X-Ray crystallographic analysis and the photochemical reaction of *N*-benzyl-*N*-methylmethacrylthioamide in solution and the solid state

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Photochemical reaction of asymmetrically substituted *N*-benzyl-*N*-methylmethacrylthioamide both in solution and in the solid state was investigated. The thioamide exists in an equilibrium between two rotamers owing to rotation about the C(=S)–N bond. The free energy of activation for the bond rotation was estimated as 22.7 kcal mol^{-1} by temperature-dependent ^{1}H NMR spectroscopy. The thioamide crystallized in a chiral fashion, and the photoreaction in the solid state gave the optically active β-thiolactam whereas both the β-thiolactam and the corresponding thiazolidinethione were obtained by solution-phase photochemistry.

Introduction

Solid-state photoreaction has received much attention from both mechanistic and synthetic perspectives, because the reaction provides chemoselectivity as well as stereoselectivity for a wide range of products compared with reactions that occur in solution, due to restriction of molecular movement imposed by the environment.[1–6] Recently, we reported that unsymmetrically substituted *N*-benzyl-*N*-isopropyl-α,β-unsaturated thioamides existed in an equilibrium between two rotamers owing to rotation about the C(=S)–N bond in solution; however, the mixture converged to only one isomer in the crystallization step.[7] We have now found that achiral *N*-benzyl-*N*-methylmethacrylthioamide crystallized into a chiral form, and that photoreaction provides not only a new example of absolute asymmetric synthesis but also affords unique chemoselectivity according to the reaction media.

Results and discussion

N-benzyl-*N*-methylmethacrylthioamide **1** was conveniently synthesized by thionation of the corresponding amide with Lawesson's reagent.[8] The ^{1}H NMR spectrum measured at 60 °C showed that **1** existed as a mixture of two rotamers owing to rotation about the C(=S)–N bond, and the distribution of **1A**:**1B** was 55:45 as shown in Fig. 1(1). The free energy of activation of the rotational barrier was measured by the temperature-dependent ^{1}H NMR spectra. Fig. 1 shows the spectra of **1** in [$^2H_6$]DMSO at various temperatures. Two independent peaks at around δ 3.2 owing to methyl protons on the nitrogen atom became equivalent on raising the temperature to 110 °C. The free energy of activation of the rotation about the (C=S)–N bond could be estimated as 22.7 kcal mol^{-1}† from the temperature of the coalescence point (T_C) and the difference in the chemical shifts of the signals of the two conformers ($\Delta\nu$).[9–11]

Recrystallization of **1** from hexane yielded yellow crystals, which were analyzed by X-ray crystallography; the space group was $P2_12_12_1$. It is notable that the conformation of the thioamide chromophore is *Z* (s-*cis*) in which the thiocarbonyl sulfur atom and the benzyl group are closely placed as shown in Fig. 2. The absolute configuration was not determined. The alkenyl double bond is remarkably twisted from the amide plane; the twist angle C(7)–C(3)–C(5)–S(1) is −101.6°.

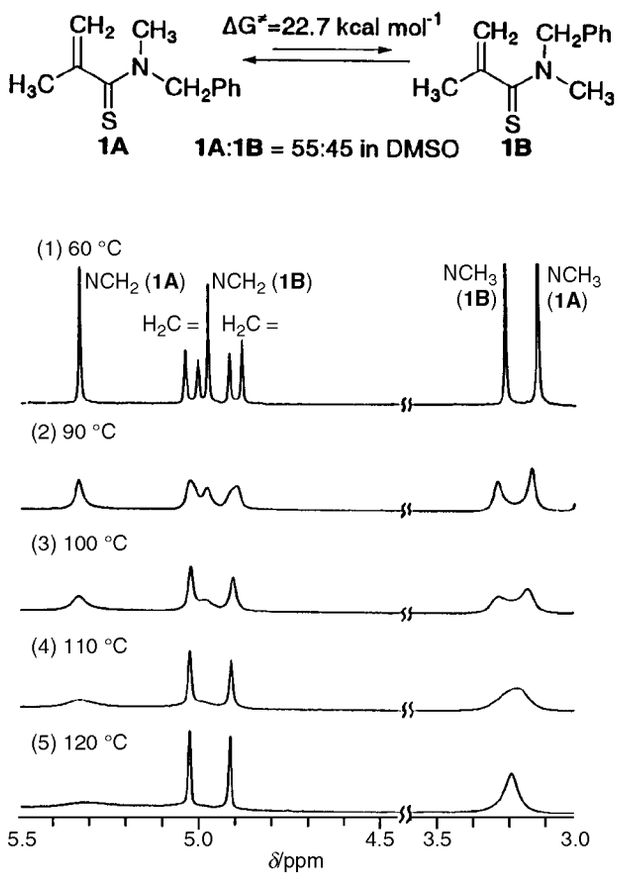
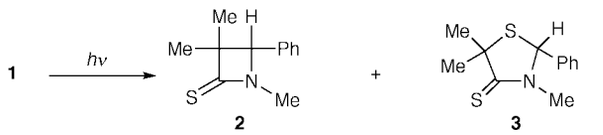


