Chem. Pharm. Bull.
32(2) 538—542 (1984)

Intramolecular Photo[2+2]cycloaddition of 2-Alkenoyloxycyclohex-2-enones

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(Received June 15, 1983)

Photoirradiation of 2-(3-butenoyloxy)- and 2-(4-pentenoyloxy)cyclohex-2-enones resulted in the formation of 2-oxabicyclo[3.2.0]heptan-3-one and 2-oxabicyclo[4.2.0]octan-3-one derivatives (head-to-head adducts), respectively.

Keywords——intramolecular photo[2+2]cycloaddition; 2-oxabicyclo[3.2.0]heptane; 2-oxabicyclo[4.2.0]octane; Baeyer–Villiger oxidation; cyclobutanone; cyclohexane-1,2-dione

We have been investigating intramolecular photo[2+2]cycloaddition reactions of 2- and 3-alkenyloxycyclohex-2-enones (**1** and **2**), which give head-to-head or head-to-tail adducts, depending upon the number of the atoms between the two olefinic functions (Chart 1).[1-3] In general, the orientation of the intramolecular photo[2+2]cycloaddition can be explained in terms of the so-called "rule of five":[4] the initial formation of the five-membered ring biradical is preferred to that of possible six- and four-membered ring biradicals in terms of strain and entropy factors. Thus, in the 1,5-diene systems the preferred orientation is head-to-tail, while head-to-head addition is favored in the 1,6-dienes.[5] In this context, however, the formation of the head-to-tail adduct from **1** ($n=2$) as the major product takes on special interest, since this abnormal behavior of **1** ($n=2$) may be the result of operation of an electronic factor.[2] In order to clarify this point further, we have examined the photochemical behavior of 2-alkenoyloxycyclohex-2-enones and we now wish to report results obtained with 2-(3-butenoyloxy)- (**4**) and 2-(4-pentenoyloxy)cyclohex-2-enones (**11**).

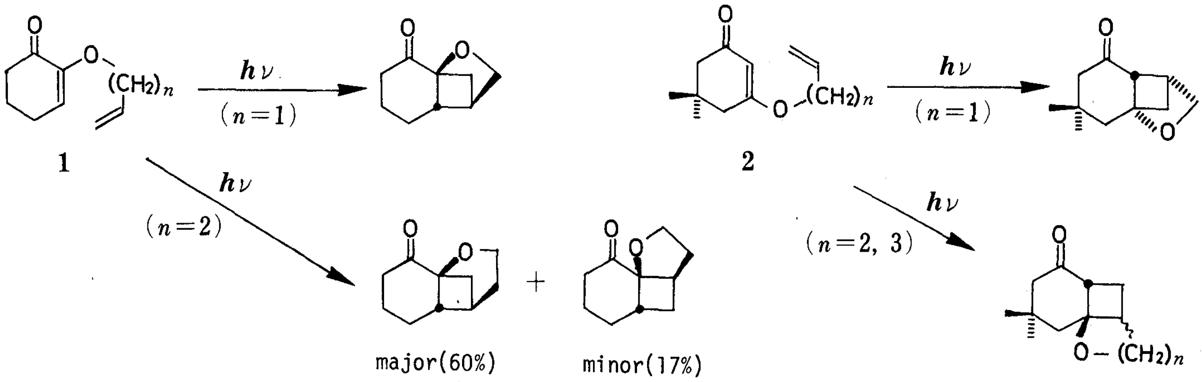


Chart 1

Compounds **4** and **11** were prepared in 58 and 44% yields by heating a solution of cyclohexane-1,2-dione (**3**) with 3-butenoyl chloride and 4-pentenoyl chloride in chloroform in the presence of pyridine at 50 °C.

