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A New Synthesis of γ-Lactams Based on the Reaction of Vinyl Sulfilimines with Dichloroketene

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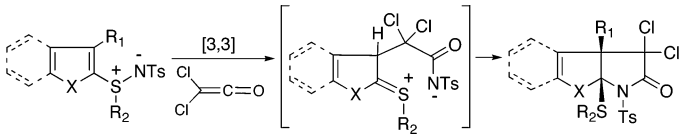
ABSTRACT



The reactions of several aryl-, furanyl-, and vinyl substituted sulfilimines with dichloroketene proceeded at 25 °C to yield thioalkyl substituted γ-lactams which, in turn, were converted to a variety of nitrogen-containing substrates.

The oxindole moiety represents a key substructure associated with many biologically active natural products and medicinal entities.[1] Various methods have been developed for the construction of this ring system. Among the techniques commonly used in their synthesis are derivatization of other heterocycles,[2] radical cyclizations,[3] intramolecular Heck reactions,[4] arylation of amides[5] and variants of the Friedel−Crafts reaction (Stolle synthesis).[6] Stolle syntheses, however, are of limited scope because of the harshly acidic conditions required, while many of the other methods require a specifically functionalized precursor. Oxindole syntheses based on the cyclization of *o*-aminophenylacetic acid derivatives[7] and reduction of isatins[8] are also limited by the availability of starting materials. The method reported by Gassman and co-workers,[9] which proceeds from a substituted aniline and ethyl (methylthio)acetate via chlorination of the sulfide and subsequent treatment with an arylamine and base, is one of the most generally useful methods in terms of scope, starting material availability, brevity and reproducibility (Scheme 1, path A).

In recent years, our research group has been involved in a program whereby Pummerer chemistry has been used for the synthesis of aza-heterocycles.[10] It occurred to us that it might be possible to modify the Gassman method by simply switching the sulfur and nitrogen positions and that this might constitute a new method to prepare oxindoles as outlined in Path B of Scheme 1. Taking into account the earlier and elegant studies by Marino and co-workers on the chemistry of vinyl sulfoxides with dichloroketenes,[11] we expected that

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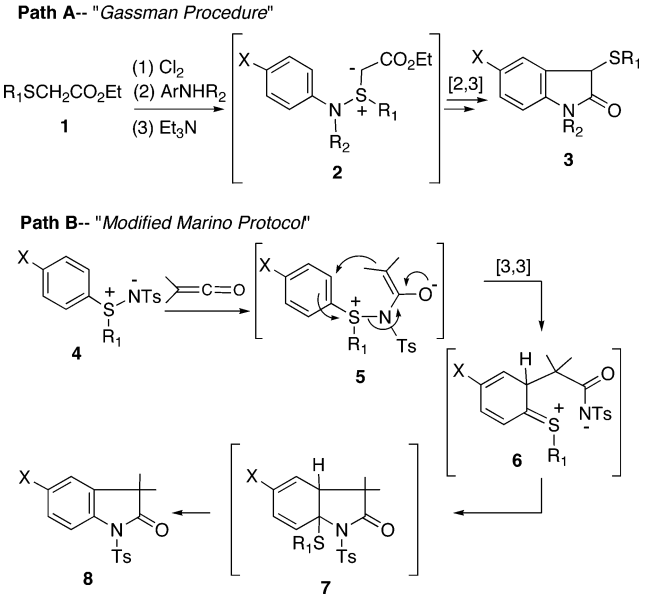
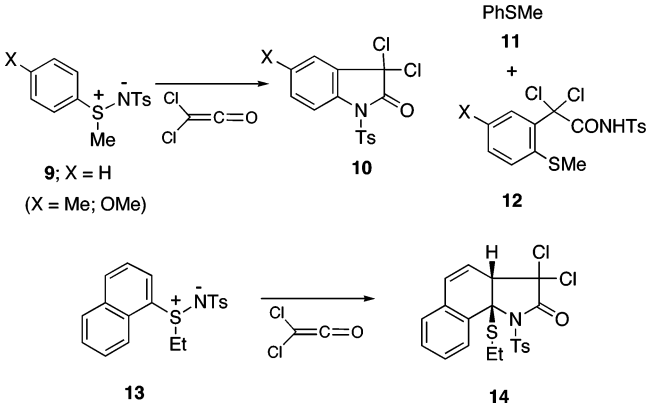
Scheme 1



