Communications to the Editor

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DOUBTS ABOUT THE LIBIT'S METHOD FOR THE SYNTHESIS OF THE "COREY" INTERMEDIATE USING PHOTOCYCLOADDITION AS A KEY STEP

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Irradiation of 4-(2-tetrahydropyranyloxy)-2-cyclopentenyl 3-acetoxyacrylate (**2**) resulted only in an *E*-*Z* isomerization. Also, the corresponding 4-oxo-2-cyclopentenyl derivative (**7**) did not give the cyclized product on irradiation. These facts clearly indicate that the Libit's method is only an idea without any experimental verification.

KEYWORDS —— Corey intermediate; prostaglandin; photochemical synthesis; photocycloaddition; 2-cyclopentenyl 3-acetoxyacrylate; 4-oxo-2-cyclopentenyl 3-acetoxyacrylate; *E*-*Z* isomerization; Libit's method; intra- *versus* inter-molecular photoaddition

Among many methods so far reported for the synthesis of the "Corey" intermediate, the one reported by Libit[1] is outstanding in its short step from the readily available mono-tetrahydropyranyl ether (1)[2] of *cis*-2-cyclopentene-1,4-diol. The method consists of three steps from **1**: 1) esterification of **1** with 3-acetoxyacryloyl chloride to give the ester (**2**), 2) photocyclization of **2** to **3**, and 3) treatment of **3** in methanol with a base to give the Corey intermediate (**4**). However, the method reported in a patent form is full of serious ambiguities. Namely, i) the patent does not contain any physical or spectroscopic data for **2**-**4**, ii) in the photoaddition step, the use of sensitizers (such as acetophenone or benzophenone) is obviously unnecessary, iii) neither the *E*-*Z* photoisomerization of **2** nor the stereochemistry of **3** is commented upon, and iv) construction of a 2-oxatricyclo$[4.2.1.0^{4,9}]$nonane system (the skeleton of **3**) by the same photochemical method has no precedent.[3]

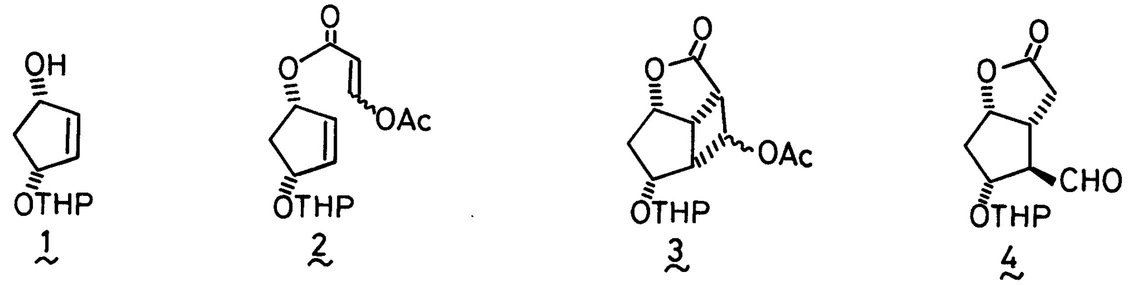

Chart 1

Recently, we established a novel method for synthesizing a variety of formylacetates in a one-pot reaction by merely heating formyl Meldrum's acid in toluene in the presence of an alcohol.[4] Since these formylacetates would give the corresponding 3-acetoxyacrylates, 2 should now be readily available in large quantities from the mono-tetrahydropyranyl ether (1) of cis-2-cyclopentene-1,4-diol.5) Actually, when 1 was refluxed in toluene in the presence of formyl Meldrum's acid (1 mol eq. to 1), the corresponding formylacetate was obtained. This, by treatment with acetic anhydride in pyridine, gave the enol acetate having the E-configuration at the double bond (2-E)6) in 57% overall yield from 1. The ready accessibility of 2-E has prompted us to examine its photoreaction.