Irradiation of **4** in acetone for a period of 3.5 h gave a single adduct **5** in 69% yield. The head-to-head structure of **5** was deduced from the infrared (IR) spectrum, which showed strong absorption at $1770\,\mathrm{cm}^{-1}$, typical of a five-membered lactone carbonyl group. This was further confirmed by transformation of **5** to the cyclobutanone **7**; Baeyer–Villiger oxidation of **5** with *m*-chloroperoxybenzoic acid (*m*-CPBA) gave a bislactone **6** which was subjected to methanolysis to give the cyclobutanone **7**. In the ^{1}H-nuclear magnetic resonance (NMR) spectrum, a two-proton multiplet due to the protons on the α-carbon atoms of the cyclobutanone ring was observed between δ 3.1 and 3.7.[6] In addition, the mass spectrum (MS) showed its base peak at m/z 114, corresponding to the $[O=C=CHCH_2CO_2Me]^+$ ion, as anticipated for the cyclobutanone structure **7**. The stereochemistry of **5** was defined by the following evidence. Sodium borohydride reduction of **5** afforded a single alcohol **8**. Mesylation of **8** followed by treatment of the resulting mesylate **9** with sodium methoxide in methanol gave an oxirane **10**. The formation of the oxirane **10** from **9** requires the stereochemical relationship of the mesyloxy group and C_1–O bond to be *trans*. In the NMR spectrum of **9** the C_2 proton α to the mesyloxy group appeared at δ 4.56 as a doublet of doublets with $J = 11$ and 6 Hz, indicating it to be axial, and thus the mesyloxy group to be equatorial.[7] An inspection of molecular models reveals that such stereochemistry can be attained only when the six- and four-membered rings are *cis*-fused.

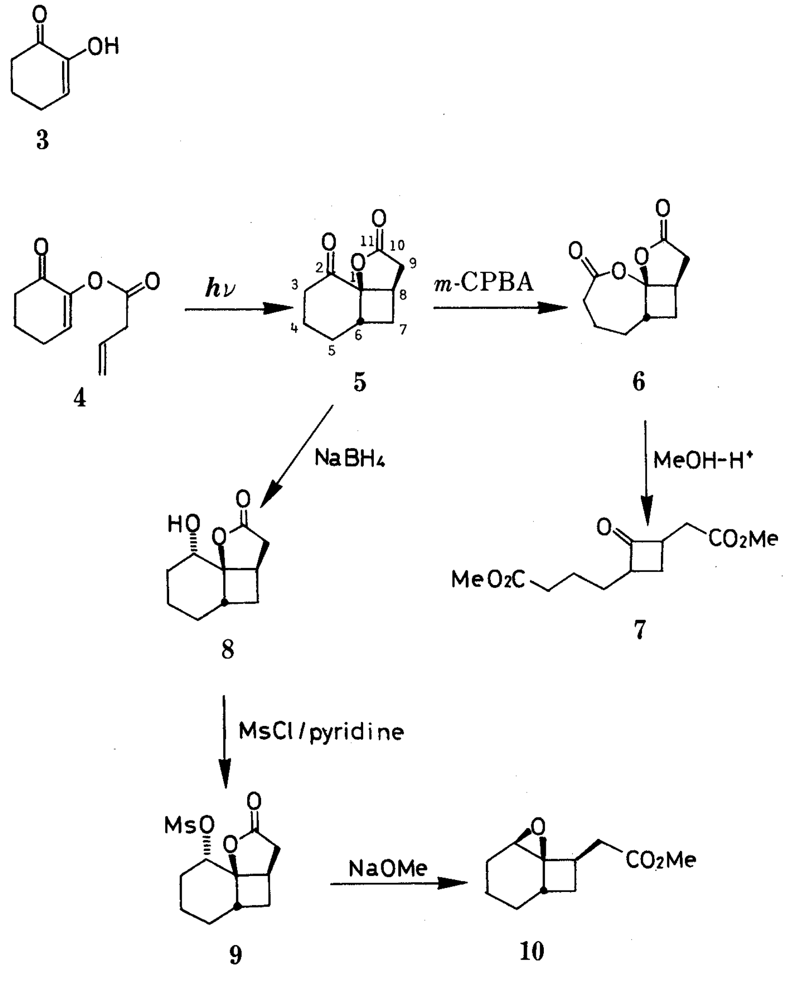
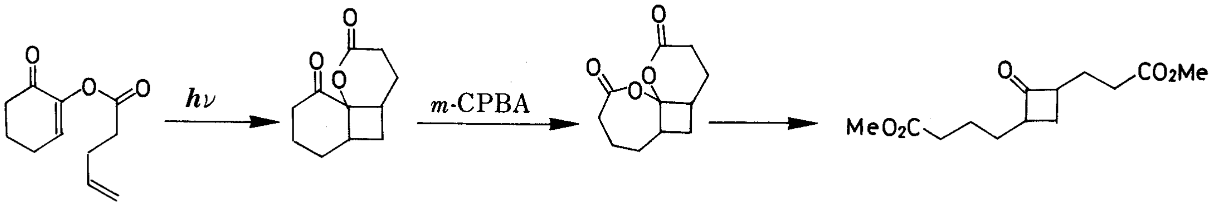