Scheme 2

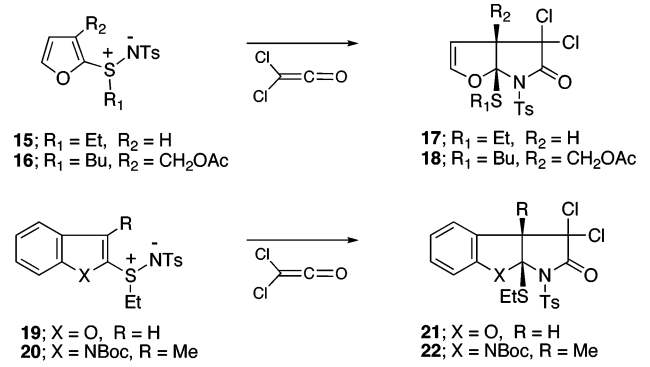


the reaction of an aryl sulfilimine such as **4** with a ketene would first afford zwitterion **5** where the nitrogen and sulfur atoms were switched relative to the analogous Gassman intermediate **2**. A subsequent [3,3]-sigmatropic rearrangement would then deliver the Pummerer-thionium ion intermediate **6**. Cyclization and loss of the mercaptan should yield the desired oxindole **8**. In this communication, we give an account of our efforts dealing with this unique cyclization method for the synthesis of a variety of functionalized γ-lactams.

First, we examined the reaction of phenyl sulfilimine **9** with dichloroketene[12] in THF at 25 °C which afforded oxindole **10** (Scheme 2) together with varying amounts of methyl phenyl sulfide (**11**) and amide **12**.[13] Similar results were obtained using a variety of aryl substituted sulfilimines (i.e., X = Me, OMe) with oxindole **10** always being formed in low yield (ca. 20%). Apparently, the key rate determining step of the process (i.e., **5** → **6**) possesses a relatively high activation energy as a consequence of the disruption of aromaticity. To minimize this difficulty, we opted to study the reaction of the more reactive naphthyl substituted sulfilimine **13** with dichloroketene. In contrast to the results obtained with sulfilimine **9**, the cyclization reaction of **13** proceeded in high yield and the somewhat labile γ-lactam **14** could be obtained after chromatographic purification in 56% yield as the only detectable product isolated from the crude reaction mixture.

Next, we turned our attention to the related reaction of several 2-furanyl substituted sulfilimines (i.e., **15** and **16**). The results we obtained showed that these cyclizations also proceeded at room temperature in THF and furnished the novel dihydrofuranyl γ-lactams **17** and **18** in 58% and 40% yield, respectively. With the related benzofuranyl (**19**) and indolyl substituted (**20**) sulfilimines, good yields of the cyclized lactams **21** and **22** (52% and 56%) were also obtained (Scheme 3). Interestingly, all of the γ-lactams that were isolated were unexpectedly robust and did not undergo loss of mercaptan, even under somewhat forcing conditions (i.e., heat, acid). Compound **22** encompasses the key scaffold found in the pyrroloindoline and bis-pyrroloindole alkaloids[14] and its ready formation points out the potential use of this method for target oriented synthesis.

Scheme 3



To further explore the scope and generality of the method, we carried out a series of reactions using a variety of vinyl substituted sulfilimines as outlined in Scheme 4. The reaction

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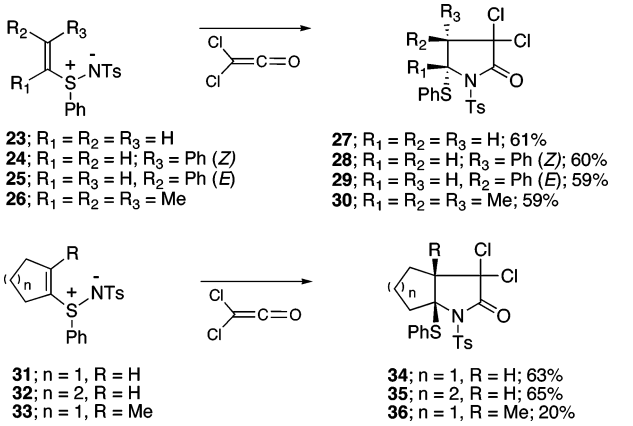
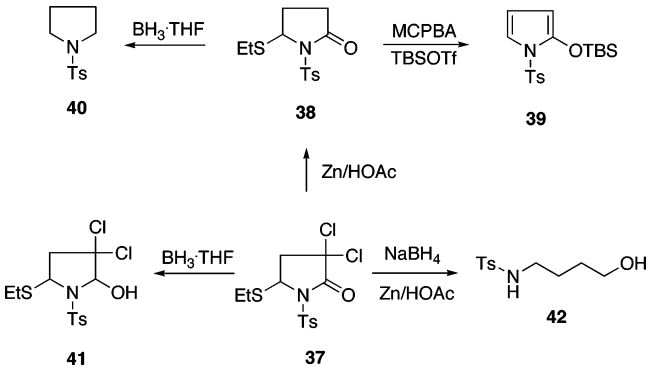
Scheme 4



