Heterocyclic Synthesis via the Tandem Thionium/*N*-Acyliminium Ion Cascade

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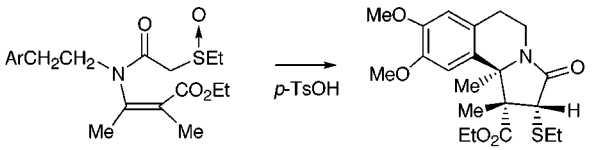
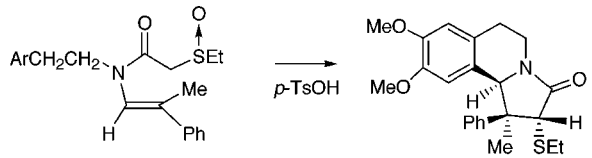
The formation of carbocyclic ring systems based on the cationic stitching of polyene acyclic precursors has emerged as an extremely powerful synthetic method.[1] The attraction of this synthetic construction is the high degree of molecular complexity furnished in a single step.[2] Cationic cyclizations also play an important role in heterocyclic natural product synthesis.[3] Reactions of *N*-acyliminium ions with tethered π-bonds are among the most important methods for preparing complex nitrogen-containing heterocycles.[3−6] Pummerer-based cyclizations are also finding widespread application in both carbo- and heterocyclic syntheses.[7−9] The combination of a Pummerer/N-acyliminium ion cyclization sequence offers unique opportunities for the assemblage of complex target molecules.[10,11] As a consequence of our interest in domino ring-forming reactions,[12] we have examined a new approach toward heterocyclic synthesis which involves a *tandem thionium/N-acyliminium ion cyclization strategy* as depicted in Scheme 1. In this communication we describe our preliminary observations in this area which utilize enamido sulfoxides of type **1** in cascade cyclization reactions.

Initial efforts were focused on the cyclization reactions of α-sulfinylenamides **5** and **6**. These compounds were conveniently prepared in 60−80% yield from the condensation of 3,4-dimethoxyphenethylamine with the appropriate aldehyde or ketone followed by reaction of the resulting imine with ethylthioacetyl chloride.[13] Treatment of **5** with 2 equiv of *p*-TsOH in refluxing benzene afforded **7** in 78% yield. It is important to note that only one of several possible diastereomers of the fused isoquinoline lactam **7** was observed under the reaction conditions as indicated by ^{1}H and ^{13}C NMR spectral data. The stereochemical assignment was unequivocally established by X-ray crystallographic analysis which revealed a *syn* relationship between the thioethyl, carbethoxy, and methyl groups. α-Sulfinylenamide **6** underwent an analogous cyclization affording the fused isoquinoline lactam **8** in 69% yield. This cyclization



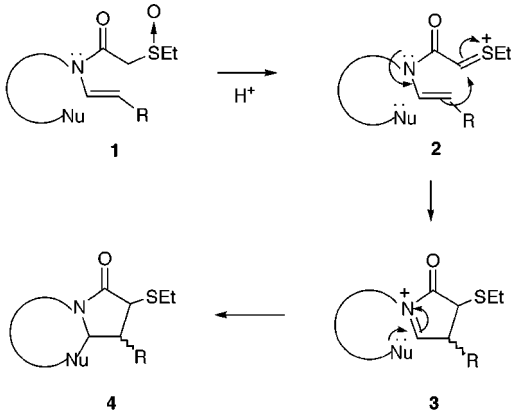
5; Ar = $C_6H_3(OMe)_2$ **7**



6; Ar = $C_6H_3(OMe)_2$ **8**

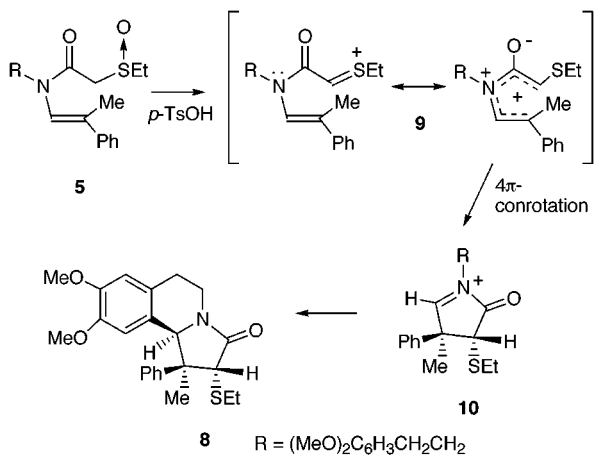
reaction also proceeded with high diastereospecificity and led to a single diastereomer where the methyl and thioethyl groups are on the same side of the ring (NOE). The NOE enhancement between the tertiary hydrogen adjacent to the nitrogen atom of the lactam ring and the vicinal methyl group further defines the stereochemical relationship of the substituent groups present in **8**.

