"Absolute" Asymmetric Synthesis Using the Chiral Crystal Environment: Photochemical Hydrogen Abstraction from Achiral Acyclic Monothioimides in the Solid State

Masami Sakamoto,[*,†] Masaki Takahashi,[‡]
Motoki Shimizu,[†] Tsutomu Fujita,[†] Takehiko Nishio,[§]
Ikuo Iida,[§] Kentaro Yamaguchi,[⊥] and
Shoji Watanabe[†]

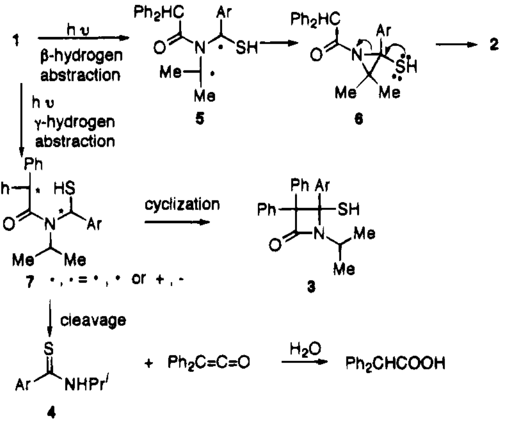
Department of Applied Chemistry, Faculty of Engineering, Chiba University, Yayoi-cho, Inage-ku, Chiba 263, Japan, Graduate School of Science and Technology, Chiba University, Yayoi-cho, Inage-ku, Chiba 263 Japan, Department of Chemistry, The University of Tsukuba, Tsukuba, Ibaraki 305, Japan, and Analytical Center, Chiba University, Yayoi-cho, Inage-ku, Chiba 263, Japan

Received June 26, 1995

Solid-state photoreactions are unique in that they proceed with different regio-, stereo-, and even product-selectivities than in solution medium because conformational equilibria are severely restricted and molecular movement is minimized in the crystalline phase.[1,2] Furthermore, one of the most attractive features of a solid-state photoreaction is the potential for absolute asymmetric control. This provides not only a plausible explanation for the prebiotic origin of optical activity but may also provide an attractive general method of asymmetric synthesis.[3−6] In this paper, we will describe how the photochemical reaction of acyclic monothioimides can proceed product-selectively in the solid state and will present a new example of "absolute" asymmetric synthesis involving a photochemical hydrogen abstraction by a thiocarbonyl sulfur atom.

Recently, we reported that the photochemical reaction of acyclic monothioimides in solution entails hydrogen abstraction by the thiocarbonyl sulfur atom from the β, γ, and δ positions and that the regioselectivity depends on the substituents on the nitrogen atom and the acyl group.[7−9] When *N*-(diphenylacetyl)-*N*-isopropylthiobenzamide (**1a**) was irradiated in benzene solution, hydrogen abstraction from both the β- and γ-positions by the thiocarbonyl sulfur proceeded to give thioketone **2a** (24% yield), azetidin-2-one **3a** (47% yield), and thioamide **4a** (12% yield); diphenylacetic acid was also detected. Photolysis of another monothioimide, **1b**, under the same conditions gave the corresponding thioketone **2b** (27% yield) and azetidin-2-one **3b** (56% yield) accompanied by small amount of thioamide **4b** (Table 1). A mechanistic explanation is offered in Scheme 1. 1,3-Diradical **5**, formed by β-hydrogen abstraction, and 2-mercaptoaziridine **6** are the intermediates in the formation of thioketone **2**. The alternative γ-hydrogen abstraction leads to a 1,4-diradical or zwitterionic intermediate which cyclizes to azetidinone **3** or cleaves to thioamide **4** and diphenylketene.

Scheme 1



Irradiation of the powdered crystals of **1** with a high-pressure mercury lamp under argon at 0 °C showed different photochemical behavior from that in benzene solution. Contrary to the photochemical results in solution media in which azetidin-2-ones **3** (γ-hydrogen abstraction products) were formed as major products, thioketones **2** (β-hydrogen abstraction products) were obtained as major products of the solid-state photoreactions. The propensity is clearly shown in the low temperature photolysis (at −45 °C). When the monothioimides **1** were irradiated at −45 °C, the red color faded with irradiation time and colorless crystals were obtained. The photolysate gradually turned to a purple color derived from thioketones **2** upon warming to room temperature. The colorless precursor to the thioketones is ascribed to the 2-mercaptoaziridines which are stable at low temperature.

More striking is that the photoproducts **3a** and **3b** obtained in the solid-state photoreaction are optically active; the $[\alpha]_D$ values and the enantiomeric excesses are shown in Table 1.

