6-Dimethylfulvene (**2**) (6.4 g, 60.0 mmol, 6 mol eq) was added to a solution of 3-methoxycarbonyl-2*H*-cyclohepta[*b*]furan-2-one (**1b**) (2.05 g, 10.0 mmol) in ethanol (150 ml) and the mixture was refluxed for 3 h. After being cooled to room temperature, the solvent was removed under reduced pressure, then a small amount of benzene was added to the resulting oil. The separated precipitates were collected by filtration to give unchanged **1b** (0.73 g, 35.8% recovered). The filtrate was chromatographed on a silica-gel column eluted with benzene to give the [8+2] cycloadduct (**4**) (0.44 g, 16.5%) as red crystals. Further elution gave the [4+2] cycloadduct (**3**) (1.17 g, 44.1%) as pale yellow crystals.

3: Pale yellow plates (from ethyl acetate); mp 161.0—162.0 °C; UV (MeOH) 253.5 (logε 4.29) and 286 nm(4.13); IR (KBr) 1754, 1725, and 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.77(s, Me), 1.82(s, Me), 3.27(m, H-a,b), 3.63(broad dd, *J*=8.0 and 8.0 Hz, H-6), 3.92(s, OMe), 5.96(ddd, *J*=8.8, 1.0, and 1.0 Hz, H-8), 5.98(broad d, *J*=6.0 Hz, H-c), 6.21(dd, *J*=8.8 and 8.0 Hz, H-7), 6.53(dd, *J*=6.0 and 1.5 Hz, H-d), 7.05(dd, *J*=10.5 and 8.0 Hz, H-5), and 7.27(dd, *J*=10.5 and 1.0 Hz, H-4). Found: C, 73.18; H, 5.94%. Calcd for $C_{19}H_{18}O_2$: C, 73.53; H, 5.85%. MS *m*/*z* 310 (M^+, 0.8%), 204 (M^+—fulvene, 44.6%), and 173 (M^+—fulvene—OMe, 100%).

4: Dark red prisms (from ethyl acetate); mp 105.5—107.0 °C; UV (MeOH) 232(logε 4.39), 270(sh, 4.00), 376(4.15), 450(sh, 2.99), 480(sh, 2.85), and 520 nm(sh, 2.65); IR (KBr) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ=1.84(s, Me″), 1.92(s, Me′), 3.76(s, OMe), 3.95(broad d, *J*=7.0 Hz, H-9a), 4.12(d, *J*=7.0 Hz, H-3a), 5.94(broad d, *J*=6.5 Hz, H-1), 6.00—6.16(m, H-4, 5, 6, and 7), 6.46(dd, *J*=6.5 and 1.7 Hz, H-2), and 7.55(dd, *J*=12.5 and 1.0 Hz, H-8). Found: *m*/*z* 266.3390. Calcd for $C_{18}H_{18}O_2$: M, 266.1299.

b) Reaction in Benzene. 6,6-Dimethylfulvene (**2**) (650 mg, 6.1 mmol, 6 mol equiv) was added to a solution of **1b** (224 mg, 1.1 mmol) in benzene (16 ml) and the mixture was refluxed for 72 h. After being cooled to room temperature, the reaction mixture was chromatographed on a silica-gel column eluted with benzene to give the [8+2] cycloadduct (**4**) (61 mg, 21.0%) as red crystals. Further elution of the column with ethyl acetate gave a mixture of the unchanged **1b** and **3**. Rechromatography of this mixture on a reversed phase column (Merck, RP-18, Gross B) eluted with acetonitrile–water (7 : 3) gave **1b** (87 mg, 38.0%) followed by the [4+2] cycloadduct (**3**) (96 mg, 28.0%).

c) Reaction in Xylene. 6,6-Dimethylfulvene (**2**) (1.6 g, 15.1 mmol, 3 mol equiv) was added to a solution of **1b** (1.0 g, 4.9 mmol) in xylene (40 ml) and the mixture was refluxed for 25.5 h. After being cooled to room temperature, the solvent was removed under reduced pressure, then a small amount of benzene was added to the resulting oil. Precipitates formed were filtered off, and the filtrate was chromatographed on a silica-gel column eluted with benzene to give the [8+2] cycloadduct (**4**) (456.4 mg, 35%) as reddish crystals.

Preparation of Methyl 3-Isopropyl-1*H*-cyclopent[*a*]azulene-9-carboxylate (5). a) From the [8+2] Cycloadduct (4). The [8+2] cycloadduct (**4**) (40 mg, 0.15 mmol) was dissolved in 100% phosphoric acid (8 ml) and the mixture was heated at 95 °C for 10 min with occasional shaking. After being cooled to room temperature, the reaction mixture was poured into water, and extracted with benzene. The organic layer was dried over anhydrous $MgSO_4$, then the solvent was removed under reduced pressure. Chromatography of the resulting oil on a silica-gel column eluted with benzene gave the cyclopent[*a*]azulene derivative (**5**) (25.5 mg, 63.8%) as light green crystals.

5: Light green needles (from cyclohexane); mp 113.0—114.0 °C; UV (MeOH) 232(logε 4.23), 274.5(4.59), 285.5(4.62), 312(4.54), 322.5(4.53), 375(sh, 3.74), 398(3.93), 420(3.92), 550(2.68), and 592 nm(2.72); IR (KBr) 1692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.33(d, *J*=6.0 Hz, -CH$\underline{\mathrm{Me}}_2$), 3.12(dm, *J*=6.0 Hz, -C$\underline{\mathrm{H}}$Me$_2$), 3.50(dd, *J*=3.0 and 3.0 Hz, H-1), 3.93(s, -OMe), 6.20(m, H-2), 7.03—7.70(m, H-5, 6, and 7), 8.93(d, *J*=10.0 Hz, H-4), and 9.40(d, *J*=10.0 Hz, H-8). Found: C, 81.47; H, 6.99%. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.76%. MS *m*/*z* 267(M^++1, 17.1%), 266(M^+, 71.8%), and 223(M^+—isopropyl, 100%).

b) From Methyl 3-Isopropylidene-3*H*-cyclopent[*a*]azulene-9-carboxylate (6). $NaBH_4$ (145 mg, 3.8 mmol, 10 molar amounts) was added to a solution of **6** (1.0 g, 3.8 mmol) in THF(25 ml)–MeOH(5 ml) and the mixture was stirred at room temperature for 1 h. Water was then added to the reaction mixture and the mixture was extracted with benzene. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the resulting oil on a silica gel column eluted with benzene gave **5** (1 g, 99.1%). The compound (**5**) was identified with the sample obtained from the [8+2] cycloadduct (**4**) by comparison of their IR spectra.

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