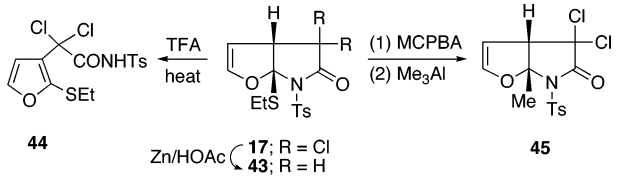
of dichloroketene with both acyclic (**23**−**26**) and cyclic (**31**−**33**) sulfilimines proceeded smoothly to give the expected γ-lactams in good yield. The reactions of dichloroketene with *Z*-(**24**) and *E*-phenyl styryl sulfilimine (**25**) afforded different diastereomeric lactams (i.e., **28** and **29**) and parallel Marino's observations with the corresponding vinyl sulfoxides.[15] The complete stereospecificity of the cyclization process is undoubtedly related to the highly ordered transition state of the sigmatropic rearrangement. The resulting Pummerer intermediate is rapidly trapped by the amido anion before C−C bond rotation can occur.

As part of an effort to further broaden the utility of this cyclization protocol, we decided to carry out some simple chemical manipulations of these highly functionalized γ-lactams to probe their usefulness for the synthesis of various nitrogen containing substrates. It was anticipated that lactam **37**, derived from the reaction of dichloroketene with *S*-ethyl-*S*-ethenyl-*N*-(toluene-4-sulfonyl)sulfilimine, could be used to prepare a variety of substituted pyrrolidine derivatives. Indeed, the reaction of **37** with zinc/HOAc cleanly led to the dechlorinated lactam **38** in 88% yield. Oxidation of **38** with *m*-CPBA followed by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (Scheme 5) provided pyrrole **39** in 86% yield. This activated pyrrole corresponds to an attractive intermediate for the eventual synthesis of several

Scheme 5



Scheme 6



pyrrolidine alkaloids. *N*-(*p*-Toluenesulfonyl)pyrrolidine **40** was obtained in 83% yield when lactam **38** was reduced with BH_3**.**THF. We also subjected **37** to reduction with BH_3·THF and found that carbinolamide **41** was cleanly formed in 84% yield. Reduction of **37** with $NaBH_4$ followed by further reaction with zinc/HOAc furnished the 1,4-amino alcohol **42** in 81% yield.

A structure−activity relationship using γ-lactam **17**, which contains a fused dihydrofuran ring as part of its skeleton, was also investigated. Smooth dechlorination occurred when **17** was treated with zinc in acetic acid affording the novel heterocycle **43** in 84% yield (Scheme 6). The loss of the thioethyl group proved to be more difficult than originally anticipated. All of our attempts to induce the elimination of ethyl mercaptan from **17** with various thiophilic reagents failed. When treated with trifluoroacetic acid at 100 °C, **17** was smoothly converted into furan **44** in 71% yield by preferential elimination of the *N*-(*p*-toluenesulfonyl) group. However, by first oxidizing the thio group with *m*-CPBA and then treating the resulting sulfone with trimethylaluminum, it was possible to introduce a methyl substituent on the carbon atom adjacent to the two heteroatoms (i.e., formation of **45**).

In conclusion, we have disclosed a new and efficient method for the synthesis of highly functionalized γ-lactams. The overall process involves the reaction of a vinyl substituted sulfilimine with the highly electrophilic dichloroketene to first generate a zwitterionic intermediate. A subsequent [3,3]-sigmatropic rearrangement is followed by intramolecular trapping of the Pummerer cation by the amido anion to furnish the observed γ-lactam products. The heavily functionalized lactams are easily converted to a variety of nitrogen containing substrates. We are currently exploring the generality of the rearrangement/cyclization process and its application to alkaloid synthesis.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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