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Solid-State Photochemistry: Diastereoselective Synthesis of Thietane-Fused β-Lactams from an Acyclic Monothioimide with a Chiral Group

Masami Sakamoto,* Masaki Takahashi, Noriko Hokari, Tsutomu Fujita, and Shoji Watanabe

Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoi-cho, Inage-ku, Chiba, Japan 263

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Irradiation of *N*-[(*R*)-1-phenylethyl]-*N*-tigloythiobenzamide in benzene solution resulted in both [2 + 2] thietane and thioketone formation reactions (via β-hydrogen abstraction by the thiocarbonyl sulfur). Diastereoselectivity in the thietane formation was not observed, in that four β-lactams were obtained in similar yields. In contrast to the solution photochemistry, irradiation of the crystals provided remarkably high diastereoselectivities. At 15 °C, de of the *syn*-β-lactams was 61% and the ratio of *syn*/*anti* was to 8.7 (chemical yield: 78%). The solid-state photoreaction proceeded even at −78 °C, with higher diastereoselectivity. At low conversion (9%), only *syn* isomers (de = 93%) were obtained, and 71% de was observed even at 90% conversion. An X-ray crystal structure analysis of the monothioimide indicates that the crystal is orthorhombic, of space group $P2_12_12_1$, and the distances between the sulfur atom and the alkenyl carbon, and from the thiocarbonyl carbon to the alkenyl carbon, are 4.29 and 3.00 Å, respectively. The twist angle τ of the C(=O)–N bond is 40.8° and that of the C(=S)–N bond is 19.9°. On the other hand, the sulfur atom and abstractable hydrogen atom are in close proximity, and the value for d is 2.40 Å, for Θ is 127.3°, for Δ is 67.9°, and for ω is 6.2°. From these values, it is apparent that this reactant is well-positioned for hydrogen transfer in the crystalline state.

Achiral materials are capable of crystallizing in chiral space groups by spontaneous resolution, and this chirality can be a source of asymmetry to induce optical activity in the products of chemical reactions carried out in the solid state.[1] Recently we reported "absolute" asymmetric thietane and oxetane syntheses via solid-state photochemical reactions of achiral substrates using chiral crystal environments.[2] However, these examples are very rare[1,3] and don't represent a general method of asymmetric synthesis of organic compounds. On the other hand, it is known that chiral space groups are obligatory for optically active compounds. For chemical reactions carried out in the solid state, the chiral handle exerts a second asymmetric influence that is not present in isotropic solvents.[4] In this paper, we describe a diastereospecific thietane-fused β-lactam synthesis involving the photochemistry of *N*-[(*R*)-1-phenylethyl]-*N*-tigloylthiobenzamide in the solid state.[5] Having a chiral auxiliary as a substituent on the nitrogen atom affords an opportunity for desymmetrization of the thietane ring. We show that competing and nearly isoenergetic unimolecular photocycloadditions, known in solution, can proceed selectively in the solid state.

When a monothioimide **1** was irradiated in benzene solution, both [2 + 2] thietane formation and β-hydrogen abstraction from the thiocarbonyl group proceeded, producing four β-lactams, *syn*-**2** (**A** and **B**) and *anti*-**2** (**C** and **D**), and thioketones **3** (*syn* and *anti*) (Scheme 1).[6] However, diastereoselectivity in the thietane formation was not observed, and four β-lactams were obtained in almost equal yields (Table 1).[7]

In contrast to the solution photochemistry of **1**, irradiation of the crystals provided remarkably high diastereo-

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[⊛] Abstract published in *Advance ACS Abstracts*, May 1, 1994.

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(6) We already reported that thioketones were produced via β-hydrogen transfer to a thiocarbonyl group to form 2-mercaptoaziridine followed by ring opening: see Sakamoto, M.; Omote Y.; Aoyama, H. *J. Org. Chem.* **1984**, *49*, 1837; and see ref 5b.