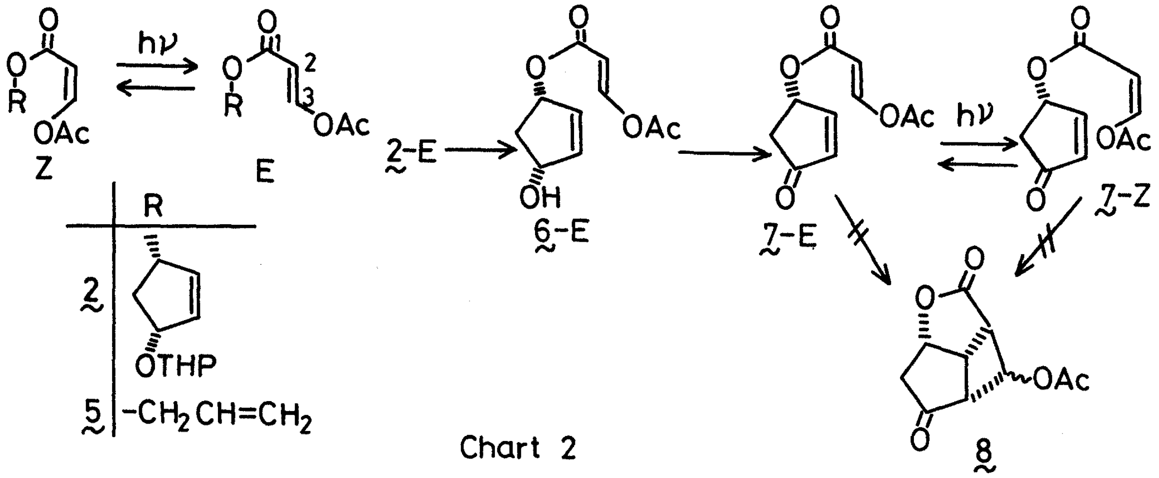

Chart 2

Irradiation of 2-E in ether or hexane at a variety of wavelengths7) gave no cyclized product (3). The only product obtained was a mixture of Z- and E-isomers of 2 in which 2-Z was a major product irrespective of the wavelength employed [2-Z: ^{1}H-NMR (CDCl$_3$)δ : 2.26 (3H, s, CH$_3$), 5.30 (1H, d, J=7 Hz, 2-H), 7.52 (1H, d, J=7 Hz, 3-H)]. A simpler system, irradiation of 5-E,8) was examined, but again only a mixture of 5-Z and 5-E was obtained. Though we irradiated these compounds (2-E and 5-E) in a mixture of hexane and ether (10:1 v/v) in the presence of acetophenone at $\geq$ 300 nm (the same condition that Libit employed), again the same photo-equilibration between E-Z isomers resulted9) and none of the cyclized product was obtained. In general the double bond of an enone undergoing efficient cycloaddition to an alkene must be part of a ring of six or fewer members. Without this constraint the enone double bond on excitation (T$_1$) undergoes energy-wasting E-Z isomerization at the expense of the cycloaddition reaction.10,11) In accordance with this explanation, formylacetic ester12) and its enol derivatives13,14) cannot photoadd to unactivated olefins. Knowing that 2-cyclopentenone does photoadd intermolecularly to various enol derivatives of formylacetic ester to afford cyclobutane-containing adducts,13,14) we then tried the irradiation of 4-oxo-2-cyclopentenyl 3-acetoxyacrylate (7-E). This compound15) can be synthesized from 2-E in 90% yield by partially deblocking the tetrahydropyranyl group (TsOH/EtOAc-MeOH) followed by PCC oxidation. The fact that irradiation of 7-E in ether at $\geq$ 300 nm gave no cyclized product (8) but again afforded an E-Z mixture of 7 (yield; 54% with Z/E ratio; ca. 4:3) shows that geometrical constraints imposed on the reacting functional groups in these intramolecular reactions of 7 and 2 to 2-oxatricyclo[4.2.1.0^{4,9}]nonane system (8 and 3) are less favorable than the corresponding intermolecular ones.

Thus, we now conclude that the method reported by Libit (Chart 1) is only an idea without any experimental verification.

REFERENCES AND NOTES

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2) E.J. Corey and P.L. Fuchs, J. Am. Chem. Soc., 94, 4014 (1972).

3) To the present authors' knowledge, photocyclization of 3-(3-butenyl)cyclopentene derivatives to tricyclo[4.2.1.0^{3,9}]nonanes (carbocyclic analogues of 3) in the presence of copper(I) trifluoromethanesulfonate (CuOTf) is the only method for the construction of such tricyclic compounds: R.G. Salomon, S. Ghosh, M.G. Zagorski, and M. Reitz, J. Org. Chem., 47, 829 (1982).

4) M. Sato, N. Yoneda, N. Katagiri, H. Watanabe, and C. Kaneko, Synthesis, in press.

5) C. Kaneko, A. Sugimoto, and S. Tanaka, Synthesis, 1974, 876.

6) 2-*E*: oil; IR (CHCl$_3$) 1780, 1715, 1655 cm^{-1}; ^{1}H-NMR (CDCl$_3$)δ : 1.3-2.1 (7H, m), 2.20 (3H, s), 2.87 (1H, ddt, *J*=2, 14, 7 Hz), 3.3-4.3 (2H, m), 4.5-4.9 (2H, m), 5.58 (1H, m), 5.70 (1H, d, *J*=13 Hz), 6.10 (2H, m), 8.29 (1H, d, *J*=13 Hz).

7) Irradiation conditions: All irradiation was performed under argon atmosphere. a) Irradiation at ≥ 300 nm: the photolyses were carried out in a Pyrex immersion apparatus equipped with a Riko UVL 400HA high-pressure mercury lamp. b) Irradiation at 300 nm or 350 nm: irradiation for the photochemical reactions at these wavelengths was performed in a quartz vessel using Rayonet photochemical reactor lamps (RPR-3000Å or RPR-3500Å).

8) 5-*E* was prepared by heating Meldrum's acid and allyl alcohol in toluene followed by acetylation with acetic anhydride-pyridine in 75% overall yield. bp 84°C (6 mmHg); ^{1}H-NMR (CDCl$_3$)δ : 5.63 (1H, d, *J*=13 Hz, 2-H), 8.20 (1H, d, *J*=13 Hz, 3-H).

9) All irradiation was continued until there was no further change in the *Z*/*E* ratio. The ratios (total yields) of *Z*/*E*-isomers of 2 and 5 were *ca.* 4:3 (66%) and 2:1 (53%), respectively.

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14) M.V. Andenhove, D. Termont, D.D. Keukeleire, M. Vandewalle, and M. Claeys, Tetrahedron Lett., 1978, 2057.

15) 7-*E*: mp 77-79°C (ether-hexane); IR (CHCl$_3$) 1780, 1720, 1655 cm^{-1}; ^{1}H-NMR (CDCl$_3$)δ : 2.23 (3H, s), 2.30 (1H, dd, *J*=2.5, 18 Hz), 2.88 (1H, dd, *J*=6, 18 Hz), 5.70 (1H, d, *J*=12 Hz), 5.93 (1H, m), 6.34 (1H, dd, *J*=1.5, 6 Hz), 7.60 (1H, dd, *J*=2, 6 Hz), 8.30 (1H, d, *J*=12 Hz).

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