Fig. 1 ^{1}H NMR spectra of thioamide **1** in [$^2H_6$]DMSO at various temperatures from 60 to 120 °C.

When a 0.02 M benzene solution of thioamides **1** was irradiated with a high-pressure mercury lamp under argon, β-thiolactam **2** and thiazolidinethione **3** were obtained in 44 and 11%

† 1 cal = 4.184 J.

Table 1 Photoreaction of thioamides **1** in both solution and the solid state



Entry	Conditions	Recovered **1** (%)	Yield (%) [b] **2**	**3**	ee% [c]
1	benzene (0.02 M) [a]	35	29(44)	7(11)	0
2	benzene (0.2 M) [a]	40	21(35)	12(20)	0
3	solid state (0 °C)	81	9(47)	0	31(−29)

[a] Concentration of **1**. [b] Numerals in parentheses are the chemical yields determined on the basis of consumed **1**. [c] ee% of **2** and the numeral in parentheses is the $[\alpha]_D^{20}$ of **2** (*c* 1.0, $CHCl_3$), in units of 10^{-1} deg cm^2 g^{-1}.

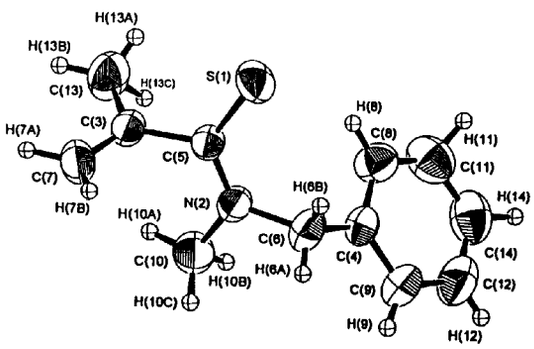


Fig. 2 ORTEP drawing of **1** with crystallographic numbering scheme. The absolute configuration is tentative. Selected bond lengths (Å) and angles (°): S(1)–C(5) 1.663(2), N(2)–C(5) 1.331(3), N(2)–C(6) 1.468(3), N(2)–C(10) 1.453(4), C(3)–C(5) 1.505(3), C(3)–C(7) 1.383(3), C(3)–C(13) 1.423(4), C(4)–C(6) 1.510(3); C(5)–N(2)–C(6) 122.1(2), C(5)–N(2)–C(10) 123.8(2), C(6)–N(2)–C(10) 114.0(2), C(5)–C(3)–C(7) 117.8(2), C(5)–C(3)–C(13) 118.8(2), C(7)–C(3)–C(13) 123.2(2), C(6)–C(4)–C(8) 121.2(2), C(6)–C(4)–C(9) 120.0(2), C(8)–C(4)–C(9) 118.7(2), S(1)–C(5)–N(2) 125.4(2), S(1)–C(5)–C(3) 117.7(2), N(2)–C(5)–C(3) 116.9(2), N(2)–C(6)–C(4) 113.7(2); C(6)–N(2)–C(5)–S(1) −9.6(2), C(6)–N(2)–C(5)–C(3) −168.8(3), C(10)–N(2)–C(5)–S(1) −174.4(3), C(10)–N(2)–C(5)–C(3) 7.2(2), C(5)–N(2)–C(6)–C(4) −107.6(3), C(10)–N(2)–C(6)–C(4) 76.0(3), C(7)–C(3)–C(5)–S(1) −101.6(3), C(7)–C(3)–C(5)–N(2) 77.0(3), C(13)–C(3)–C(5)–S(1) 74.4(3), C(13)–C(3)–C(5)–N(2) −107.1(3), C(8)–C(4)–C(6)–N(2) 55.5(3).

yield, respectively, at 65% conversion (Table 1, entry 1). The structure of **2** was determined on the basis of its spectral data. The high-resolution mass (FAB) spectrum showed the protonated molecular-ion peak at *m*/*z* 206.0987; Calc. for $C_{12}H_{16}NS$ (MH^+, 206.1003), which indicates that **2** is an isomer of the starting thioamide **1**.

