Solid-State Photochemistry: "Absolute" Asymmetric Oxetane Synthesis from an Achiral Acyclic Imide Using the Chiral Crystal Environment

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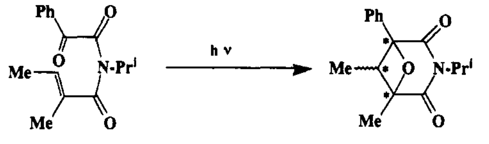
Summary: Photolysis of chiral crystals of an achiral *N*-isopropyl-*N*-tiglylbenzoylformamide in the solid state proceeded [2 + 2] cycloaddition to give a chiral oxetane, 5,7-dimethyl-3-isopropyl-1-phenyl-6-oxa-3-azabicyclo[3.1.1]-heptane-2,4-dione, in high chemical and optical yields.

Stereospecific solid-state chemical reactions of chiral crystals are defined as "absolute" asymmetric syntheses, and they provide not only a plausible explanation for the prebiotic origin of optical activity but may also be an attractive general method of asymmetric synthesis. Since the concept of a topochemically controlled reaction was established, various approaches to asymmetric synthesis using a solid-state reaction of chiral crystals have been attempted.[1] In contrast to a number of examples for photodimerization of unsymmetrically substituted conjugated diolefin crystals, only a few successful "absolute" asymmetric syntheses for unimolecular photochemical reactions have been reported.[2] Recently, we reported the "absolute" asymmetric thietane synthesis including the solid-state photochemistry of achiral monothioimide.[3] In the present paper, we wish to report the first example of an "absolute" asymmetric oxetane synthesis via a topochemically-controlled unimolecular photochemical [2 + 2] cycloaddition.

The "absolute" asymmetric synthesis was performed in oxetane formation from *N*-isopropyl-*N*-tiglylbenzoylformamide (1). This material forms colorless needle crystals from hexane–chloroform, mp 63–64 °C, and an X-ray crystal structure analysis indicated the chiral space group $P2_1$, $a = 5.933$ (1) Å, $b = 12.552$ (1) Å, $c = 10.594$ (2) Å, $V = 776.1$ Å^3, $Z = 2$, $\rho = 1.16$ g/cm^3, $\mu = 0.8$ cm^{-1}. The structure solved by the direct method and refined by the method of full-matrix least-squares. Final R and R_w were 0.052 and 0.047 for 1518 reflections.

Scheme I



1

2

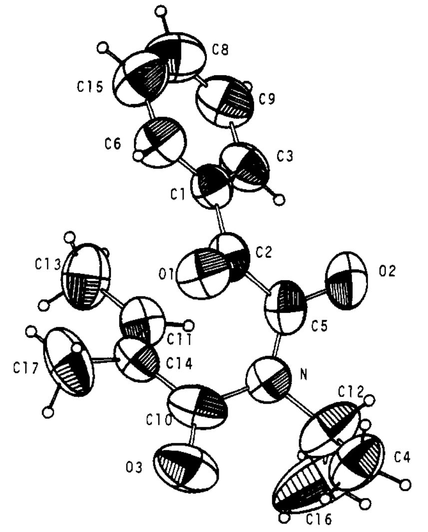


Figure 1. The ORTEP drawing of the molecule 1. The el[illegible]oid are drawn at 50% probability. The absolute configuration is tentative.

Irradiation of the imide 1 in benzene undergoes [2 + 2] cyclization to afford the bicyclic oxetane, 5,7-dimethyl-3-isopropyl-1-phenyl-6-oxa-3-azabicyclo[3.1.1]heptane-2,4-dione (2), quantitatively as a mixture of two stereoisomers (2-*syn*/2-*anti* = 2.1) which have three chiral centers (Scheme I).[4] The structure of the photoproducts was determined on the basis of elemental analysis and spectral data; particularly, the configurations (syn or anti) were assigned by ^{1}H-NMR NOE techniques.[5] An important goal was to determine whether the transformation of 1 to 2 occurs in the crystalline state. In the reactant 1, the distances between the oxygen atom (O1) and the alkenylcarbon (C14) and between the carbonyl carbon (C2) and the alkenyl carbon (C11) are 2.98 and 2.99 Å, respectively.[6] The reacting carbonyl and alkenyl double bonds incline to each other at an angle of 22.9 degrees (Figure 1).