Chart 2

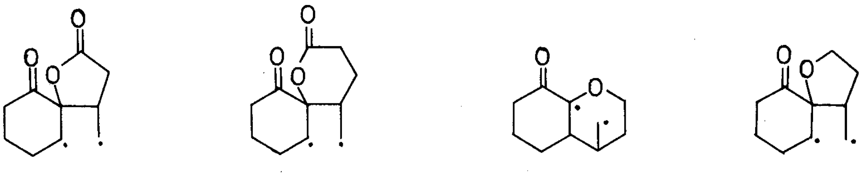
Irradiation of **11** in acetone for a period of 13 h produced a single adduct **12** in 62% yield. The structure of **12** was defined by transformation to the cyclobutanone derivative **14**. The NMR spectrum showed a two-proton multiplet between δ 2.8 and 3.5 due to the protons on the α-carbon atoms of the cyclobutanone ring. In the MS, a peak at m/z 128 corresponding to the $[O=C=CHCH_2CH_2CO_2CH_3]^+$ ion was observed. The stereochemistry of **12** is not clear at the present time.



11 **12** **13** **14**

Chart 3

In summary, the "rule of five" can be successfully applied to the photochemical reaction of both **4** and **11**; of the possible four biradical intermediates in each case, A and B would be most favored in terms of the entropic factor. The present result, together with the fact that the closely related 2-(4-pentenyl)cyclohex-2-enones undergo a head-to-head addition,[8] strongly suggests that the unusual behavior of **1** ($n=2$) originates from an electronic effect of the oxygen atom at the 2-position: the ether oxygen atom may enhance the stability of the six-membered biradical C, and thus the reaction proceeds preferentially through C rather than the five-membered biradical D which is entropically favored but less stable.



A B C D

Chart 4

Finally, an attempt to rearrange the mesylate **9** under solvolytic conditions (at reflux in acetic acid in the presence of potassium acetate) gave at least three products (on TLC). This result is in contrast to the case of the mesylates derived from the photoproducts of **1** ($n=1$ and 2), which underwent stereospecific rearrangement to bicyclo[3.3.0]- and bicyclo[3.2.1]octane ring systems.[2] The ether oxygen atom in **1** plays an important role in the solvolytic reactions too.

Experimental[9]

2-(3-Butenoyloxy)cyclohex-2-enone (4)——3-Butenoyl chloride (3.5 g, 34 mmol) was added dropwise to a solution of **3** (3.4 g, 30 mmol) and pyridine (2.7 g, 34 mmol) in dry $CHCl_3$ (60 ml) at 0 °C. The mixture was heated with stirring at 50 °C for 4 h. After cooling, the mixture was washed with water, 10% HCl, saturated $NaHCO_3$, and brine, then dried ($MgSO_4$) and concentrated. The residual oil was distilled to give **4** (3.2 g, 58%), bp 115—117 °C (4 mmHg). IR ν_{max}^{neat} cm^{-1}: 1760, 1690, 1645. UV λ_{max}^{EtOH} nm (log ε): 230 (3.87). NMR ($CDCl_3$) δ: 1.8—2.3 (2H, m), 2.4—2.8 (4H, m), 3.25 (2H, dt, $J=6.5$, 1 Hz, $OCOCH_2$), 5.05—5.35 (2H, m, $CH=C\underline{H}_2$), 5.91 (1H, ddt, $J=17$, 10, 7 Hz, $C\underline{H}=CH_2$), 6.51 (1H, t, $J=5$ Hz, H-3). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.67; H, 6.83.

2-(4-Pentenoyloxy)cyclohex-2-enone (11)——By means of a procedure similar to that described above, **11** (1.22 g, 44%) was obtained from **3** (1.5 g, 13 mmol) and 4-pentenoyl chloride (1.75 g, 15 mmol) as an oil, bp 122—126 °C (4 mmHg). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1765, 1700, 1640. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (log ε): 230 (3.91). NMR ($CDCl_3$) δ: 1.85—2.2 (2H, m), 2.2—2.8 (8H, m), 4.9—5.2 (2H, m, $CH=C\underline{H}_2$), 5.81 (1H, ddt, J = 17, 10, 7 Hz, $C\underline{H}=CH_2$), 6.48 (1H, t, J = 5 Hz, H-3). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.93; H, 7.33.

