

# Efficient Aziridine Synthesis in Metastable Crystalline Phases by Photoinduced Denitrogenation of Crystalline Triazolines

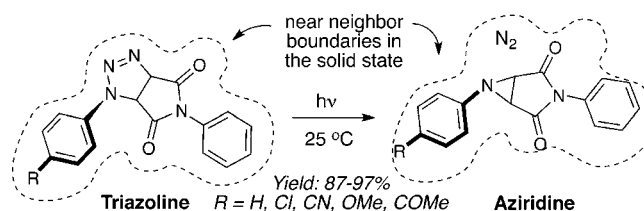
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## ABSTRACT



The solid-state photodenitrogenation of crystalline triazolines proceeds with high efficiency to form the corresponding aziridines in high chemical yields upon selection of the proper irradiation wavelength. It was shown that the solid-to-solid reactions occur by formation of the product in metastable crystalline phases.

Aziridines (**2**, Scheme 1) are three-membered ring nitrogen-containing heterocycles that are frequently used as intermediates for selective ring-opening reactions<sup>1</sup> and can be found in the structure of several natural products. Some synthetic aziridines exhibit antitumor and antibiotic activities.<sup>2</sup> Among the many strategies developed to prepare them,<sup>3</sup> the thermal and photochemical denitrogenation of 2-triazolines (**1**) provides a simple approach to form the strained three-membered ring by taking advantage of a highly energetic 1,3-aminyl-alkyl biradical

intermediate (**BR**, Scheme 1) and its propensity to form a cycle by making a C–N bond.<sup>4</sup>

We have been interested in the development and exploration of synthetically promising solvent-free reactions in crystalline solids,<sup>5</sup> as these reactions tend to be more selective than analogous reactions in solution.<sup>6</sup> With that in mind, we recognized an opportunity to explore a two-step strategy for the stereospecific synthesis of substituted aziridines. As illustrated in Scheme 2, we propose the use of diastereomerically pure (*Z*)- or (*E*)-alkenes **3** in 1,3-dipolar cycloadditions with suitable azides **4** to form substituted 2-triazolines **5**. On the basis of numerous observations by us and others,<sup>5,6</sup> one may expect that the photochemical reaction of crystalline **5** (Scheme 2b) will proceed in the crystal lattice by irreversible loss of N<sub>2</sub> followed by a

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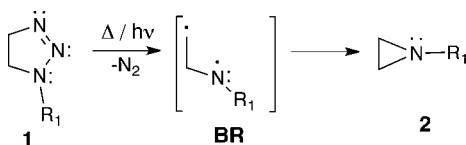
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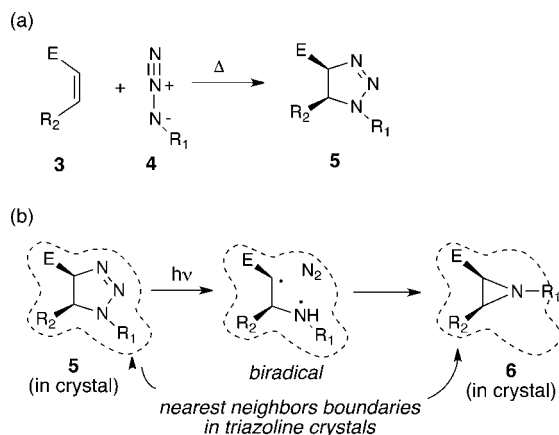
### Scheme 1. Denitrogenation of 2-Triazolines



stereospecific ring closure to give the diastereomerically pure aziridine **6** in high chemical yields.

As the first step toward this goal, we set out to determine whether the solid state reactions of 2-triazolines are indeed feasible, and whether they occur in good chemical yields. While we considered it likely that the reaction would take place in the solid state, we had concerns about the structural changes required in going from a bent 2-triazolines structure to the more linear aziridine plus  $N_2$ . These changes could result in the destruction of the crystal lattice with melting and loss of reaction control.<sup>7</sup>

### Scheme 2. Stereospecific Synthesis of Substituted Aziridines

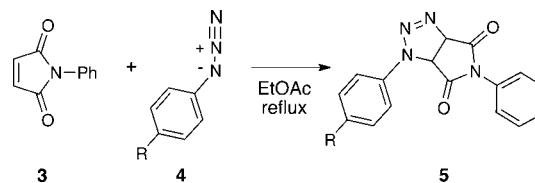


As a simple test for the two step strategy depicted in Scheme 2, we decided to explore the synthesis, crystallization and solid state reactivity of readily available bicyclic triazolines **5a–5e**, obtained by dipolar cycloaddition of *N*-phenyl maleimide with a series of substituted aryl azides (Table 1). The selection of *N*-phenyl-maleimide was based on the activated nature of its double bond and expectations of high crystallinity arising from the two carbonyls and the phenyl group. Relatively simple variations on the aryl azides were intended to explore the generality of the reaction with substituents that varied from electron-donating *p*-chloro (**5b**) and *p*-methoxy (**5d**) to electron-withdrawing *p*-cyano (**5c**) and *p*-acetyl (**5e**). It was also expected that these structures would provide a

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range of crystal structures and melting points that could help establish the feasibility and generality of the solid state photochemical reaction.

