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Ring Size Effect on [2+2] Photochemical Cycloaddition of Enones with Cyclic Olefins

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Synopsis. Photochemical reaction of 3-substituted 2-cyclohexen-1-ones with methyl 1-cyclohexene-1-carboxylate gave only head-to-tail, cis-transoid-cis photoadduct. The photoadducts of 3-methyl-2-cyclohexen-1-one with methyl 1-cyclopentene-1-carboxylate and with methyl 1-cyclobutene-1-carboxylate had head-to-head, cis-transoid-cis ring systems.

Photochemical [2+2] cycloaddition of enones with olefins is one of the most famous photochemical reactions. The application of this reaction for the synthesis of natural products has been well-documented.[1] Corey et al.[2] and Loutfy and De Mayo[3] investigated the mechanism of photocycloaddition of enones with olefins in an attempt to explain the regio- and stereoselectivity. Weedon made a general statement concerning the stereochemistry of enone photochemical cycloaddition.[4] Wender reported that irradiation of 3-methyl-2-cyclohexen-1-one (**1**) with methyl 1-cyclobutene-1-carboxylate (**2**) produced a head-to-head, cis-transoid-cis photoadduct **3** in dichloromethane.[5] Lange obtained a similar head-to-head, cis-transoid-cis photoadduct **5** by the photochemical reaction of enone **1** with methyl 1-cyclopenetene-1-carboxylate (**4**) in toluene.[6] In the course of our synthetic investigation of natural products using photochemical cycloaddition, we found that the products of 3-substituted 2-cyclohexen-2-ones with methyl 1-cyclohexene-1-carboxylate have a head-to-tail, cis-transoid-cis ring system. We report here that the regiochemistry of the photoadducts of enone with cycloolefins is dependent on the ring size of the cycloolefins.

Results and Discussion

A dichloromethane solution of equimolar mixture of 3-methyl-2-cyclohexen-1-one (**1**) and methyl 1-cyclohexene-1-carboxylate (**6**) was irradiated by a 100 W high-pressure Hg-lamp for 8 hours. The photoadduct **7** was obtained in 74.4% yield along with unreacted starting materials. The same adduct was also obtained as a major product by the photochemical reaction of **1** with **6** in methanol, or in CH_3CN. The structure of the compound **7** was determined as follows. The compound **7** showed the M^+ at m/z 250 by mass spectrum and was found to have a ketone and an ester group by IR spectrum (1726, 1697, 1223. and 1155 cm^{-1}). The ^{13}C NMR spectrum of the compound **7**, showed the signals assigned to a ketone, a methyl ester, two methyls, 7 methylenes, 2 methines, a quaternary carbon and no C=C double bond. In the ^1H-^1H COSY of the compound **7** spectrum,[7] a large coupling (J=10.8 Hz) between the C-12H (δ 2.50, d, J=10.8 Hz) and the C-12H (δ 2.96, ddd, J=2.1, 5.2, 10.8 Hz) was observed. The coupling constants ($J_{1,12}$=10.8, $J_{12,11}$=5.2, and $J_{12,11}$=2.1 Hz) of compound **7** could be satisifactorily assigned only by one of the conformations of the cis-transoid-cis ring system. In the NOESY spectrum[8] of the compound **7**, cross peaks were appeared between C-6Me and C-1H. Whereas no NOE was observed between C-12H and C-1H, between C-12H and C-6Me and between C-12H and the ester methyl. Finally, the compound **7** was converted to a hydroxy ketone **8** by the successive treatment of acetalization, reduction, and hydrolysis (acetone–TsOH). The signal of C-12H of compound **8** was observed at higher chemical shift (δ 2.36, dd, J=5.0, 10.2 Hz) compared to that of the compound **3**, whereas no remarkable change of chemical shifts were observed on C-1H and C-6Me in ^1H NMR. These results reveal that the photoadduct **7** has a head-to-tail, cis-transoid-cis ring system.

The regiochemistry of the photoadduct **7** is different from that of the photoadducts **3** and **5**. The photochemical reaction of the other six-membered ring compounds were examined from the mechanistic interest.

The photochemical reaction of the enone **1** with 1-cyclohexene-1-carboxylic acid (**9**) gave a major product **10** under the similar conditions in CH_2Cl_2. The major product **10** was converted to the compound **7** by methylation with diazomethane showing that the major product of the photochemical reaction of the enone **1** with the acid **9** is a similar head-to-tail, cis-transoid-cis adduct **10** (9.3%). The photochemical reaction of the enone **1** with 1-cyclohexenylmethanol was very slow and no photoadduct obtained under similar conditions. Irradiation of the CH_2Cl_2 solution of the 2-cyclohexen-1-one (**11**) and the ester **6** for 5 hours gave a major product **12** (7.4%) with unreacted starting materials. The structure of **12** was clarified by the NMR spectra (^1H, ^{13}C NMR, and ^1H-^1H COSY) as in the case of the compound **7**. No photochemical reaction product was obtained by the irradiation of the CH_2Cl_2 solution of 3-methoxy-2-cyclohexen-1-one (**13**) and the ester **6** for 16 hours. Acetophenone (1%) was thus, used for a photosensitizer and the solution was irradiated for 8 hours to give a head-to-tail, cis-transoid-cis compound (**14**) in a yield of 10.5%. The structure proof of the product **14** was obtained from the NMR experiments (^1H, ^{13}C NMR, ^1H-^1H COSY, and NOESY). The signal of the C-12H (δ 2.47, ddd, J=2.5, 5.4, 10.8 Hz) of compound **14** was appeared in very similar splittung pattern as that of compound **7**.