The structure of **3** was also determined by its spectral data. The mass spectrum (FAB) showed the protonated molecular-ion peak at *m*/*z* 238.0724 (MH^+); Calc. for $C_{12}H_{16}NS_2$ (MH^+, 238.0724), which showed that a sulfur atom had been added to the thioamide **1**. Finally, the structure was established by X-ray structural analysis as shown in Fig. 3.

Achiral substrates sometimes adopt a chiral orientation in the crystal lattice, even in the absence of any outside influence.[1–6,12–14] The chirality can be transformed *via* a solid-state photoreaction to give a single enantiomer as the product. The thioamide **1** crystallized in a chiral space group, $P2_12_12_1$, which indicates that one enantiomeric molecule comprises one single crystal. When powdered thioamide **1** was irradiated in the solid state at 0 °C, at up to 19% conversion, optically active β-thiolactam **2** was isolated (Table 1, entry 3). When the solid unfortunately changed to an amorphous substrate at around 20% conversion, the irradiation was terminated.

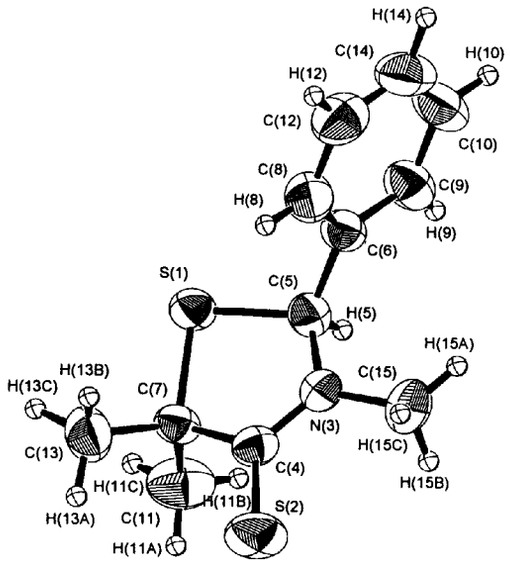
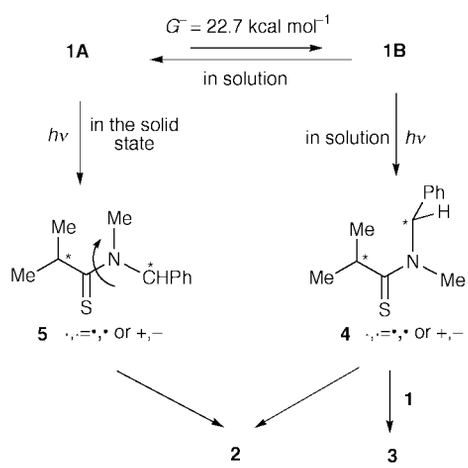


Fig. 3 ORTEP drawing of **3** with crystallographic numbering scheme. Selected bond lengths (Å) and angles (°): S(2)–C(4) 1.660(1), N(3)–C(4) 1.323(2), N(3)–C(5) 1.476(2), N(3)–C(15) 1.455(2), C(4)–C(7) 1.523(2), C(5)–C(6) 1.515(2), C(7)–C(11) 1.526(2), C(7)–C(13) 1.523(2); C(4)–N(3)–C(5) 118.5(1), C(4)–N(3)–C(15) 123.1(1), C(5)–N(3)–C(15) 117.8(1), S(2)–C(4)–N(3) 125.5(1), S(2)–C(4)–C(7) 121.4(1), N(3)–C(4)–C(7) 112.9(1), N(3)–C(5)–C(6) 112.3(1); C(5)–N(3)–C(4)–S(2) 179.1(2), C(5)–N(3)–C(4)–C(7) 3.0(1), C(15)–N(3)–C(4)–S(2) 8.3(1), C(15)–N(3)–C(4)–C(7) −167.8(2), C(4)–N(3)–C(5)–C(6) 136.0(2), C(15)–N(3)–C(5)–C(6) −52.7(1), S(2)–C(4)–C(7)–C(11) −77.1(1), S(2)–C(4)–C(7)–C(13) 45.8(1), N(3)–C(4)–C(7)–C(11) 99.2(1), N(3)–C(4)–C(7)–C(13) −137.9(2).