Scheme 1



A plausible mechanism which nicely rationalizes the stereochemical results involves initial formation of an α-acylthionium ion (*i.e.*, **9**) followed by a Nazarov type[14] 4π-electrocyclic ring closure which occurs in a conrotatory fashion to give *N*-acyliminium ion **10** (Scheme 2). The final cyclization step proceeds in a stereoselective manner by attack of the proximal aromatic ring from the less hindered side of the iminium ion framework.

Scheme 2



Attention was next turned to the acid-induced cyclization of the related enamides **11** and **12** where the point of attachment of the tethered aromatic ring was switched from nitrogen to carbon. Treatment of **11** with *p*-TsOH under identical conditions to that used for the cyclization of **5** gave **13** as a single diastereomer in 79% yield. Likewise, reaction of the indolyl substituted α-sulfinylenamide **12** with *p*-TsOH also produced a single crystalline polycycle **14** in 80% yield. The structures and stereochemistries of products **13** and **14** follow from analysis of their NMR spectroscopic data, and their formation is perfectly consistent with the *tandem thionium/iminium ion cascade sequence* outlined in Scheme 2.

The reaction of iminium ions with tethered alkenes represents one of the most general methods for the synthesis of alkaloids.[3] Since the previous examples of our *tandem Pummerer/iminium ion cyclization* involve aromatic π-bonds, we decided to study several systems which possess a simple

(1) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 341.

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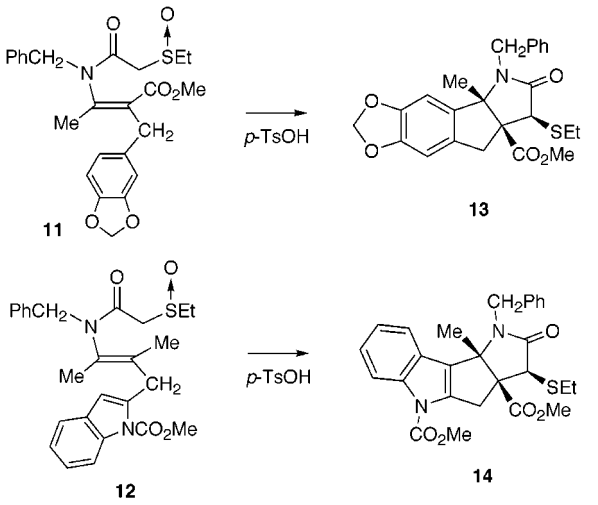
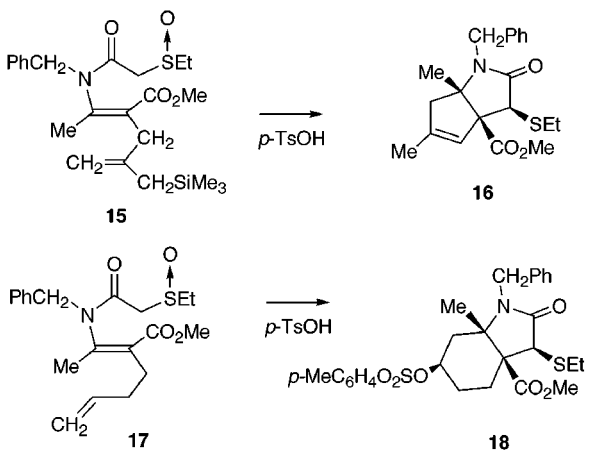
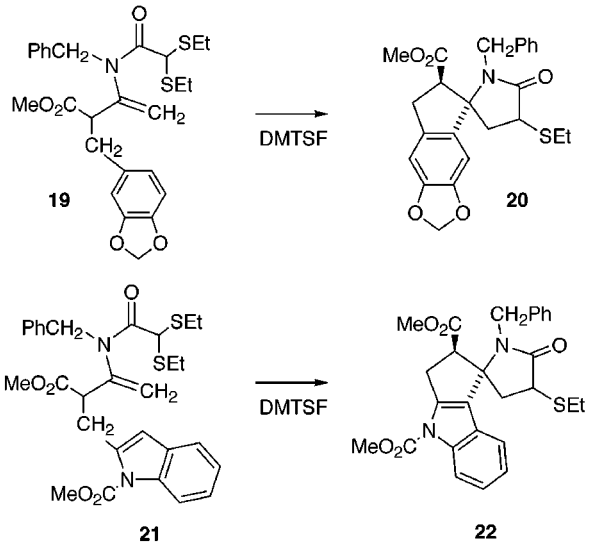