(1*RS*,6*SR*,8*RS*)-11-Oxatricyclo[6.3.0.0^{1,6}]undecane-2,10-dione (5)——A degassed solution of **4** (460 mg, 2.5 mmol) in acetone (46 ml) was irradiated in a Pyrex tube for a period of 3.5 h under a nitrogen atmosphere. The solvent was removed and the residual solid was recrystallized from benzen–*n*-hexane to give **5** (310 mg, 69%), mp 125—126 °C. IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 1770, 1700. NMR ($CDCl_3$) δ: 1.4—3.35 (12H, m). *Anal.* Calcd for $C_{10}H_{12}O$: C, 66.65; H, 6.71. Found: C, 66.48; H, 6.74.

(1*RS*,7*SR*,9*RS*)-2,12-Dioxatricyclo[7.3.0.0^{1,7}]dodecane-3,11-dione (6)——*m*-CPBA (60 mg, 0.35 mmol) was added portionwise to a mixture of **5** (50 mg, 0.28 mmol) and $NaHCO_3$ (12 mg) in dry CH_2Cl_2 (2 ml) under ice-cooling. The mixture was stirred at room temperature for 8 h. The mixture was diluted with benzene and washed with 10% Na_2SO_3, 10% Na_2CO_3, and brine, then dried ($MgSO_4$) and concentrated. The residue was chromatographed [silica gel; benzene–ethyl acetate (4 : 1)] to give **6** (31 mg, 57%), mp 108—109 °C (from benzene–*n*-hexane). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1810, 1780. NMR ($CDCl_3$) δ: 1.4—3.2 (12H, m). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 60.71; H, 6.07.

Methyl 4-[4-Carbomethoxymethyl-1-oxocyclobut-2-yl]butanoate (7)——A solution of **6** (39 mg, 0.20 mmol) and *p*-toluenesulfonic acid (3.5 mg) in methanol (2 ml) was stirred at room temperature overnight. The solvent was evaporated off *in vacuo*, and then benzene (15 ml) was added. The benzene was evaporated off and the residue was redissolved in benzene. This solution was washed with brine, dried ($MgSO_4$), and concentrated to give **7** (39 mg, 90%) as an oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1780, 1745. NMR ($CDCl_3$) δ: 1.15—2.9 (10H, m), 3.1—3.7 (2H, m), 3.68 (3H, OCH_3), 3.69 (3H, OCH_3). MS *m/z*: 242 (M^+, 1%), 211 (14), 179 (16), 142 (8), 114 (100). Exact MS: Calcd for $C_{12}H_{18}O_5$: 242.1152. Found: 242.1146.

(1*RS*,2*SR*,6*SR*,8*RS*)-2-Hydroxy-11-oxatricyclo[6.3.0.0^{1,6}]undecan-10-one (8)——$NaBH_4$ (21 mg, 0.56 mmol) was added portionwise to a solution of **5** (100 mg, 0.56 mmol) in methanol (5 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo*, diluted with water, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was purified by column chromatography [silica gel; ethyl acetate–*n*-hexane (1 : 1)] to give **8** (83 mg, 83%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3605, 3450, 1765. NMR ($CDCl_3$) δ: 1.0—3.9 (12H, m), 3.20 (1H, q, J = 8 Hz, H-8), 3.58 (1H, br s, OH). Exact MS: Calcd for $C_{10}H_{14}O_3$: 182.0941. Found: 182.0935.

(1*RS*,2*SR*,6*SR*,8*RS*)-10-Oxo-11-oxatricyclo[6.3.0.0^{1,6}]undecan-2-yl Methanesulfonate (9)——A solution of **8** (70 mg, 0.38 mmol), pyridine (36 mg), 4-(*N*,*N*-dimethylamino)pyridine (5 mg), and methanesulfonyl chloride (53 mg, 0.46 mmol) was stirred at room temperature for 15 h. Methanol (0.5 ml) was added and the mixture was stirred for 30 min. The mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine, then dried ($MgSO_4$) and concentrated. The residue was chromatographed [silica gel; ethyl acetate–*n*-hexane (1 : 1)] to give **9** (75 mg, 75%), mp 110—110.5 °C (from ether). IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 1765, 1360, 1180. NMR ($CDCl_3$) δ: 1.1—3.1 (11H, m), 2.95 (3H, s), 3.28 (1H, br q, J = 7 Hz, H-8), 4.56 (1H, dd, J = 11, 6 Hz, H-1). *Anal.* Calcd for $C_{11}H_{16}O_5S$: C, 50.75; H, 6.21. Found: C, 50.36; H, 6.23.