In summary, photochemical cycloaddition of 3-substituted 2-cyclohexen-1-one with cyclohexene-1-carboxylic acid and with its ester gave head-to-tail, cis-transoid-cis compounds. The regiochemistry of the adduct **7**, **10**, **12**, and **14** are opposite to the photoadducts **3** and **5**. These results suggest that the difference of the regiochemistry of the photoadducts depends on

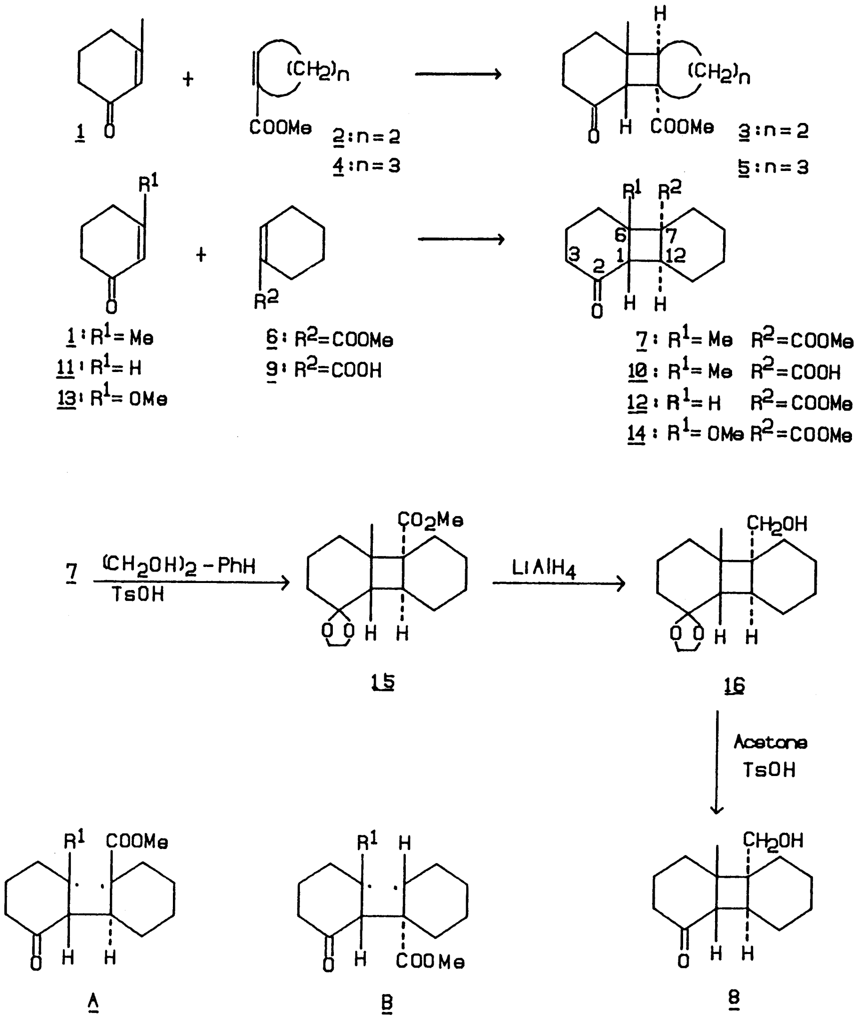

Fig. 1.

the ring size of the cyclic olefinic esters.

The photoadducts **7**, **10**, **12**, and **14** should be produced via the more stable biradical **A** rather than the less stable biradical **B**. The unambigious mechanistic explanation for the ring size effect could not be accomplished yet.

Experimental

NMR spectra were measured with a JEOL GX-270 spectrometer in $CDCl_3$ solution containing tetramethylsilane as an internal standard. IR spectra measured on JASCO IR-810 spectrometer. HPLC was performed on JASCO BIP-1 HPLC system with RI detector (RID-300) and silica-gel column (LiChrosorb Si-60 10 μm, 7,5 *500 mm). Thin-layer chromatography was carried out on Kieselgel GF_{254} (Merck) in 0.25 mm thickness. Wakogel C-200 (Wako Pure Chemical Industries) was used for column chromatography.

