

# Diels-Alder Reactions of Cyclohexadienes Derived from Decarboxylation of Photo[4 + 2]cycloadducts between 4,6-Dimethyl-2-pyrone and Cyclic Olefins

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Labile photo [4 + 2] adducts between 4,6-dimethyl-2-pyrone and cyclic olefins reacted with second olefins to give cross adducts, and with acetylenes to afford both bis-adducts and benzene derivatives with the concurrent decarboxylation, respectively. The reaction mechanism of the latter was considered.

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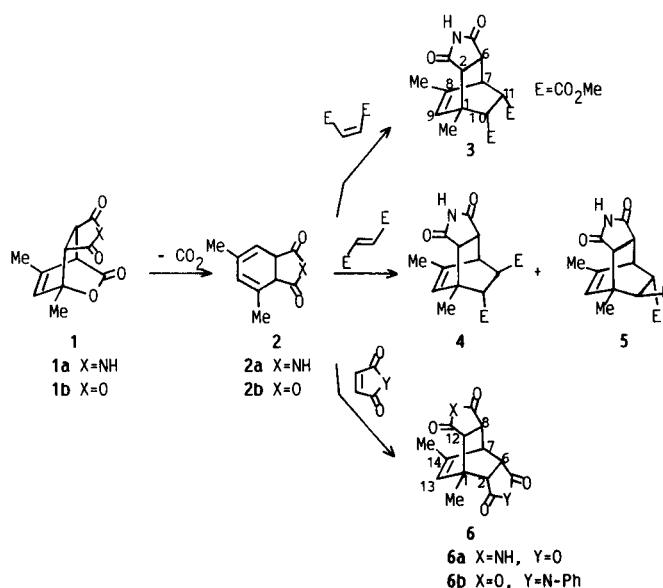
The Diels-Alder (DA) reactions of 2-pyrone and the continuous decarboxylations were used as key steps to synthesize interesting compounds, such as colchicine [1] and barbelene [2]. The DA adducts of 2-pyrone, which are cyclohexadiene equivalents by decarboxylation, may be also attractive starting materials for the preparation of polyfunctionalized bicyclo[2.2.2]octenes, bicyclo[2.2.2]octadienes and also stereocontrolled cyclohexanes by their continuous oxidation. We could isolate the labile photo [4 + 2] cycloadducts, **1a** and **1b**, from the low-temperature photoreaction of 4,6-dimethyl-2-pyrone with maleimide and maleic anhydride, respectively [3]. They were not obtained from the thermal reaction. As the 1:2 photoadduct of benzene and maleimide has been found to have very high anti-tumor activity and the clinical trials are being prepared [4], our reactions and 1:2 photoadducts are also interesting in pharmacological activity.

The present paper describes the DA reactions of the cyclohexadiene equivalents, **1a** and **1b**, with olefinic and acetylenic dienophiles.

The photo [4 + 2] adducts, **1a** and **1b**, were easily decarboxylated at 110° to give 1,2-dihydrocyclohexadienes, **2a** and **2b**, in 78% and 90% yields, respectively. No other products were obtained by additional heating. The diene equivalent **1a** directly reacted with dimethyl maleate in toluene under reflux to afford only product **3** in 13% yield together with the recovery of **2** (52%) (Scheme 1). The stereochemistry of **3** was assumed to be endo-endo configuration of the imide group and of 10-, 11-ester groups by considering the Alder-rule mechanistically. Similar reaction of **1a** with dimethyl fumarate gave a mixture of products **4** and **5** (*ca* 1:1 mixture) in 53% yield. As they did not have the same spectral data as **3**, the configurations of two methoxycarbonyl groups at the 10- and 11-positions in **4** and **5** were thought to be *trans*. Similarly, the adduct **1a** reacted with maleic anhydride in toluene under reflux to give a product **6a** in 70% yield. The adduct **1b** reacted

with *N*-phenylmaleimide in acetonitrile at 50° to give a product **6b** in 80% yield, whose structural elucidation was accomplished on the basis of spectral data. The endo-endo configuration of **6** was assumed by inspection of the <sup>1</sup>H-nmr spectral data at the positions of 2-, 6-, 10- and 11-H in comparison with the data of the endo-endo bis-adduct **9** mentioned below.