Methyl (1*RS*,2*RS*,6*SR*,8*RS*)-(1,2-Epoxybicyclo[4.2.0]octan-8-yl)acetate (10)——A solution of **9** (340 mg, 1.3 mmol) and sodium methoxide (71 mg, 1.3 mmol) in methanol (20 ml) was stirred at room temperature for 3 h. The mixture was concentrated, diluted with water, and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concentrated. The residual oil was chromatographed [silica gel; ethyl acetate–*n*-hexane (1 : 4)] to give **10** (160 mg, 62%) as an oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1730. NMR ($CDCl_3$) δ: 0.7—3.15 (13H, m), 3.64 (3H, s, OCH_3). MS *m/z*: 196 (M^+). *Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.63; H, 8.35.

12-Oxatricyclo[6.4.0.0^{1,6}]dodecane-2,11-dione (12)——A solution of **11** (686 mg, 3.5 mmol) in acetone (70 ml) was irradiated under a nitrogen atmosphere for a period of 13 h. Work-up gave **12** (426 mg, 62%), mp 63.5—64 °C (from ether). IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 1745, 1705. NMR ($CDCl_3$) δ: 1.3—3.3 (14H, m). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.93; H, 7.35.

2,13-Dioxatricyclo[8.3.0.0^{1,7}]tridecane-3,12-dione (13)——By means of a procedure similar to that described for **6**, **13** (73 mg, 82%) was obtained from **12** (82 mg, 0.42 mmol), mp 92.5—93.5 °C (from benzene–*n*-hexane). IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1780, 1770. NMR ($CDCl_3$) δ: 1.4—3.2 (14H, m). *Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.78; H, 6.72.

Methyl 4-[4-(2-Carbomethoxy)ethyl-1-oxocyclobut-2-yl]butanoate (14)——By means of a procedure similar to that described for **7**, **14** (51 mg, 85%) was obtained from **13** (49 mg, 0.2 mmol) as an oil. IR $\nu_{\max}^{\mathrm{CCl_4}}$ cm^{-1}: 1780, 1745. NMR ($CDCl_3$) δ: 1.1—2.6 (12H, m), 2.8—3.5 (2H, m), 3.66 (6H, $2\times OCH_3$). MS *m/z*: 256 (M^+, 1%), 225 (5), 193 (15), 128 (25), 114 (97), 100 (100). Exact MS: Calcd for $C_{13}H_{20}O_5$: 256.1311. Found: 256.1326.

References and Notes

1) M. Ikeda, M. Takahashi, K. Ohno, Y. Tamura, and M. Kido, *Chem. Pharm. Bull.*, **30**, 2269 (1982).

2) M. Ikeda, M. Takahashi, T. Uchino, K. Ohno, Y. Tamura, and M. Kido, *J. Org. Chem.*, **48**, 4142 (1983).

3) *a*) Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, *J. Org. Chem.*, **40**, 2702 (1975); *b*) M. Ikeda, K. Ohno, K. Homma, H. Ishibashi, and Y. Tamura, *Chem. Pharm. Bull.*, **29**, 2062 (1981); *c*) M. Ikeda, K. Ohno, M. Takahashi, K. Homma, T. Uchino, and Y. Tamura, *Heterocycles*, **20**, 1005 (1983).

4) *a*) R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.*, **89**, 4932 (1967); *b*) R. S. H. Liu and G. S. Hammond, *ibid.*, **89**, 4936 (1967); *c*) S. Wolff and W. C. Agosta, *ibid.*, **105**, 1292, 1299 (1983).

5) If a five-membered ring cannot be formed, a six-membered ring formation is next most favored. Thus, in the 1,7-diene system, the head-to-head addition is preferred.

6) T. R. Hoye, S. J. Martin, and D. R. Peck, *J. Org. Chem.*, **47**, 331 (1982).

7) The formation of the oxirane **10** from **9** may proceed *via* initial cleavage of the O–CO bond of the lactone ring followed by ring flipping of the cyclohexane ring and then S_N2 type displacement reaction.

8) R. L. Cargill, J. R. Dalton, S. O'Connor, and D. G. Michels, *Tetrahedron Lett.*, **1978**, 4465.

9) All melting points and boiling points are uncorrected. NMR spectra were determined with a Hitachi R-22 (90 MHz) spectrometer (tetramethylsilane as an internal standard). IR spectra were recorded with a JASCO IRA-1 spectrophotometer and UV spectra with a Hitachi 124 spectrophotometer. High- and low-resolution mass spectra were obtained with a JMS-D-300 instrument at 70 eV. Photoirradiation was carried out in a Pyrex tube using an Eikosha 350-W high-pressure mercury lamp.