Thiazolidinethione **3** was not detected under these reaction conditions. The enantiomeric excess (ee) was 31% as determined by HPLC using a chiral cell OD column (Daicel Chemical Ind.). The solid-state photoreaction did not proceed at a lower temperature (−50 °C).

We previously reported the mechanism for the formation of β-thiolactam **2** in the photoreaction of related α,β-unsaturated thioamides.[7,15] In solution photochemistry, the alkenyl carbon can abstract a benzylic hydrogen from the conformer **1B**, which process was followed by cyclization to **2** *via* a zwitterionic or biradical intermediate **4** (as depicted in Scheme 1). The origin



Scheme 1

of the formation of thiazolidinethione **3** is not well understood; however, it is apparent that the sulfur atom is derived from another molecule of thioamide **1**, and it is conceivable that the zwitterionic intermediate was trapped by the thiocarbonyl group intermolecularly. When the thioamide **1** was irradiated in higher concentration (0.2 M), the ratio of thiazolidinethione

increased as shown in Table 1, entry 2. The concentration effect indicated that **3** is formed by an intermolecular reaction.

In the solid state, all crystals are composed of only conformer **1A**, and the alkenyl β-carbon is closely placed to a hydrogen atom of the methyl group. In the solid-state reaction, conformational factors become more important because interconversion involving dramatic movement of the substituents cannot usually occur. From the X-ray analysis, hydrogen abstraction from the benzyl group is unfavored, because the benzyl hydrogen is far from the alkenyl carbon atom. If the hydrogen abstraction proceeds, drastic conformational reorientation for the cyclization to β-thiolactam **2** is necessary in the solid state. In compound **1** the alkenyl group is nearly orthogonal to the thioamide plane, and the distance between the nearest benzyl hydrogen and the alkenyl β-carbon is 4.52 Å, which is much longer than the sum of the van der Waals radii of the two atoms (2.90 Å). When the reaction sites are far apart, hydrogen abstraction from the benzyl group occurred. Furthermore, drastic molecular movement involving rotation about the C=(S)–N bond is necessary for cyclization to the β-thiolactam, as shown in intermediate **5** in Scheme 1. Therefore, it is difficult to maintain a crystalline phase throughout the reaction. It is presumed that the initial hydrogen abstraction takes place at defective crystals or in a disordered zone, and is followed by cyclization with a minimum amount of molecular movement affected by steric repulsion of the neighboring molecules.

In conclusion, unsymmetrically substituted *N*-benzyl-*N*-methylmethacrylthioamide exists as a mixture of two rotational isomers owing to rotation about the C(=S)–N bond under homogeneous conditions, whereas the crystals were composed of only one conformer. The reaction provides a fine example of absolute asymmetric synthesis using a chiral crystalline environment, and marked differences resulted in the chemoselectivity depending on the reaction media.

Experimental

General

NMR spectra were recorded on $CDCl_3$ solutions on a JEOL GSX-400 and 500 operating at 400 and 500 MHz, respectively, for ^1H and ^{13}C NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard. Elemental analyses were made using a Perkin-Elmer-240 instrument. IR spectra were recorded on a JASCO FT/IR-230 spectrometer.

General procedure for the preparation of *N*-benzyl-*N*-methylmethacrylthioamide 1

The thioamide **1** was prepared by treatment of the corresponding methacrylamide with Lawesson's reagent. To a toluene solution containing 1.0 g (4.9 mmol) of *N*-benzyl-*N*-methylmethacrylamide was added 0.5 g (2.5 mmol) of Lawesson's reagent at room temperature. The reaction mixture was heated at 80 °C for 3 h and then cooled to room temperature. The solvent was removed *in vacuo*, the residual mixture was subjected to chromatography on silica gel, and the crystalline thioamide **1** was recrystallized from a $CHCl_3$–hexane mixture to afford slightly yellow prisms.