olefinic tether. The well documented reactivity of allylsilanes toward electrophiles[15] suggested that the acid-promoted reaction of sulfinylenamide **15** should provide access to a bicyclic lactam. Indeed, treatment of **15** with *p*-TsOH afforded the cyclized product **16** in 61% yield. We suspect that the initially formed lactam, which possesses an exocyclic double bond, gets isomerized under the reaction conditions. In light of the successful π-cyclization of **15**, we next examined the Pummerer reaction of α-sulfinylenamide **17** and were pleased to find that tosylate **18** was formed in 80% yield. Further studies are aimed at extending this cascade reaction toward the synthesis of the *Sceletium* class of alkaloids.

To further explore the scope and generality of the tandem cyclization process, we carried out a variation of the Pummerer initiation reaction using dithioacetal-substituted enamides as thionium ion precursors. Sequential treatment of benzylamine with 2-benzo[1,3]-dioxol-5-ylmethyl-3-oxobutyric acid methyl ester[16] followed by reaction with 2,2-diethylthioacetyl chloride[17] produced enamide **19** in 63% yield. A similar synthetic sequence[3] was used to prepare the related indolyl-substituted enamide **21**. Interestingly,



only the methylene-substituted enamides **19** and **21** are produced from this reaction. Dimethyl(methylthio)sulfonium fluoroborate (DMTSF) is known to exhibit a remarkable thiophilicity for initiation of cyclization reactions of thioketals.[18] Accordingly, treatment of enamides **19** and **21** with DMTSF initiated cyclization to deliver spirocycles **20** (53%) and **22** (59%) as single diastereomers.[19] These two examples further demonstrate the facility with which the *thionium/iminium ion cascade* can occur.



In summary, we have shown that α-sulfinylenamides are readily available substrates for stereoselective heterocycle-forming reactions. Additional work is now in progress to evaluate and utilize the *thionium/iminium ion cyclization cascade* for alkaloid synthesis.

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Supporting Information Available: Experimental procedures, compound characterization data, copies of spectra, and an ORTEP of **7** (26 pages).

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(2) Taylor, S. K. *Org. Prep. Proced. Int.* **1992**, *24*, 245. Fish, P. V., Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849.
(3) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1007−1046. Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.
(4) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
(5) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047−1082.
(6) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367. Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555. Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255.
(7) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353.
(8) Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 909−947.
(9) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 193-216.
(10) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209. Ishibashi, H.; Sato, K.; Maruyama, K.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 4593. Ishibashi, H.; Sato, T.; Takahashi, M.; Hayashi, M.; Ikeda, M. *Heterocycles* **1988**, *27*, 2787.
(11) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61*, 4888.
(12) Padwa, A. *J. Chem. Soc., Chem. Commun.* **1998**, 1417.
(13) Mooradian, A.; Cavallito, C. J.; Bergman, A. J.; Lawson, E. J.; Suter, C. M. *J. Am. Chem. Soc.* **1949**, *71*, 3372.
(14) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 751−784.
(15) Fleming, I.; Dunogues, J.; Smithers, R. The Electrophilic Substitution of Allylsilanes and Vinylsilanes. In *Organic Reactions*; Kende, A. S., Ed.; John Wiley and Sons: New York, 1989; Vol. 37, Chapter 2, p 57.
(16) Barry, R. H.; Mattocks, A. M.; Hartung, W. H. *J. Am. Chem. Soc.* **1948**, *70*, 693.
(17) Bellus, D. *Helv. Chim. Acta* **1975**, *58*, 2509.
(18) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.
(19) One explanation to rationalize formation of a single diastereomer from the DMTSF-induced cyclization would involve facile equilibration of the carbomethoxy-bearing stereogenic center via tautomerization of the *N*-acyliminium ion intermediate prior to the final ring closure. Alternatively, the direction of conrotatory closure may be influenced by the presence of the neighboring carbomethoxy group. Further work is in progress to clarify this issue and unequivocally established the stereochemistry of the cyclized products.