**Table 1.** Isolated Yields and Melting Points of Triazolines **5a–5e**



triazoline	substituent R	isolated yield <sup>a</sup>	melting point (°C)
<b>5a</b>	H	72	152–153
<b>5b</b>	Cl	68	159–160
<b>5c</b>	CN	75	118–134 <sup>b</sup>
<b>5d</b>	OCH <sub>3</sub>	54	150–151
<b>5e</b>	COCH <sub>3</sub>	70	174–175

<sup>a</sup> Products were isolated by simple solvent evaporation and recrystallization. <sup>b</sup> Amorphous solid. Temperature range corresponds to visual observation for softening and clearing.

As shown in Table 1, triazolines **5a–5e** were obtained by reaction of *N*-phenyl maleimide (1 mmol) and substituted phenylazides (1.5 mmol) in refluxing ethyl acetate.<sup>8</sup> *N*-Phenyl maleimide was prepared from maleic anhydride and aniline,<sup>9</sup> and the phenylazides **5a–5e** were prepared from the corresponding anilines by reaction of the diazonium salts with sodium azide.<sup>10</sup> Recrystallization from ethyl acetate and hexanes gave isolated yields of pure solids between 50 and 80% (Table 1), in agreement with reports on the influence of substituents in the 1,3-dipolar cycloaddition of phenyl azides with norbornene.<sup>11</sup> Four of the five triazolines were crystalline solids with melting points above 150 °C, and only the cyano-substituted analogue **5c** turned out to be an amorphous solid (Table 1). Their crystalline or the amorphous nature were confirmed by visual melting observations and by powder X-ray diffraction measurements (PXRD). The identity of triazolines **5a–5e** was established by the expected <sup>1</sup>H NMR, <sup>13</sup>C NMR, FTIR and UV–vis spectroscopy, as well as by mass spectrometry (MS). The mass spectra of **5a–5e** showed peaks that correspond to the protonated molecular ions [ $M + H^+$ ] and peaks attributed to the loss of molecular nitrogen [ $M^+ - N_2$ ].

**Thermolysis of Triazolines 5a–5e.** Thermolysis experiments were carried out with the neat solids (Scheme 3). Loss of nitrogen was observed in the form of  $N_2$  bubbles formed upon melting in the case of the crystalline triazolines and upon liquification in the case of the amorphous

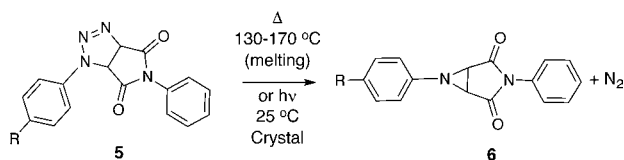
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### Scheme 3. Thermolysis of Triazoline **5**



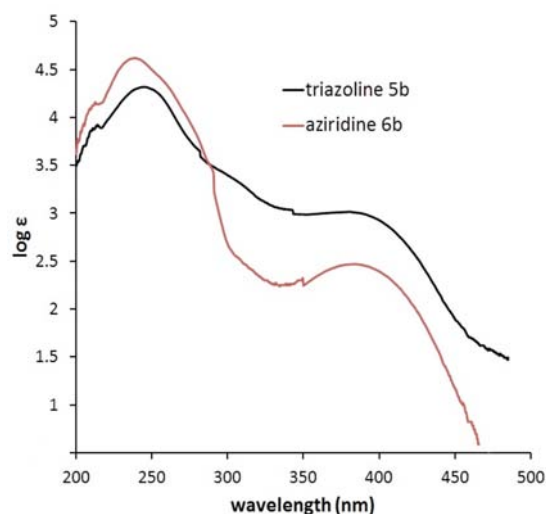
*p*-cyano **5c**. The loss of nitrogen was also documented by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC),<sup>12</sup> which showed the loss of weight corresponding to the nitrogen molecule and an exothermic peak overlapping with the incipient melting endotherm, respectively (Figures S21–S30, Supporting Information). Thermolysis reactions were very clean, with the major products identified as aziridines **6a–6e** by their expected FTIR, UV–vis, <sup>1</sup>H NMR and <sup>13</sup>C NMR, as well as MS. All five aziridines are crystalline solids with melting points that range from 103 to 104 °C in the case of **6b** to 160–161 °C for **6e** (Supporting Information). Both the <sup>1</sup>H NMR and <sup>13</sup>C NMR were characterized by a reduction in the number of signals as compared to the triazolines **5**, as expected by the increase in molecular symmetry. Singlets in the <sup>1</sup>H NMR at ca. 3.86–3.96 ppm were assigned to the equivalent protons of the aziridine rings, and the aromatic hydrogens of the *N*-aromatic aziridine and the *N*-phenyl succinimide were easily distinguishable. The *ortho*-hydrogens of the latter displaying an unusual chemical shift in the range of 6.40–6.58 ppm with broadening suggested a dynamic process in the intermediate exchange regime.<sup>13</sup> The carbon atoms of the aziridine ring were found to resonate at ca. 40 ppm in the <sup>13</sup>C NMR spectra (Supporting Information).