***N*-Benzyl-*N*-methylmethacrylthioamide 1.** Yield 70%; mp 41–42 °C; IR (KBr)/cm^{-1} 1505; UV (C_6H_{12})/nm 283 (ε 10 900), 385 (140); ^1H NMR ([$^2H_6$]DMSO) δ 3.22 and 3.30 (each s, total 3H, NMe), 4.88, 4.90, 5.00, 5.04 (each br s, total 2H, H_2C=C), 4.97 and 5.32 (s, 2H, CH_2Ph), 7.3–7.5 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ_C 22.3 and 23.3 (each q, 2-Me), 40.0 (q, NMe), 56.5 (t, NCH_2), 112.5 (t, 3-C), 127.1 (d, Ph), 128.1 (d, Ph), 128.3 (d, Ph), 129.1 (d, Ph), 129.2 (d, Ph), 135.5 (s, Ph), 147.2 (s, 2-C), 204.3 (s, C=S) (Calc. for $C_{12}H_{15}NS$: C, 70.21; H, 7.37; N, 6.83. Found: C, 70.01; H, 7.37; N, 6.78%). The structure was established by X-ray crystallographic analysis.

X-Ray structural analysis of 1

Recrystallization of **1** from hexane yielded yellow crystals, which were analyzed by X-ray crystallography; orthorhombic, space group $P2_12_12_1$, $a = 7.165(2)$, $b = 23.285(6)$, $c = 6.981(2)$ Å, $V = 1164.5(5)$ Å^3, $Z = 4$, $\rho = 1.169$ g cm^{-3}, μ(Cu-Kα) = 20.993 cm^{-1}, $T = 298$ K. The structure was solved by direct methods and expanded using Fourier techniques. Final R and R_w were 0.042 and 0.058, respectively, for 1283 reflections. The absolute configuration was not determined and Fig. 2 shows the tentative configuration. CCDC reference number 207/372.

Photochemical reaction of 1 in benzene solution

A benzene solution (20 cm^3) of **1** (0.02 M) under argon was irradiated for 4 h with a 1000 W high-pressure mercury lamp. After evaporation of the solvent, the residual mixture was subjected to chromatography on silica gel with toluene–ethyl acetate (10 : 1) as eluent.

Solid-state photoreaction of the thioamide 1

The solid-state run was done under an atmosphere purged with dry argon. The solid sample was irradiated for 4 h as a powder prepared by grinding, and placed inside a Pyrex slide. The chemical yields are summarized in Table 1. The optical purity was determined by HPLC using a chiral cell OD column (Daicel Chemical Ind.).

1,3,3-Trimethyl-4-phenylazetidine-2-thione 2. IR ($CHCl_3$) 2965 and 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3H, 3-Me), 1.43 (s, 3H, 3-Me), 3.14 (s, 3H, NMe), 4.82 (s, 1H, 4-H), 7.3–7.4 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ_C 20.6 (q, 3-Me), 24.5 (q, 3-Me), 47.5 (d, NMe), 58.6 (s, 3-C), 74.4 (d, 4-C), 126.0 (d, Ph), 127.0 (d, Ph), 128.5 (d, Ph), 136.1 (s, Ph), 211.2 (s, C=S); HRMS (FAB): Calc. for $C_{12}H_{16}NS$: (MH^+), 206.1003. Found: *m*/*z*, 206.0987.

3,5,5-Trimethyl-2-phenylthiazolidine-4-thione 3. IR (KBr) 2964, 1638 and 1451 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H, 5-Me), 1.80 (s, 3H, 5-Me), 3.09 (s, 3H, NMe), 5.81 (s, 1H, 2-H), 7.3–7.4 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ_C 32.4 (q, 5-Me), 33.0 (q, 5-Me), 37.5 (q, 3-Me), 61.9 (s, 5-C), 71.1 (d, 2-C), 127.6 (d, Ph), 129.2 (d, Ph), 129.4 (d, Ph), 137.8 (s, Ph), 207.2 (s, C=S); HRMS (FAB): Calc. for $C_{12}H_{16}NS_2$: (MH^+), 238.0724. Found: *m*/*z*, 238.0724.

X-Ray structural analysis of 3

Recrystallization of **3** from a mixture of chloroform and hexane gave yellow crystals; monoclinic, space group $P2_1/a$, $a = 15.237(4)$, $b = 10.006(4)$, $c = 8.257(2)$ Å, $\beta = 90.48(2)°$, $V = 1258.8(7)$ Å^3, $T = 293$ K, $Z = 4$, $\rho = 1.25$ g cm^{-3}, μ(Cu-Kα) = 35.594 cm^{-1}, $F(000) = 503$. The structure was solved by direct methods and refined by full-matrix least-squares, where the final R and R_w were 0.056 and 0.083, respectively, for 2101 reflections. CCDC reference number 207/372.

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