Scheme 1

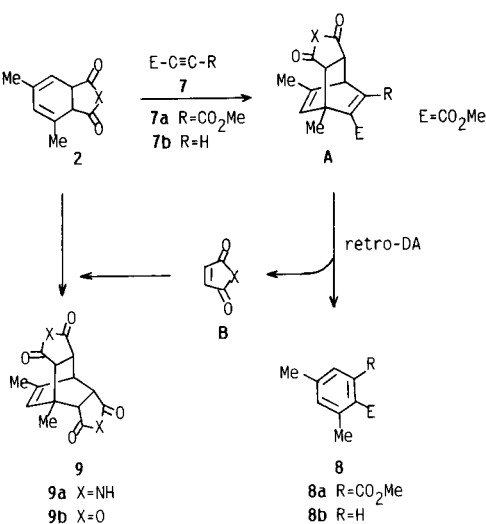


The adduct **1a** reacted with dimethyl acetylenedicarboxylate (**7a**) in acetonitrile under reflux to afford a bis-adduct **9a** and dimethyl 3,5-dimethylphthalate (**8a**) in 39% and 33% yields, respectively. But the similar reaction of **1a** without **7a** gave only **2a** in 80% yield. Similarly, the reaction of **1b** with **7a** gave a bis-adduct **9b** and **8a** in 35% and 42% yields, respectively. The endo-endo structure of **9** were assigned on the basis of <sup>1</sup>H-nmr spectral data showing the same chemical shifts of 6-H and 8-H, and of 2-H and 12-H, respectively.

Similarly, the adducts **1a** and **1b** reacted with methyl propiolate (**7b**) in toluene under reflux to afford a bis-adduct **9a** (41% yield) and methyl 2,4-dimethylbenzoate (**8b**) (38% yield), and a bis-adduct **9b** (31% yield) and **8b** (24% yield), respectively.

The novel reaction of **1** with **7** can be explained as shown in Scheme 2. Thus, **1** is readily decarboxylated under the reaction conditions to generate a 1,2-dihydrocyclohexadiene **2**. The DA reaction of **2** with **7** gives a labile DA adduct **A**, which undergoes retro-DA reaction to yield **8** and maleimide or maleic anhydride **B**. Since the formed **B** is more reactive than **7**, the cyclohexadiene **2** easily reacts with **B** to give **9**.

Scheme 2



## EXPERIMENTAL

All the melting points were measured on a Yanagimoto Meltemp apparatus and are uncorrected. The ir, <sup>1</sup>H-nmr and mass spectra were recorded on JASCO A-3, JEOL JNM-MH-100 (100 MHz), and JEOL JMS-OISG spectrometers, respectively. The <sup>1</sup>H-nmr spectra were recorded with TMS as an internal standard.

2,4-Dimethyl-8-azabicyclo[4.3.0]nona-2,4-diene-7,9-dione (**2a**) and 2,4-dimethyl-8-oxabicyclo[4.3.0]nona-2,4-diene-7,9-dione (**2b**).

1) After a solution of **1a** (85 mg, 0.38 mmole) in toluene (2 ml) was refluxed for 0.5 hour, the solvent was removed and the residue was recrystallized from chloroform to give **2a** (53 mg, 78%). 2) A solution of **1b** (30 mg, 0.14 mmole) in toluene (2 ml) was refluxed for 0.5 hour and then the solvent was removed to give **2b** (22 mg, 90%). Compound **2a** had mp 106-109°; ir (potassium bromide): 1770, 1705 cm<sup>-1</sup>; <sup>1</sup>H-nmr (deuteriochloroform): δ = 1.68, 1.98 (bs, 3H), 3.42 (d, 1H, J = 12.0 Hz), 3.70 (dd, 1H, J = 12.0, 3.0 Hz), 5.26 (bs, 1H), 5.53 (s, 1H), 8.90 (bs, 1H); ms: m/z (relative intensity) 177 (M<sup>+</sup>, 45), 106 (100).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.01; H, 6.30; N, 7.99.

Compound **2b** was obtained as an oil; ir (neat) 1860, 1790 cm<sup>-1</sup>; <sup>1</sup>H-nmr (deuteriochloroform): δ = 1.76, 2.00 (bs, 3H), 3.72 (dd,

1H, J = 12.0, 2.0 Hz), 4.04 (dd, 1H, J = 12.0, 5.0 Hz), 5.42 (bs, 1H), 5.80 (bs, 1H); ms: m/z (relative intensity) 178 (M<sup>+</sup>, 15), 90 (100).

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>3</sub>: C, 67.41; H, 5.66. Found: C, 67.20; H, 5.53.