**Photochemical Reaction in the Solid-State.** The first set of irradiation experiments were carried out with chlorosubstituted triazoline **5b** using a medium-pressure Hg lamp with a quartz filter that transmits light with  $\lambda \geq 200$  nm. The formation of aziridine **6b** was monitored every 15 min by analysis of the <sup>1</sup>H NMR spectrum. We followed the appearance and growth of the two equivalent aziridine hydrogens at ca. 3.87 ppm and the concomitant disappearance of the two triazoline bridgehead doublets at ca. 4.94 and 5.92 ppm. The photoreaction occurred in the solid phase from beginning to end and was complete after ca. 60 min. While the initial 15 min of the reaction proceeded cleanly to give aziridine **6b** as the only photoproduct, by the time the reaction was completed, the yield of aziridine **6b** had reached about 80% with unidentified products accounting for the rest. This suggested that the loss of selectivity as a function of conversion might be due to secondary photoreactions of the aziridine under the reaction conditions. Partial support

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(13) Studies in progress indicate that the signals corresponding to the *ortho*-hydrogens of the *N*-phenyl succinimide are affected by the relatively slow inversion of the aziridine nitrogen. This process will be described in a subsequent paper.

for this hypothesis was obtained when samples of aziridine **6b** were exposed to UV light under the same conditions ( $\lambda > 200$  nm), and some of the same byproducts were observed by <sup>1</sup>H NMR and gas–liquid chromatography. These results are also consistent with the expectations that result from analysis of the UV spectra of the reactant and the product shown in Figure 1.

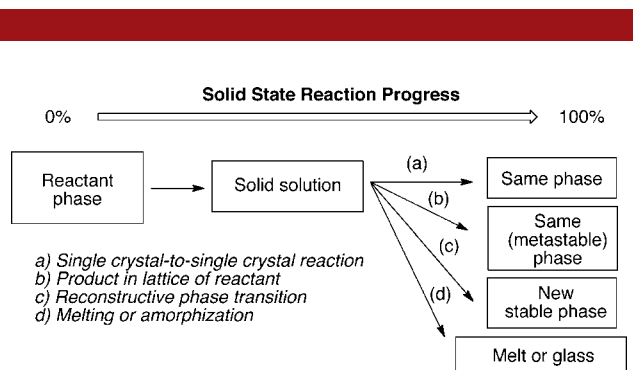


**Figure 1.** UV–vis triazoline **5b** (black) and aziridine **6b** (red) in methanol.

The spectrum of triazolines **5b** presents an absorption band at ca. 350–370 nm with  $\epsilon \approx 1000 \text{ M}^{-1} \text{ cm}^{-1}$  attributed to the triazoline chromophore and another one around 250 nm with  $\epsilon \approx 20000 \text{ M}^{-1} \text{ cm}^{-1}$  that is attributed to the aromatic rings. Notably, the spectrum of the aziridine has a stronger absorption in the short wavelength band and a weaker absorption at lower energies, suggesting that preferential excitation of the reactant triazoline may be accomplished by irradiation at longer wavelengths. Knowing that the absorption of the triazoline is much stronger than that of the aziridine above 300 nm, we carried out the next set of reactions with triazoline **5b** using a Pyrex filter with a cutoff of  $\lambda \leq 290$  nm. The formation of byproduct under those conditions occurred in much lower quantities ( $< 2\%$ ) and only after prolonged irradiation. Noting that analogous compounds with other substituents have similar absorption properties, we were able to show that all triazolines react in analogous manner to give the corresponding aziridine in good to quantitative yields. Solid state photoreactions of **5b**, **5c** and **5d** in the form of dry powders were completed within 60–120 min to yield the corresponding aziridines **6b**, **6c** and **6d** in 97–100% yields.<sup>14</sup> Compound

(14) A modest scale up experiment with ca. 300 mg of triazoline **5b** recrystallized from ethyl acetate were crushed on a glass plate forming a layer 2–3 mm thick and irradiated under conditions reported in the Supporting Information. The time needed to complete conversion was 2 h.

