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Intramolecular Photocycloaddition of Cyclic Thioimides as a Method for Heterocyclic Synthesis

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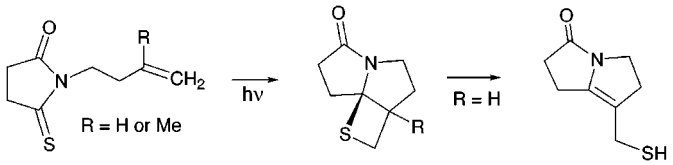
ABSTRACT



Cyclic thioimides undergo photocycloaddition with tethered π-bonds in a regiospecific manner to afford spirocyclic amidothietanes. These highly strained multicycles undergo a subsequent ring opening reaction to furnish novel fused pyrrolizinones.

Thiocarboxamides continue to be the focus of intense research by organic chemists.[1] A principal reason for this is that these systems undergo an assortment of chemical transformations[2] which make them attractive for synthetic applications. Thioamides can be readily oxidized to carbonyl compounds,[3] reduced to amines,[4] and converted to nitriles,[5] thioimidates,[6] and amidines.[7] Thienolate anions of thioamides have been employed in a variety of condensation reactions[8] and stereoselective Michael addition to α,β-unsaturated ketones.[9] Cyclization reactions of thioamides have utilized electrophile-induced additions to olefins,[10] trimethyl phosphite-induced additions to α-dicarbonyl compounds,[11] and the Rh(II)-catalyzed reaction of thioamido-substituted α-diazomethyl vinyl ketones.[12]

Photochemical cyclizations of nitrogen-containing thiocarbonyl compounds have been studied in some detail by the Kanaoka and Machida groups[13] and represent a potentially important method for the synthesis of various heterocyclic ring systems. Most thioamides were found to be inert to both the Norrish type I (α-cleavage) and Norrish type II (hydrogen abstraction) reactions[14] in contrast to the behavior of their oxygen- and nitrogen-lacking counterparts.[15] However, many aliphatic and aromatic mono- and dithioamides (**1**) undergo both inter- and intramolecular Paterno-Büchi like photocycloadditions with olefins to give various imido-

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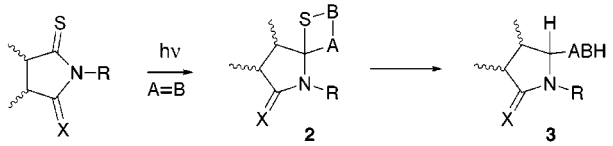
Scheme 1

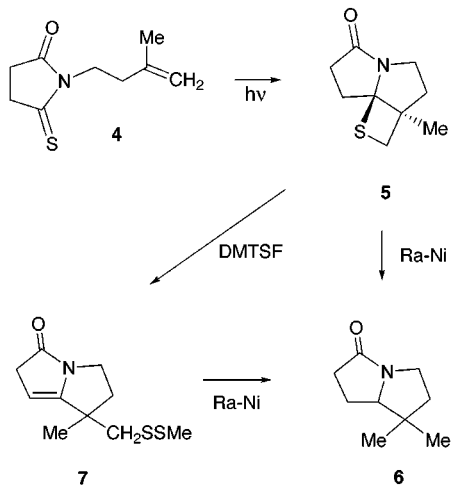


1; X = O or S

thietanes (**2**) (Scheme 1).[13] In the course of our own studies dealing with the cyclization chemistry of thioamides,[16] we became interested in using the intramolecular [2 + 2]-photocycloaddition as a method for preparing various azabicyclic ring systems commonly found in pyrrolizidine alkaloids. We reasoned that loss of sulfur from the initially formed cycloadduct (i.e., **2** → **3**) would represent an efficient approach for the synthesis of fused heterocycles. Details associated with the intramolecular photocycloaddition reaction of several cyclic thioimides are the subject of this Letter.