10-endo, 11-endo-Dimethyl 1,8-Dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0<sup>2,6</sup>]undec-8-enedicarboxylate (**3**).

After a solution of **1a** (273 mg, 1.2 mmoles) and dimethyl maleate (199 mg, 1.4 mmoles) in toluene (10 ml) was refluxed for 52 hours, the reaction mixture was concentrated and recrystallized from benzene to give **3** (50 mg, 13%).

Compound **3** had mp 222-225°; ir (potassium bromide): 1745, 1710 cm<sup>-1</sup>; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ = 1.30, 1.81 (s, 3H, Me), 2.68 (d, 1H, J = 8.0 Hz, 2-H), 2.97 (d, 1H, J = 11.0 Hz, 10-H), 3.00 (dd, 1H, J = 8.0, 2.0 Hz, 6-H), 3.03 (m, 1H, 7-H), 3.27 (dd, 1H, J = 11.0, 2.0 Hz, 11-H) 3.46, 3.53 (s, 3H, CO<sub>2</sub>Me), 5.38 (bs, 1H, 9-H), 11.1 (bs, 1H, NH); ms: m/z (relative intensity) 321 (M<sup>+</sup>, 7), 106 (100).

*Anal.* Calcd. for C<sub>16</sub>H<sub>19</sub>NO<sub>6</sub>: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.51; H, 5.90; N, 4.30.

10-endo, 11-exo-Dimethyl 1,8-Dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0<sup>2,6</sup>]undec-8-enedicarboxylate (**4**) and 10-exo, 11-endo-Dimethyl 1,8-Dimethyl-3,5-dioxo-4-azatricyclo[5.2.2.0<sup>2,6</sup>]undec-8-enedicarboxylate (**5**).

A solution of **1a** (406 mg, 1.8 mmoles) and dimethyl fumarate (400 mg, 2.8 mmoles) in toluene (10 ml) was refluxed for 16 hours. The same work up mentioned above and recrystallization from toluene afforded an 1:1 mixture of **4** and **5** (304 mg, 53%) which was not able to separate to each compound.

The mixture of **4** and **5** had mp 145-148°; ir (potassium bromide): 1775, 1730, 1715 cm<sup>-1</sup>; <sup>1</sup>H-nmr (deuteriochloroform): δ = 1.46, 1.69, 1.78 (s, Me), 2.60 (d, J = 7.0 Hz, 2-H), 2.8-3.2 (m, 6-, 10-, 11-H), 3.40 (bs, 7-H), 3.66, 3.71 (s, CO<sub>2</sub>Me), 5.48, 5.56 (s, 9-H), 8.58 (bs, NH); ms: m/z (relative intensity) 321 (M<sup>+</sup>, 13), 106 (100).

*Anal.* Calcd. for C<sub>16</sub>H<sub>19</sub>NO<sub>6</sub>: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.40; H, 5.93; N, 4.32.

1,14-Dimethyl-4-oxa-10-azatetracyclo[5.5.2.0<sup>2,6</sup>.0<sup>8,12</sup>]tetradec-13-ene-3,5,9,11-tetraone (**6a**).

A solution of **1a** (304 mg, 1.4 mmoles) and maleic anhydride (139 mg, 1.4 mmoles) in toluene (10 ml) was refluxed for 2 hours. The same work up and recrystallization from acetonitrile gave **6a** (266 mg, 70%).

Compound **6a** had mp >300°; ir (potassium bromide): 1850, 1775, 1710 cm<sup>-1</sup>; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ = 1.62 (s, 6H, Me), 2.75 (d, 1H, J = 8.0 Hz, 12-H), 3.13 (d, 1H, J = 8.0 Hz, 2-H), 3.25 (dd, 1H, J = 8.0, 3.0 Hz, 8-H), 3.30 (bs, 1H, 7-H), 3.55 (dd, 1H, J = 3.0, 8.0 Hz, 6-H), 5.56 (bs, 1H, 13-H), 13.0 (bs, 1H, NH).

*Anal.* Calcd. for C<sub>14</sub>H<sub>13</sub>NO<sub>5</sub>: C, 61.04; H, 4.76; N, 5.09. Found: C, 61.35; H, 4.81; N, 5.25.

1,14-Dimethyl-10-phenyl-4-oxa-10-azatetracyclo[5.5.2.0<sup>2,6</sup>.0<sup>8,12</sup>]tetradec-13-ene-3,5,9,11-tetraone (**6b**).