Next, the trapping of unstable mercaptoaziridines **6** was attempted by acetylation since these should be optically active. After the powdered monothioimide **1** was irradiated at −45 °C, the photolysate was dissolved in toluene at −78 °C, and then three molecular equivalents of acetyl chloride and triethylamine were added. Three types of acetylated materials, **8**−**10**, were isolated accompanied by small amounts of thioketone **2** and thioamide **4** (Table 2). All of the acetylated materials showed optical activity. For the reaction of **1a**, 84% ee of 2-(acetylthio)aziridine **8a**, 50% ee of 4-(acetylthio)-oxazoline **9a**, and 20% ee of 4-(acetylthio)oxazolidin-2-one **10a** were obtained in 39%, 10%, and 16% yields, respectively. In the reaction of **1b**, corresponding opti-

---

[†] Department of Applied Chemistry.
[‡] Graduate School of Science and Technology.
[§] Department of Chemistry.
[⊥] Analytical Center.

(1) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York and Basel, 1987; Vol. 8, pp 249−338.

(2) (a) Zimmerman, H. E.; Zuraw, M. J. *J. Am. Chem. Soc.* **1989**, *111*, 2358. (b) Zimmerman, H. E.; Zuraw, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 5245.

(3) (a) Venkatesan, K.; Ramamurthy, V. *Photochemistry in Organized and Constrained Media*, Ramamurthy, V., ed., VCH, New York, 1991; p 133−184. (b) Scheffer, J. R.; Pokkuluri, P. R. *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; pp 185−246. (c) Vaida, M.; Popvitz-Biro, R.; Leiserowitz, L.; Lahav, M. *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; pp 247−302.

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

(5) Sakamoto, M.; Takahashi, M.; Fujita, T.; Watanabe, S.; Iida, I.; Takehiko, N.; Aoyama, H. *J. Org. Chem.* **1993**, *58*, 3476.

(6) Sakamoto, M.; Takahashi, M.; Fujita, T.; Iida, I.; Takehiko, N.; Watanabe, S. *J. Org. Chem.* **1995**, *60*, 4682.

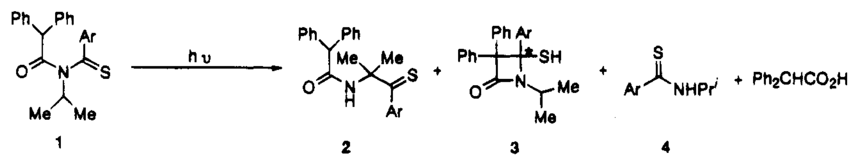
(7) (a) Sakamoto, M.; Nishio, T. *J. Synth. Org. Chem. Jpn. (Yuki Gosei Kagaku Kyokai-shi)* **1994**, *52*, 685. (b) Sakamoto, M.; Aoyama, H.; Omote, Y. *J. Org. Chem.* **1984**, *49*, 1837.

(8) (a) Sakamoto, M.; Aoyama, H.; Omote, Y. *Tetrahedron Lett.* **1985**, *26*, 4475. (b) Sakamoto, M.; Watanabe, S.; Fujita, T.; Tohnishi, M.; Aoyama, H.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2203.

(9) Sakamoto, M.; Tohnishi, M.; Fujita, T.; Watanabe, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 347.

0022-3263/95/1960-7088$09.00/0

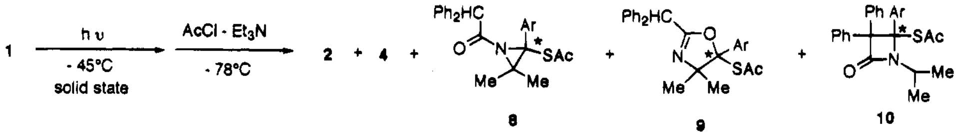
Table 1. Photochemical Reaction of Monothioimides 1a and 1b in Solution and Solid State



thioimides	Ar	condns		convn (%)	2 yields (%)	3 yields (%)	3 $[\alpha]^{20}{}_D$[a] (deg)	3 ee[b] (%)	4 yields (%)
1a	Ph	benzene	hν (20 °C)	100	24	47	0	0	12
		solid state	hν (0 °C)	60	48	17	+6	8	20
			1. hν (−45 °C) 2. warm up	62	64	16	+15	20	19
1b	*p*-ClPh	benzene	hν (20 °C)	100	27	56	0	0	10
		solid state	hν (0 °C)	70	55	18	+5	5	24
			1. hν (−45 °C) 2. warm up	80	60	19	+12	13	20

[a] c = 1.0 in $CHCl_3$. [b] The ee value was determined by ^{1}H-NMR using chiral shift reagent $Eu(hfc)_3$.