We began our investigation in this area by irradiating a sample of *N*-3-methylbut-3-enyl-5-thioxopyrrolidin-2-one (**4**)[17] in benzene using a 450 W Hanovia medium-pressure lamp under an argon atmosphere with a Pyrex filter sleeve for 2 h (Scheme 2). Silica gel chromatography of the crude

Scheme 2

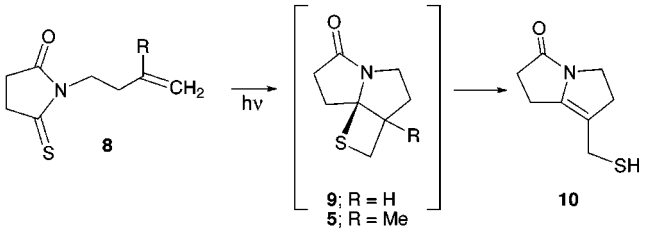


reaction mixture afforded the highly strained tricyclic thietane **5** in 73% yield whose structure was assigned on the basis of its spectral and analytical data.[18] The assignment of structure was further validated by a single-crystal X-ray analysis. Compound **5** was treated with Ra−Ni in ethanol for 2 h to give hexahydropyrrolizin-3-one **6**.

We also carried out a ring opening reaction on cycloadduct **5** using dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF),[19] which afforded 2,5,6,7-tetrahydropyrrolizin-3-one **7** in 65% yield, thereby demonstrating the facility with which the resulting photoadduct can be converted into the pyrrolizidine core skeleton. Subjection of **7** to Ra−Ni afforded **6** in good yield.

The photochemistry of the closely related *N*-butenyl thioxopyrrolidinone **8** (R = H) proceeded in a slightly different fashion and produced 7-mercaptomethyl-1,2,5,6-tetrahydropyrrolizin-3-one **10** in 68% yield (Scheme 3). More

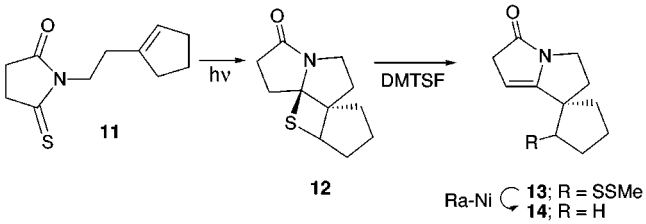
Scheme 3



than likely, the photoreaction proceeds by a Paterno-Büchi like cycloaddition. With this system, however, the initially formed cycloadduct **9** readily undergoes ring opening followed by a subsequent deprotonation to give **10** as a consequence of the available hydrogen atom (i.e., R = H). This ring opening reaction does not occur with the related 3-methylbutenyl system **5** (i.e., R = Me).

Photolysis of the *N*-cyclopentenyl derivative **11** was also carried out and, in a similar fashion, produced the tetracyclic thietane **12** as the major photoproduct in 68% yield based on recovered starting material. The ^{1}H NMR and ^{13}C NMR spectra indicate that the cycloadduct was obtained as a single stereoisomer. As was the case with photoadduct **5**, treatment of **12** with DMTSF afforded the related tetrahydropyrrolizinone **13** in 92% yield. Further reduction of **13** with Ra−Ni gave spiro pyrrolizinone **14** in good yield (Scheme 4).

Scheme 4



In contrast to the above results, irradiation of the thioxaphthalimide systems **15** and **16** containing an *N*-cycloalkenyl group in the side chain produced the mercapto-substituted

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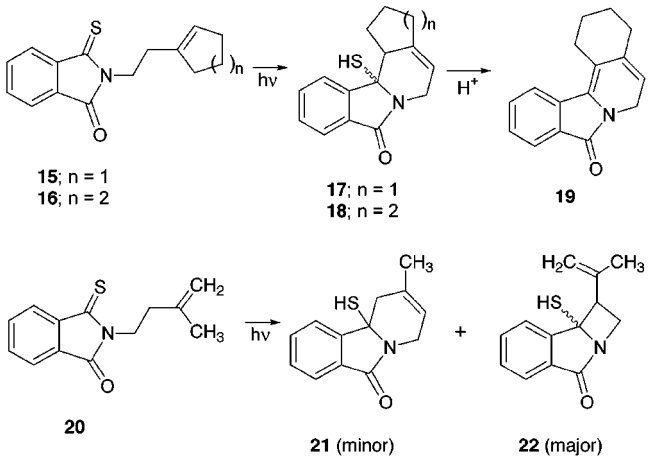
(17) The *N*-alkenyl-substituted 5-thioxopyrrolidin-2-ones used in this study were prepared from the corresponding succinimides using Lawesson's reagent.

(18) All new compounds in this study were fully characterized (IR, NMR, elemental and/or HRMS).