The imide 1 was irradiated as white powders prepared by grinding sandwiched two Pyrex slides and sealed in

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(1) (a) Cohen, M. D.; Schmidt, G. M. *J. Chem. Soc.* **1964**, 1969. (b) Schmidt, G. M. *J. Pure Appl. Chem.* 1971, *27*, 647. (c) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1979**, *101*, 2152. (d) Addadi, L.; van Mil, J.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3422. (e) van Mil, J.; Addadi, L.; Gati, E.; Lahav, M. *J. Am. Chem. Soc.* **1982**, *104*, 3429. For reviews see: (f) Hasegawa, M. *Chem. Rev.* **1983**, *83*, 507. (g) Ramamurthy, V. *Tetrahedron* **1986**, *42*, 5753. (h) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.

(2) (a) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1986**, *108*, 5648. (b) Toda, F.; Soda, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1413. (c) Sekine, A.; Hori, K.; Ohashi, Y.; Yagi, M.; Toda, F. *J. Am. Chem. Soc.* **1989**, *111*, 697. (d) Chen, J.; Pokkuluri, P. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1990**, *31*, 6803. For solid-state diastereoselective intramolecular [2 + 2] cycloaddition: (e) Schultz, A. G.; Taveras, A. G.; Taylor, R. E.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8725.

(3) Sakamoto, M.; Hokari, N.; Takahashi, M.; Fujita, T.; Watanabe, S.; Iida, I.; Takehiko, N. *J. Am. Chem. Soc.* **1993**, *115*, 818.

(4) We have reported the photochemical reaction of *N*-(α,β-unsaturated carbonyl)benzoylformamide in solution. Sakamoto, M.; Aoyama, H.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1759.

(5) NOE was showed between 5-methyl and 7-methyl protons in 2-*syn* isomer and between 5-methyl and 7-methine protons in 2-*anti* isomer.

(6) It is known from early studies that the center to center distance should be less than 4.1 Å in an intermolecular [2 + 2] photocycloaddition (cyclobutane formation) for substrates in which the reacting double bonds are parallel. (a) Bregman, J.; Osaki, K.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.* **1964**, 2021. For reviews see: (b) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. *Organic Photochemistry*; Marcel Dekker: New York and Basel, 1987; Vol. 8, pp 249–338.

0022-3263/93/1958-3476$04.00/0

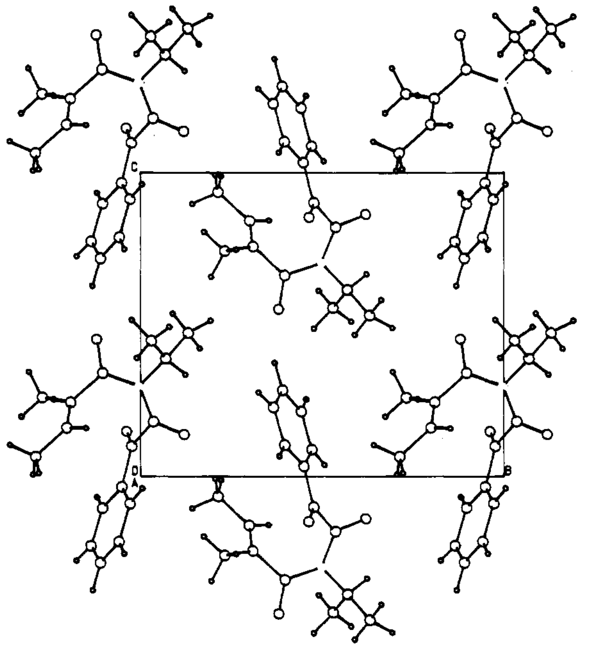

Figure 2. Crystal structure of 1 viewed along A axias.