A solution of **1b** (124 mg, 1.56 mmoles) and *N*-phenylmaleimide (150 mg, 0.89 mmole) in acetonitrile (20 ml) at 50° for 5 hours. The same work up mentioned above gave **6b** (160 mg, 80%).

Compound **6b** had mp 139-140°; ir (potassium bromide): 1850, 1780, 1710 cm<sup>-1</sup>; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ = 1.64 (s, 6H, Me), 3.04

(d, 1H, J = 8.0 Hz, 2-H), 3.26 (d, 1H, J = 10.0 Hz, 12-H), 3.34 (dd, 1H, J = 4.0, 3.5 Hz, 7-H), 3.44 (dd, 1H, J = 3.5, 8.0 Hz, 6-H), 3.71 (dd, 1H, J = 10.0, 4.0 Hz, 8-H), 5.73 (bs, 1H, 13-H), 7.20, 7.56 (m, PhH); ms: m/z (relative intensity) 351 (M<sup>+</sup>, 31), 106 (100).

*Anal.* Calcd. for C<sub>20</sub>H<sub>17</sub>NO<sub>5</sub>: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.28; H, 4.86; N, 4.06.

1,14-Dimethyl-4,10-diazatetracyclo[5.5.2.0<sup>2,6</sup>.0<sup>8,12</sup>]tetradec-13-ene-3,5,9,11-tetraone (**9a**).

After a solution of **1a** (250 mg, 1.1 mmoles) and dimethyl acetylenedicarboxylate (**7a**) (160 mg, 1.1 mmoles) in acetonitrile (10 ml) was refluxed for 10 hours, the reaction mixture was concentrated and recrystallized from dioxane to give **9a** (117 mg, 39%). The filtrate was chromatographed on silica gel using chloroform as an eluent to afford dimethyl 3,5-dimethylphthalate (**8a**) (80 mg, 33%).

Similar reaction of **1a** (208 mg, 0.94 mmole) with methyl propiolate (**7b**) (168 mg, 2.0 mmoles) in toluene (10 ml) for 8 hours gave methyl 2,4-dimethylbenzoate (**8b**) (59 mg, 38%) and **9a** (53 mg, 21%).

Compound **9a** had mp > 300°; ir (potassium bromide): 1770, 1702 cm<sup>-1</sup>; <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ = 1.60 (s, 6H, Me), 2.66 (d, 2H, J = 8.0 Hz, 2-, 12-H), 3.11 (bd, 2H, J = 8.0 Hz, 6-, 8-H), 3.13 (bs, 1H, 7-H), 5.48 (bs, 1H, 13-H), 11.10 (bs, 1H, NH); ms: m/z (relative intensity) 274 (M<sup>+</sup>, 12), 106 (100).

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.30; H, 5.14; N, 10.19.

1,14-Dimethyl-4,10-dioxatetracyclo[5.5.2.0<sup>2,6</sup>.0<sup>8,12</sup>]tetradec-13-ene-3,5,9,11-tetraone (**9b**).

A solution of **1b** (250 mg, 1.1 mmoles) and **7a** (160 mg, 1.1 mmoles) in acetonitrile (10 ml) was refluxed for 14 hours. The same work up mentioned above gave dimethyl 3,5-dimethylphthalate (**8a**) (102 mg, 42%) and **9b** (105 mg, 35%, mp 276-279°) (lit [5], mp 274°).

Similar reaction of **1b** (115 mg, 0.52 mmole) with **7b** (85 mg, 1.0 mmole) in toluene (8 ml) for 13 hours gave **8b** (21 mg, 25%) and **9b** (32 mg, 23%).

#### REFERENCES AND NOTES

- [1] J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961).
- [2] H. E. Zimmerman, G. L. Grunewald, R. M. Paufler and M. A. Sherwin, *J. Am. Chem. Soc.*, **91**, 2330 (1969).
- [3] T. Shimo, H. Yoshimura, H. Uemura, K. Somekawa and O. Tsuge, *Heterocycles*, **24**, 3031 (1986); *Chem. Abstr.*, **107**, 58783b (1987).
- [4] D. Bryce-Smith, *Photochemistry*, Vol **16**, D. Bryce-Smith eds, The Royal Society of Chemistry, London, 1985, p xix.
- [5] N. P. Shusherina, E. Ya. Vashakidze and R. Ya. Levina, *Zh. Org. Khim.*, **4**, 1291 (1968); *Chem. Abstr.*, **69**, 77055d (1968).