(19) Trost, B. Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. Trost, B. M.; Saito, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. Commercially available from Aldrich Chemical Co.

pyridoisoindolones **17** and **18** as a 1:1 mixture of diastereomers in 64% and 73% yield, respectively.[20] Further treatment of **18** with *p*-toluenesulfonic acid resulted in the loss of H_2S and afforded pyridone **19** in 91% yield. Photolysis of the closely related *N*-but-3-enyl thioxaphthalimide **20** furnished the analogous pyridoisoindolone **21** but as the minor photoproduct (40%) (Scheme 5). In this case, the

Scheme 5

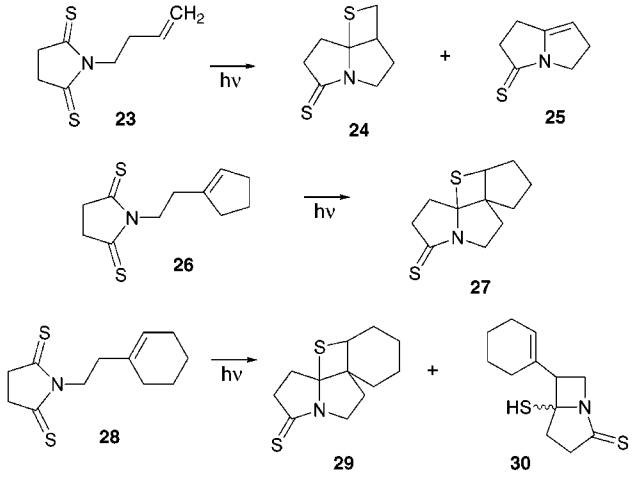


major product (57%) corresponded to the mercapto-substituted dihydroazeto[2,1-*a*]isoindolone **22**.

In an earlier report[20] Oda had suggested that, in certain cases, apparent Norrish type II products such as **17** (or **21**) are actually derived from a Paterno-Büchi photocycloaddition reaction which first produces a transient thioimide-thietane which is subsequently converted into the mercapto pyridoisoindolone system. However, we were unable to detect such an intermediate in the photolysis of **15**, **16**, or **20**. The fact that **22** was the major product formed from the irradiation of **20** is best rationalized by γ-hydrogen abstraction from the n$-\pi^*$ triplet excited state of the thioxaphthalamido chromophore. Apparently, the adjacent phthalimido ring enhances the ability of the n$-\pi^*$ excited state to abstract a γ-hydrogen relative to undergoing [2 + 2]-cycloaddition across the tethered π-bond.

As a logical extension of our photochemical program dealing with intramolecular thietane formation, the photoreaction of *N*-3-alkenyl pyrrolidine-2,5-dithiones was investigated, and the results are outlined below. Irradiation of the straight chain *N*-3-butenyl dithione **23** afforded a 4:1 mixture (64%) of thietane **24** and pyrrolizine-3-thione **25** (Scheme 6). It would appear that the excited thioamido group

Scheme 6



undergoes [2 + 2] cycloaddition and partial fragmentation of thioformaldehyde from **24** to give **25**. An analogous reaction occurred with dithione **26** giving rise to the novel fused 3-thione **27** in 48% yield. Interestingly, when the homologous cyclohexenyl system **28** was used, bicyclic azetidine **30** (28%) was obtained in addition to the expected [2 + 2]-photoadduct **29** (28%). We suspect that **30** is derived from a competitive hydrogen atom transfer reaction. No signs of a photoproduct related to **30** were observed with the cyclopentenyl thione **26**.

In conclusion, the photolysis of various thioxapyrrolidinones and thiophthalimides afford novel [2 + 2]-cycloadducts as well as cyclized photoadducts derived from hydrogen transfer chemistry. Ring opening to relieve angle strain occurs readily and this *[2+2]-photocycloaddition/ring cleavage sequence* should prove useful for the preparation of various pyrrolizidine alkaloids. Further utilization of this method for the stereocontrolled synthesis of azapolycyclic rings is under current investigation and will be reported in due course.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM60003-02) for their generous support of this work.

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(20) For related processes see: Oda, K.; Machida, M.; Kanaoka, Y. *Chem. Pharm. Bull.* **1992**, *40*, 585. Coyle, J. D.; Rapley, P. A. *J. Chem. Res.* **1986**, 142.