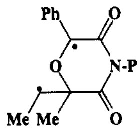

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Figure 3.

polyethylene bags with the UV light from a 500-W high-pressure mercury lamp at 0 °C for 1 h, and the photoproduct was purified by column chromatography on silica gel; the bicyclic oxetanes were obtained in 84% yield at 100% conversion (**2**-*syn*/**2**-*anti* = 3.7). Each oxetane was separated by preparative HPLC; the major isomer **2**-*syn* showed optical activity, $[\alpha]_D$ +34° (*c* 0.1 in $CHCl_3$), 35% enantiomeric excess (ee).[7] The solid-state photoreaction proceeded even at −78 °C and optical active (+)-**2**-*syn* which showed a higher ee value was formed, $[\alpha]_D$ +92° (*c* 0.1 in $CHCl_3$), >95% ee (irradiation time = 4 h, conversion 100%, chemical yield 89%, **2**-*syn*/**2**-*anti* = 6.5), whereas the minor isomer **2**-*anti* was obtained as racemates.[8] Chiral crystals were prepared as follows; one single crystal crystallized out naturally from a solution was used for next recrystallization as a seed. Chirality of crystals was decided by that of the single crystal used for seeding. In this way, it is possible that large quantity of (+)- or (−)-**1** (crystals of **1** which gave (+)- or (−)-**2** were tentatively termed (+)-**1** or (−)-**1**, respectively) was prepared selectively and in bulk by seeding with crystals of (+)- or (−)-**1** during recrystallization. Irradiation of chiral crystals of (−)-**1** under the same conditions gave optically active oxetane (−)-**2**-*syn* in almost the same ee value.

Time course for consumption of **1** and formation of **2** (syn and anti isomers) was studied to determine the reaction mechanism.[9] When **1** was irradiated in benzene, the yield of **2** increases roughly linear at the expense of **1** from the initial stage. In this photolysis *trans* isomer of **1** was not detected at all, and **2**-*syn* and **2**-*anti* were formed constantly at **2**-*syn*/**2**-*anti* = 2.1 through the whole stage, even after all **1** was consumed. It is concluded that the photoreaction proceeds via a diradical intermediate **3**, and the direct *cis–trans* isomerization of **1** and the back reactions from **3** to **1** does not occur. From these concept, the reason why racemic **2**-*anti* obtained in the solid-state photoreaction may be explainable in terms of that **2**-*anti* is formed in broken crystal lattices in which racemization of the reactant **1** already took place.[10,11]

In conclusion, *N*-isopropyl-*N*-tiglylbenzoylformamide **1** affords chiral crystals in bulk, and the solid state photoreaction gives optically active oxetane **2** in high optical and chemical yields. The present oxetane formation is a topochemically-controlled process and occurs stereospecifically in the solid state. The absolute configuration of both crystal of the reactant **1** and the oxetanes **2** have not determined yet and it remains unknown whether the crystal (+)-**1** has the structure shown in Figure 1 or its mirror image. This reaction provides the first example of an "absolute" asymmetric oxetane synthesis via a unimolecular [2 + 2] photocycloaddition in the solid state.

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[7] The optical purity was determined by chiral NMR shift reagent studies at 400 MHz ($Eu(hfc)_3$, Aldrich).

[8] The $[\alpha]_D$ value of the oxetane **2**-*anti* isolated by HPLC was nearly zero.

[9] The reaction was followed by ^1H-NMR spectroscopy.

[10] It is known that *cis–trans* photochemical isomerization of alkenes have taken place in the solid state; see: Schmidt, G. M. J. *Pure Appl. Chem.* 1971, *27*, 647. (b) Cohen, M. D.; Green, B. S. *Angew. Chem., Int. Ed. Engl.* 1975, *14*, 386. (c) Bryan, R. F.; Hartley, P. *J. Chem. Soc., Perkin Trans. 2* 1982, 191. In the present photoreaction, *cis–trans* isomerization of the reactant **1** did not take place on irradiation described above even in solution media.

[11] Scheffer et al. reported the absolute asymmetric induction diffenced in dual pathway photoreaction in which one of the di-π-methane rearrangement products is formed in near-quantitative enatiomeric excess, and the other is procuced as a racemates. They explained the fact on the basis of the difference of the reaction pathway; see ref 3d.