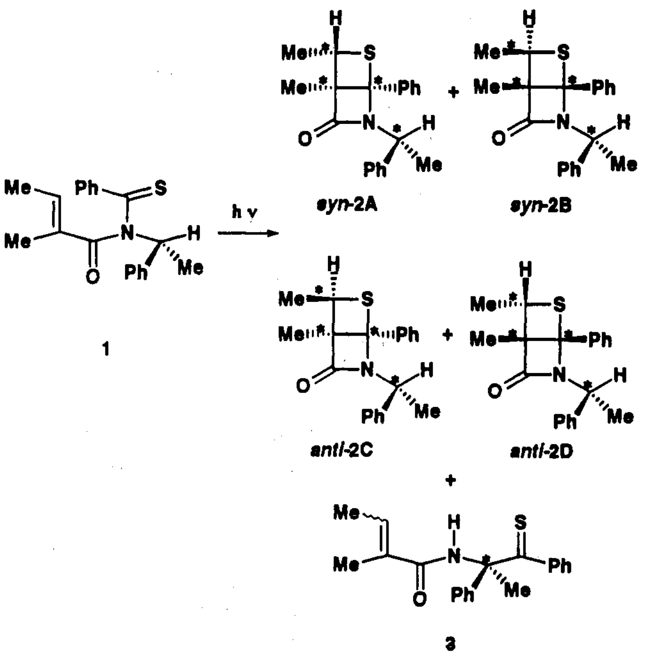
(7) The chemical yields and de values are determined by ^{1}H-NMR spectra. Since the separation of *syn*- and *anti*-**3** could not be performed, listing ee and $[\alpha]$D values was avoided.

Table 1. Product Ratios and Diastereomeric Purities from the Photoreaction of the Monothioimide 1 in Solution and Solid State

		irrad		β-lactams (2A–2D)					thioketone 3	
medium	temp	time[a]	Conv[b]	yields,[b] %	*syn*:*anti*[b] (I:II):(III:IV)[c]	*syn*/*anti*[b]	de (%) *syn*	de (%) *anti*[b]	yields,[b] %	*syn*/*anti*[b]
C_6H_6	15°C	0.5 h	98	72	(24:24):(26:26)[d]	0.9	0	0	26	1.4
solid	15°C	2.0 h	100	78	(73:17):(6:3)[d]	8.7	61	32	22	8.1
solid	−78°C	2 min	9	8	(96:4):(0:0)[d]	*e*	93	*e*	trace	*g*
solid	−78°C	5 min	19	16	(93:7):(0:0)[d]	*e*	86	*e*	3	*g*
solid	−78°C	4 h	90	64	(81:13):(3:2)[d]	19	71	*f*	26	20

[a] A 500-W high-pressure mercury lamp was used as an irradiation source. [b] Conversion, ratios, and yields were determined by ^{1}H-NMR. [c] β-Lactams were numbered temporary as *syn*-I, *syn*-II, *anti*III, or *anti*-IV, since β-lactams have unknown configurations. [d] Numbers in parentheses mean ratios of major and minor isomers for each *syn*- and *anti*-β-lactams 2. [e] *Anti*-2 was not detected. [f] The yield of *anti*-2 was low and then the exact value could not be determined. [g] The yields of thioketone 3 were low and then the value could not be determined.

Scheme 1



selectivities in the formation of 2. The temperature at which the reaction occurs is important in determining diastereoselectivity. At 15 °C, the de of *syn*-2 was 61% and the ratio of *syn*/*anti* was 8.7, which was the reverse of that in the solution reaction (*syn*/*anti* = 0.9). The solid state photoreaction proceeded even at −78 °C, and with higher diastereoselectivity. At low conversion (9%), only *syn* isomers (de = 93%) were obtained, and 71% de was observed even at 90% conversion. Furthermore, thioketone 3 was also generated in 26% yield (at 90% conv) even at −78 °C, and the yield was slightly higher than in the photolysis at 15 °C (22% yield at 100% conv).

A yellow prismatic crystal of the monothioimide 1 (mp 86–87 °C), crystallized from chloroform–hexane, was subjected to X-ray structural analysis. The crystal is orthorhombic, of space group $P2_12_12_1$, a = 13.184(4) Å, b = 15.728(8) Å, c = 8.822(3) Å, V = 1829(1) Å^3, Z = 4, ρ = 1.174(4) Å, and μ = 15.48 cm^{-1}. The structure was solved by direct methods, R = 3.7%, R_w = 3.6% for 1438 reflections.

The conformer distribution of imides is dictated by the demands of the substituents and dipole–dipole interactions.[8] As shown in the ORTEP diagram, the conformation of the imide moiety of the monothioimide 1 is *E,E* in the solid state. In our previous paper, the conformation of *N*-methacryloylthiobenzanilide was shown to be *E,Z*, and from it, thietane was obtained in good yields.[2a] It seems that the bulky α-phenylethyl substituent makes the *E,E* configuration more stable. It is apparent that these monothioimides are able to undergo [2 + 2] photocycloadditions from both the *E,Z* and *E,E* configurations, in the solid state.

