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Chiral Thietane-Fused β-Lactam from an Achiral Monothioimide Using the Chiral Crystal Environment

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The achievement of an asymmetric synthesis starting from an achiral reagent and in the absence of any external chiral source has long been an intriguing challenge to chemists. A material that crystallizes in a chiral space group is characterized by the fact that the environment of the molecules is chiral. 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.[1]

Since the concept of a topochemically controlled reaction was established by Schmidt in 1964,[2] various approaches to asymmetric synthesis using a solid-state reaction have been attempted, most actively by the research group at the Weizmann Institute.[2,3] Their studies have been concerned with the bimolecular reactions of chiral crystals in the solid state. In these studies successful absolute asymmetric syntheses have been performed by using topochemically controlled four-center type photodimerizations of a series of unsymmetrically substituted conjugated diolefin crystals.[4] On the other hand, only a few successful absolute asymmetric syntheses for unimolecular photochemical reactions have been reported. These experiments have focused on the di-π-methane rearrangement[5] and the Norrish type II reaction.[5,6] In the present communication, we report the first example of an absolute asymmetric synthesis of a thietane via a topochemically controlled unimolecular photochemical [2 + 2] cycloaddition.

As shown by X-ray crystallography, *N*-(thiobenzoyl)methacrylanilide (**1**), mp 79–81 °C, forms orange prisms from hexane that are chiral, with space group $P2_12_12_1$, $a = 9.535$ (2) Å, $b = 9.782$ (2) Å, $c = 16.428$ (3) Å, $V = 1535.3$ Å^3, $Z = 4$, $\rho = 1.22$ g/cm^3, and $\mu = 2.0$ cm^{-1}. The structure was solved by the direct method and refined by the method of full-matrix least-squares. Final R and R_w were 0.034 and 0.033 for 1330 reflections.

In solution, the monothioimide (**1**) undergoes [2 + 2] cyclization to afford the thietane-fused β-lactam (**2**), which has two chiral centers (Scheme I).[7] An important goal was to determine whether the transformation of **1** to **2** occurs in the crystalline state, because the ORTEP diagram of the monothioimide **1** indicates that the molecular conformation is compatible with cyclization (Figure 1). When powdered crystals of the monothioimide **1**, recrystallized from hexane, were irradiated under nitrogen through a Pyrex filter with the UV light from a 500-W high-pressure mercury lamp at 0 °C for 12 h, a transformation occurred and the photoproduct was purified by column chromatography on silica gel; optically active β-lactam (+)-**2** was obtained in 75% yield, $[\alpha]_D$ +23° (*c* 0.1 in $CHCl_3$), 10% enantiomeric excess (ee). The solid-state photoreaction proceeded even at −45 °C, and optically active (+)-**2** which showed a higher ee value was formed, $[\alpha]_D$ +93° (*c* 0.1 $CHCl_3$), 40% ee (conv 30%, yield 70%). The crystals were inert toward photolysis at −78 °C. Upon irradiation of chiral crystals of (−)-**1**[8] under the same conditions, optically active β-lactam (−)-**2** was obtained in almost the same ee value. The optical purity was determined by chiral NMR shift reagent studies at 400 MHz (Eu(hfc)$_3$, Aldrich). Seven of the ten photolyses gave (+)-**2** (the crystals were taken from different batches). A large quantity of (+)- or (−)-**1** was prepared selectively and in bulk by seeding with crystals of (+)- or (−)-**1** during recrystallization.

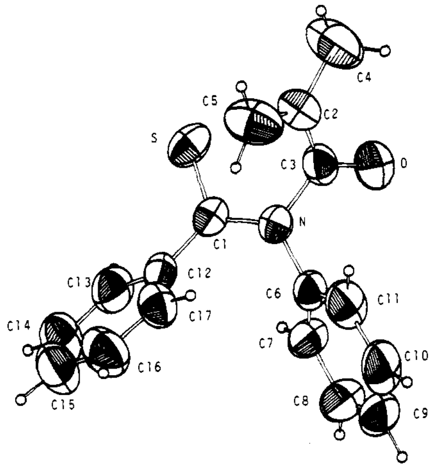
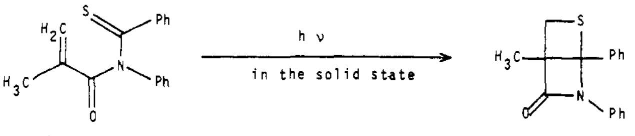


Figure 1. ORTEP drawing of the monothioimide **1**.

Scheme I



chiral crystal (1)

optically active (2)

When the chiral crystals of the monothioimide **1** were dissolved in THF at −78 °C and the solution was irradiated at that temperature, racemic β-lactam was formed and asymmetric synthesis was not observed in this photolysis.

These results indicate that *N*-(thiobenzoyl)methacrylanilide (**1**) affords chiral crystals in bulk, and the solid-state photoreaction gives optically active thietane-fused β-lactam **2**. Thietane formation is a topochemically controlled process and occurs stereospecifically in the solid state. 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 for substrates in which the reacting double bonds are parallel.[9] In the reactant **1**, the distances between the sulfur atom (S) and the alkenyl carbon (C5) and between the thiocarbonyl carbon (C1) and the alkenyl carbon (C2) are 3.59 and 3.11 Å, respectively. This reaction provides the first example of an absolute asymmetric thietane synthesis via a unimolecular [2 + 2] photocycloaddition in the solid state. We are continuing to explore the scope and limitations of this absolute asymmetric [2 + 2] thietane formation.

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