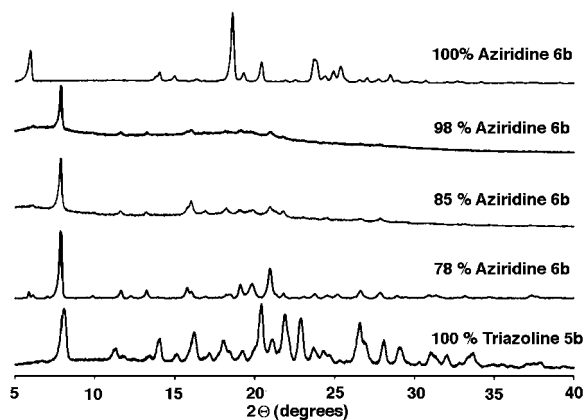
**5a** also reacted to completion, but the yield of **6a** was 86%, suggesting that the aziridine may have a more efficient reaction than the other ones. A faster photoreaction (45 min) with formation of (ca. 13%) byproducts was also observed in the case of **5e**, in agreement with a stronger absorption by the *para*-amino acetophenone moiety, which may also act as an intramolecular sensitizer.



**Figure 2.** Potential phase changes accompanying solid state reactions.

**Powder X-ray Diffraction Analysis of the Solid-to-Solid Reactions.** As indicated by the topochemical postulate, reactions in crystals tend to occur with a minimum of atomic and molecular motion.<sup>6a,b</sup> The product(s) formed at the beginning of a solid state reaction occupy initially the volume of the reactant to form a solid solution (Figure 2).<sup>7</sup> Sometimes reactions proceed along the same phase in a single crystal-to-single crystal, or topotactic transformation, which can be followed by single crystal X-ray diffraction (Figure 2, path a).<sup>7,15</sup> However, if the solubility of the product in the lattice of the reactant is limited, important structural changes may take place. Some reactions maintain a packing arrangement that is similar or related to that of the pure reactant, with the concomitant formation of a metastable disordered crystalline phase (path b). In some cases the product phase-separates in a reconstructive phase transition to form a new phase (path c), and in others, the lattice is destroyed to form either a melt or a glass (path d), depending on the glass transition temperature of the two (or more) component system.<sup>7</sup> Given the relatively large change in size and shape that occurs in going from triazolines **5** to the aziridines **6**, it was interesting to explore the nature of the solid-to-solid transformation. To accomplish that, we measured the PXRD patterns of each of the five crystalline triazolines before and after various conversion values and after completion. Then we compared them to those of the corresponding aziridines photoproducts. The PXRD diffractograms from samples of crystalline triazolines irradiated to ca. 20–99% conversion were very similar to the

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**Figure 3.** Comparison of the PXRD of triazoline **5b** before reaction (bottom diffractogram), and after different conversion values (with the amount of product indicated), and (top) the PXRD of the recrystallized aziridine product.

diffractograms of the triazolines before reaction, with addition of a broad featureless baseline. By contrast, the diffractograms from the stable aziridine crystal phases measured after recrystallization showed patterns that are significantly different (Figure 3 and Supporting Information). We interpret the PXRD data as an indication that product formation occurs in a metastable phase (path b) with some degree of amorphization. As shown in Figure 3, many of the peaks corresponding to the packing structure of the starting material remained to the highest conversion values, even after the reaction was essentially completed, with the concomitant formation of a broad featureless band assigned to the amorphous product phase.

In conclusion, we confirmed that photoinduced denitrogenation of crystalline triazolines proceeds smoothly to generate the corresponding aziridines in quantitative yields. We also found that formation of the aziridines products occurs by formation of metastable and amorphous solid phases. While the reaction studied in this work results in formation of a single product, it will be interesting to determine whether the amorphization of the sample will result in the loss of stereoselectivity in cases where more than one product can be formed. Studies are now in progress to determine whether or not this is the case.

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**Supporting Information Available.** Experimental details of sample preparation and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.