In the reactant 1, the distances between the sulfur atom (S1) and the alkenyl carbon (C3) and between the thiocarbonyl carbon (C14) and the alkenyl carbon (C2) are 4.29 and 3.00 Å, respectively.[9] The sum of the sulfur atom and the carbon atom van der Waals radii is 3.5 Å. It is surprising that the cyclization proceeds in this situation in which the interatomic distance between S1 and C3 is much larger than the sum of the van der Waals radii. Furthermore, it is notable that the imide moiety is highly twisted from a plane. The twist angle τ[10] of the C(=O)-N bond is 40.8° and that of the C(=S)-N bond is 19.9°.[11] The aromatic ring twists at 55.3° relative to the thiocarbonyl bond and the torsional angle of N–C1–C2–C3 is −38.9°.

From the ORTEP diagram, it is anticipated that the *E,Z* conformation is also favorable to photochemical hydrogen transfer by the thiocarbonyl group from the β-position. Scheffer has studied a variety of ketones that undergo intramolecular hydrogen transfer in their crystalline states and he considered ground-state parameters to be the most important in determining reactivity: d, distance between O and H; Θ, the O–C–H angle; Δ, the C(=O)–H angle; and ω, the dihedral angle that the O–H vector makes with respect to the nodal plane of the carbonyl π system.[1d,12] In the reactant 1, the sulfur atom and the abstractable hydrogen atom are closely placed, and the value of d is 2.40 Å, Θ is 127.3°, Δ is 67.9°, and ω is 6.2°. The sum of the sulfur atom and the hydrogen atom van der Waals radii is 3.0 Å. From this value, it is

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(8) Mazzocchi, P. H. *Organic Photochemistry*; Padwa, A., Ed., Marcel Dekker: New York and Basel, 1981; Vol. 5, pp 422–471.

(9) In our previous work, the distances between the sulfur atom and the alkenyl carbon and between the thiocarbonyl carbon and the alkenyl carbon for *N*-methacryloylthiobenzanilide are 3.59 and 3.11 Å, respectively; see ref 2a. Furthermore, 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. Bregman, J.; Osaki, K.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.* **1964**, 2021.

(10) Twist angle τ is defined as follows: $\tau = 1/2(\omega_1 + \omega_2)$, where ω_1 and ω_2 are torsion angles O1–C1–N1–C6 and C2–C1–N1–C14, respectively, for τ of C(=O)–N. Twist angle τ for C(=S)–N is determined in the same manner. Winkler, F. K.; Dunitz, J. D. *J. Mol. Biol.* **1971**, *59*, 169.

(11) A twist angle τ of C(=O)–N and C(=S)–N for N-methacryloylthiobenzanilide is 56.0° and 22.6°, respectively; see ref 2a. Furthermore, recently it has been reported that the C(=O)–N bond of semicyclic imide, 3-pivaloyl-1,3-thiazolidine-2-thione, is highly twisted at 74.3°. Yamada, S. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1083.

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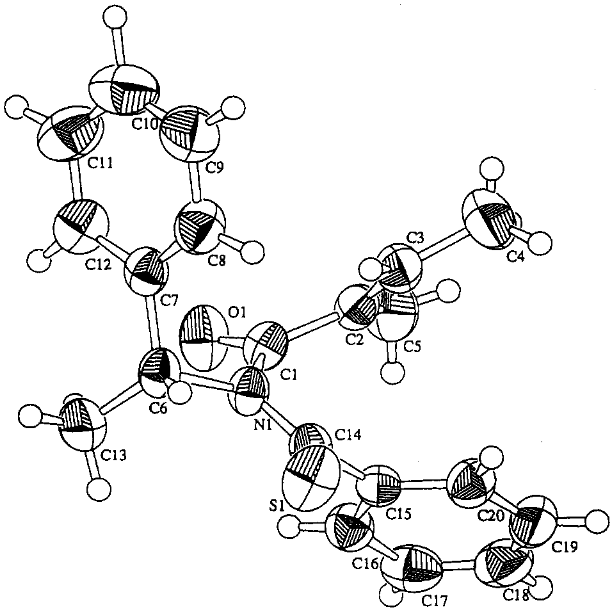

Figure 1. **ORTEP** diagram of the Monothioimide 1.