General Procedures for Irradiation of Enone with Olefin. The enone **1** (1 m mol, 110 mg) and the ester **6** (1 m mol, 140 mg) were dissolved in 50 ml of CH_2Cl_2, and the mixture was irradiated through Pyrex glass vessel for 8 h under nitrogen atmosphere with 100 W high-pressure Hg-lamp. The reaction mixture was concentrated, and the residue was column chromatographed on silica gel eluted with hexane-EtOAc and purified by HPLC to give 186.0 mg (74.4%) of **7**: IR (neat) 1726, 1697, 1223, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.72 (3H, s), 2.96 (1H, ddd, J=2.1, 5.2, 10.8 Hz), 2.50 (1H, d, J=10.8 Hz), 1.14 (3H, s); ^{13}C NMR ($CDCl_3$) δ=20.51(q), 21.15(t), 21.24(t), 21.59(t), 23.54(t), 27.54(t), 31,39(t), 36.83(d), 38.14(t), 44.92(s), 49.64(s), 50.17(d), 51.16(q), 175.70(s), 211.79(s); MS m/z 250.

Photochemical reaction of the other enones with olefins were performed by the similar procedures. The acid **10** was methylated with a ether solution of diazomethane as usual procedures before the separation. Acetophenone (1 mg) was added to the benzene (50 ml) solution of the enone **13** (117.5 mg) and the ester **6** (126.3 mg) as a photosensitizer before the irradiation. Compound **12**: ^1H NMR ($CDCl_3$) δ=3.70 (3H, s), 3.07 (1H, dd, J=5.4, 10.8 Hz), 2.90 (1H, dd, J=7.0, 10.8 Hz); ^{13}C NMR ($CDCl_3$) δ=21.29, 21.93, 22.32, 24.10, 24.32, 32.64, 38.79, 38.90, 41.51, 44.06, 46.81, 51.53, 175.56, 212.55; compound **14**: IR 1723, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.75 (3H, s), 3.31 (3H, s), 2.66 (1H, d, J=10.8 Hz), 2.47 (1H, ddd, J=2.5, 5.4, 10.8 Hz); ^{13}C NMR ($CDCl_3$) δ=19.18, 20.94, 21.15, 23.45, 25.08, 25.26, 23.03, 38.54, 50.34, 51.72, 51.88, 52.97, 80.52, 175.55, 210.78.

Acetalization of the Photoadduct 7. A mixture of **7** (96.6 mg), ethylene glycol (1 g), TsOH (5 mg), and benzene (20 ml) was refluxed for 12 h with Dean-Stark water trap. The raction mixture was poured into brine, and extracted with ether. The organic layer was washed with aqueous sodium carbonate (5%) and brine, dried over sodium sulfate and concentrated. The residue was column chromatographed on silica gel eluted with EtOAc to give the acetal **15** (70.4 mg, 62%): IR(neat) 1725, 1225, 1207 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 1.08 (3H, s), 2.63 (1H, dd), 3.65 (1H, s), 3.9 (4H, m); ^{13}C NMR

(CDCl$_3$) δ=19.93(t), 20.48(q), 21.88(t), 22.08(t), 24.06(t), 27.78(t), 31.70(t), 32.25(t), 33.78(d), 42.92(s), 43.36(d), 49.94(s), 51.00(q), 64.10(t), 64.14(t), 109.42(s), 176.68(s).

Reduction of Acetal 15. A solution of the acetal **15** (262.6 mg) in ether (10 ml) was added dropwise to a stirred slurry of lithium aluminum hydride (75 mg) in ether (10 ml). After being stirred for 3 h, saturated aqueous sodium sulfate solution was added and the product was extracted with ether. The ether solution was washed with brine, dried over sodium sulfate and evaporated. The silica-gel column chromatographed of the residue afforded the hydroxy acetal **16** (198 mg, 83.4%): IR (neat) 3450 (br.), 1093 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=1.05 (3H, s), 3.58 (1H, d, J=10.5 Hz), 3.67 (1H, d, J=10.5 Hz), 3.9 (4H, m); ^{13}C NMR (CDCl$_3$) δ=20.07, 21.63, 22.10, 22.14, 24.74, 25.57, 30.08, 32.28, 34.43, 41.10, 43.16, 43.58, 64.08, 64.12, 64.89, 109.83.

Deprotection of the Hydroxy Acetal 16. A solution of the hydroxy acetal **16** (53 mg) and TsOH (50 mg) in acetone (15 ml) was stirred for 16 h at room temperature. The reaction mixture was evaporated and the residue was disolved in EtOAc. The solution was washed with 5%-Na$_2$CO$_3$ and brine, and evaporated. The product was purified with HPLC to give the hydroxy ketone **8** (33 mg, 75%): IR (neat) 3480, 1680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ=3.73 (1H, d, J=11.1 Hz), 3.66 (1H, d, 11.1 Hz), 2.57 (1H, d, J=10.2 Hz), 2.36 (1H, dd, J=5.0, 10.2 Hz), 1.13 (3H, s); ^{13}C NMR (CDCl$_3$) δ=21.16, 21.28, 21.84, 22.06, 24.35, 25.70, 29.59, 37.77, 38.76, 43.12, 43.44, 50.84, 64.36, 213.54.

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