Table 2. Photochemical Reaction of Monothioimides 1a and 1b at Low Temperature Followed by Acetylation



thioimides	convn (%)	2 yields (%)	4 yields (%)	8 yields (%)	8 $[\alpha]^{20}{}_D$[a] (deg)	8 ee[b] (%)	9 yields (%)	9 $[\alpha]^{20}{}_D$[a] (deg)	9 ee[b] (%)	10 yields (%)	10 ee[c] (%)
1a	70	15	15	39	−56	84	10	−116	50	16	20
1b	80	10	18	37	−43	70	13	−76	40	19	13

[a] c = 1.0 in $CHCl_3$. [b] The ee value was determined by HPLC using chiral cell OJ (DAICEL chemical industries). [c] The ee was determined by ^{1}H-NMR using chiral shift reagent $Eu(hfc)_3$.

cally active materials **8b**–**10b** were obtained as shown in Table 2. The structures of **8a** and **9a** were established by X-ray crystallographic analyses.[10,11,15]

As for the formation of oxazoline **9**, it is known that *N*-acyl derivatives of aziridines are readily converted upon heating to 2-oxazolines and that the rearrangement occurs by intramolecular attack of the carbonyl oxygen at the ring carbon to cause rupture of the system.[12] It seems that the diminution of ee values for oxazolines **9** relative to those of aziridines **8** resulted from this transformation.

Concomitant with the photochemical studies, the crystal and molecular structures of the monothioimides **1** were determined by a direct method, single crystal X-ray diffraction. The crystals of **1a** and **1b** are orthorhombic and of chiral space group $P2_12_12_1$.[13-15] These monothioimides show preferential *E*,*E* geometry in the crystalline state which is favorable to photochemical β-hydrogen transfer by the thiocarbonyl group. Table 3 summarizes the C=S···H_β and C=S···H_γ distances for the monothioimides. Scheffer has studied a variety of ketones that undergo intramolecular hydrogen transfer in their crystalline state and has indicated that hydrogen atom abstraction by oxygen fails when the C=O···H contacts exceed the sum of the van der Waals radii by 0.3–0.4 Å. In the monothioimides **1**, the C=S···H_β contact is 2.57 Å for **1a** and 2.52 Å for **1b** which is considerably shorter than the sum of the van der Waals radii of the sulfur atom and the hydrogen atom, 3.0 Å. Thus, these reactants are favorably positioned for β-hydrogen transfer in the crystalline state. On the other hand, the C=S···H_γ distances are considerably greater than the sum of the van der Waals radii. In fact, the hydrogen abstraction by the sulfur atom takes place for distances 0.79 and 0.84 Å longer than the sum of van der Waals radii.

Table 3. Crystallographic Constants in Monothioimides 1a and 1b

thioimides	C=S···H_β (Å)	C=S···H_γ (Å)
1a	2.57	3.79
1b	2.52	3.84

Optically ctive photoproducts that show reversed optical rotations were also obtained, with similar ee values, by the photolysis of the crystals of **2a** and **2b** recrystallized from other batches. Furthermore, each chiral crystal could be prepared selectively and in bulk by seeding methods.[4-6] This reaction provides a fine example of lattice-induced stereoselectivity.

JO951148H

---

(10) **8a**: colorless prismatic crystals from hexane–chloroform, mp 91–92 °C, and X-ray diffraction indicated the space group $P1$, a = 11.665(3) Å, b = 13.296(4) Å, c = 8.837(2) Å, V = 1166.3(7) Å^3, α = 97.75(3)°, β = 104.62(2)°, γ = 115.19(2)°, Z = 2, ρ = 1.183 g/cm^3, μ = 13.90 cm^{-1}; R = 0.055, R_W = 0.056.

(11) Racemic **9a**: colorless prismatic crystals from hexane–chloroform, mp 115–116 °C, the space group $P2_1/c$, a = 6.6290(6) Å, b = 20.656(6) Å, c = 16.878(3) Å, V = 2154.7(3) Å^3, β = 99.70(1)°, Z = 4, ρ = 1.281 g/cm^3, μ = 15.05 cm^{-1}; R = 0.051, R_W = 0.053.

(12) (a) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202. (b) Heine, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 528.

(13) **1a**: red prismatic crystals from hexane, mp 89.5–90.5 °C, and the X-ray crystal structure analysis indicated the chiral space group $P2_12_12_1$, a = 10.322(3) Å, b = 11.547(3) Å, c = 17.295(3) Å, V = 2061.6 Å^3, Z = 4, ρ = 1.20 g/cm^3, μ = 1.6 cm^{-1}; R = 0.039, R_W = 0.04.

(14) **1b**: red prismatic crystals from hexane–chloroform, mp 80–81 °C, space group $P2_12_12_1$, a = 10.091(1) Å, b = 22.6806 (9) Å, c = 9.437(1) Å, V = 2160.0(4) Å^3, Z = 4, ρ = 1.254 g/cm^3, μ = 25.66 cm^{-1}; R = 0.079, R_W = 0.065.

(15) The author has deposited atomic coordinates for **1a**,**b**, **8a**, and **9a** 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.