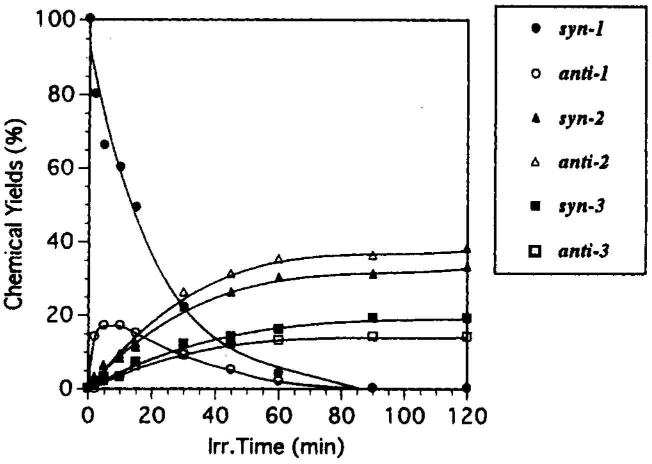

Figure 2. Correlation diagram of the photoreaction of 1 in benzene solution.

apparent that this reactant is also positioned for hydrogen transfer in the crystalline state.

The time required for the consumption of 1 and the formation of 2 (*syn* and *anti*) and 3 (*syn* and *anti*) was studied both in solution (at 15 °C) and in the solid state (at −78 °C). When 1 was irradiated in benzene solution, *syn–anti* isomerization of 1 took place early and the yields of both 2 and 3 increased roughly linearly at the expense of 1. In this photolysis, the ratios for *syn*-**2**/*anti*-**2** and *syn*-**3**/*anti*-**3** were constant at 0.9 and 1.4, respectively, throughout the reaction, even after all of 1 was consumed (Figure 2). It is concluded that the same six-membered biradical intermediate **4**, generated from both *syn*- and *anti*-**1**, led to four β-lactams (**2A–D**) (Figure 4). On the other hand, *syn*- and *anti*-thioketones **3** resulted from the corresponding *syn*- and *anti*-**1** via β-hydrogen abstraction followed by cyclization and C–N bond cleavage of an aziridine ring.[5] The ratio of *syn*-**3**/*anti*-**3** is reflective of that of the monothioimide **1**, since *syn–anti* isomerization of thioketones **3** does not take place upon prolonged irradiation.

In the solid-state reaction at −78 °C, *syn–anti* isomerization of 1 was not observed (<2%), and the yields of *syn*-**2** and *syn*-**3** increased at the expense of **1** from the start (Figure 3). In this photolysis, the formation of *anti*-**3** from *anti*-**1** is also inhibited (<2%).[13]

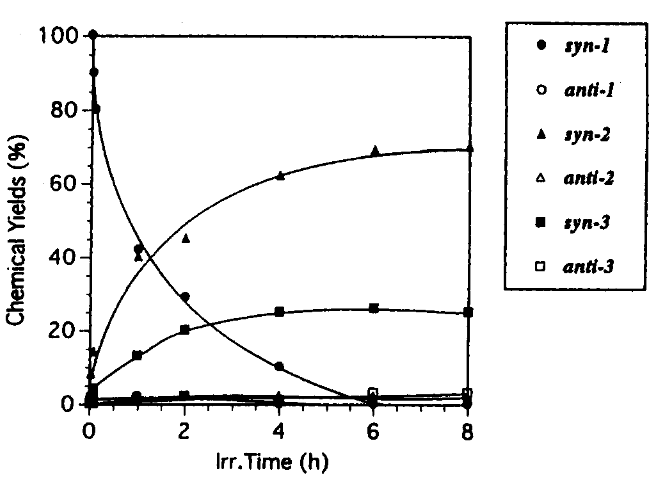

Figure 3. Correlation diagram of the photoreaction of 1 in the solid state at −78 °C.

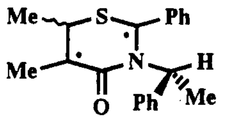

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Figure 4.

For the absolute configuration of the β-lactams *syn*-**2**, it can be speculated that the major *syn*-**2** obtained in the solid state is *syn*-**2A**, (1*R*,4*R*,5*S*)-4,5-dimethyl-1-phenyl-2-[(*R*)-1-phenylethyl]-6-thia-2-azabicyclo[2.2.0]hexan-3-one, and minor *syn*-**2** is *syn*-**2B**, on the basis of the absolute configuration of **1**, as established by X-ray structural analysis (Figure 1). Those of the *anti* isomers have uncertain structures.

In conclusion, the monothioimide **1**, with its chiral group, crystallizes in chiral space group $P2_12_12_1$ and a nearly isoenergetic unimolecular [2 + 2] photocycloaddition in solution can also proceed, and with high diastereoselectivity, in the solid state. Furthermore, this reaction is the first example of hydrogen transfer to a thiocarbonyl group in the solid state.

Experimental Section

^{1}H-NMR and ^{13}C-NMR were recorded at 400 MHz using tetramethylsilane as an internal standard, and $CDCl_3$ was used as a solvent. An Eikohsya 500-W high pressure mercury lamp was used as an irradiation source.

Preparation of *N*-[(*R*)-1-Phenylethyl]-*N*-tigloylthiobenzamide (1). Triethylamine (530 mg, 5.2 mmol) was added dropwise to a solution of *N*-[(*R*)-1-phenylethyl]thiobenzamide (960 mg, 4.0 mmol) and tigloyl chloride (570 mg, 4.8 mmol) in dry benzene (50 mL) at 0 °C under argon and the reaction mixture was then stirred for 2 h. The precipitated triethylamine hydrochloride was removed by filtration through a Celite (545) column, and the filtrate was subjected to flash chromatography on silica gel (Merk, kieselgel 60, 230–400 mesh)

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[13] It is known that photochemical *cis–trans* isomerization of alkenes takes place in the solid state; see (a) 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 in the solid state at −78 °C (<2%).

[eluent benzene–hexane 20:1)]. A yellow solid, *N*-[(*R*)-1-phenylethyl]-*N*-tigloylthiobenzamide (**1**) (1.2 g, 93%), was recrystallized from chloroform–hexane mixture.

Photochemical Reaction of 1 in Benzene Solution. A benzene solution of **1** (0.03 M) under argon was irradiated with a 500-W high pressure mercury lamp for 1 h until the starting material had almost disappeared as determined by TLC. After evaporation of the solvent, the residual mixture was subjected to chromatography on silica gel with benzene–ethyl acetate as eluent. The first fraction was obtained as a mixture of four β-lactams **2** (two *syn*-**2** and two *anti*-**2**), 4,5-dimethyl-1-phenyl-2-[(*R*)-1-phenylethyl]-6-thia-2-azabicyclo[2.2.0]hexan-3-one (**2**), in the ratio of 24:24:26:26 as determined from the ^{1}H-NMR spectrum as shown in Table 1. The second fraction was obtained as a mixture of *syn* and *anti* thioketones **3**, and the ratio of the two thioketones, 2-phenyl-2-[(2-methylbut-2-enoyl)amino]thiopropiophenone (**3**), was determined on the basis of ^{1}H-NMR spectra and was shown in Table 1.

Solid-State Photoreaction of the Monothioimide 1. All of the solid-state runs were done under an atmosphere purgged with dried argon. Solid sample was irradiated as powders prepared by grinding attached inside a Pyrex tube. The solid sample was cooled during the photolysis in either a water bath or a dry ice/methanol bath. The chemical yields and the ratios of *syn*/*anti*-**2** or -**3** were determined by ^{1}H-NMR spectra and were summarized in Table 1.

Procedure for Single-Crystal X-ray Structural Analysis of Compound 1. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu Kα radiation and a 12-kW rotating anode generator. Cell constants and an orientation matrix for data collection, obtained from a least-square refinement using the setting angle of 25 carefully centered reflections in the range $78.26 < 2\Theta < 79.97°$ corresponded to a primitive orthohombic cell. The data were collected at a temperature of 23 ± 1 °C using the ω–2Θ scan technics to a maximum 2Θ value of 120.2°. A total of 1599 reflections was collected. The intensities of three representatitve reflections were measured after every 150 reflections. The data were corrected for Lorentz and polarization effects. The structure was solved by and expanded using Fourier techniques.[14] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 1438 observed reflections ($I > 3.00\sigma(I)$) and 293 variable parameters resulted in $R = 0.037$ and $R_w = 0.036$.

Supplementary Material Available: Spectral data for *N*-[(*R*)-1-phenylethyl]-*N*-tigloylthiobenzamide (**1**) and all photoproducts, 4,5-dimethyl-1-phenyl-2-[(*R*)-1-phenylethyl]-6-thia-2-azabicyclo[2.2.0]hexan-3-one (**2**), 2-phenyl-2-[(2-methylbut-2-enoyl)amino]thiopropiophenone (**3**), and ^{1}H and ^{13}C-NMR spectra of all new compounds (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) (a) DIRDIF92: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; Garcia-Granda, S.; Gould, R. O.; Smith, J. M. M.; Smykalla, C. (1992). The DIRDIF program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands. (b) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.