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π-Cyclization Reactions of Thio *N*-Acyliminium Ions for Heterocyclic Synthesis

*Scott M. Sheehan, L. Scott Beall and Albert Padwa**
Department of Chemistry, Emory University, Atlanta, Georgia 30322

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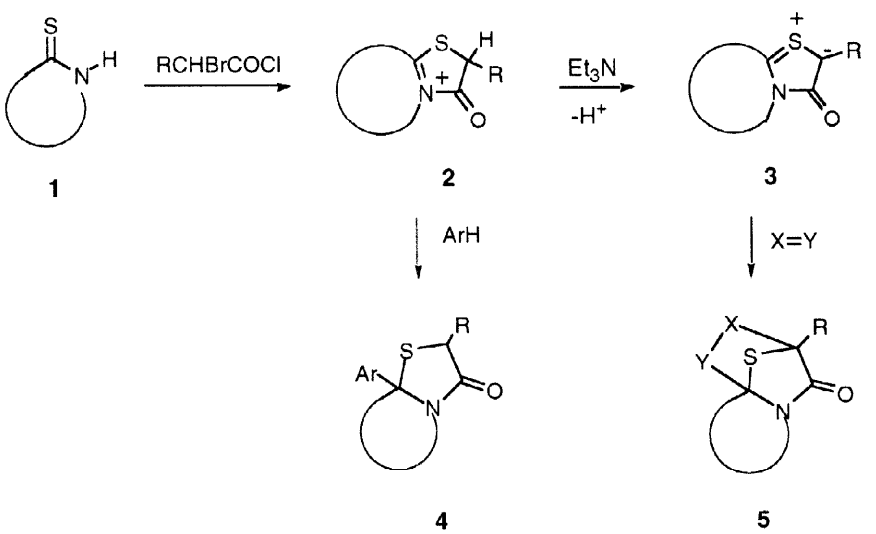
Abstract: Thio *N*-acyliminium ions are readily generated from the reaction of thioamides with bromoacetyl chloride. In the presence of tethered π-nucleophiles, cyclization occurs to give *S,N*-acetals which can be further converted into various alkaloid skeletons.

Carbon-carbon bond-forming reactions involving *N*-acyliminium ions play an extremely important role in the synthesis of nitrogen heterocycles.[1] These cyclizations have been utilized as the key step in the preparation of several alkaloids, including the tetrahydroisoquinoline, β-carboline and lycopodium classes.[2] The versatility of these reactive intermediates for heterocyclic synthesis underscores the continuing need to find new methods for their preparation.[3] *N*-Acyliminium ions are traditionally generated from the *N*-acylation of imines,[4] *N*-protonation[5] and oxidation[6] of amides, electrophilic additions to enamides[7] and the heterolysis of amides bearing a leaving group adjacent to nitrogen.[1]

Our earlier studies dealing with the 1,3-dipolar cycloadditions of thioisomünchnones[8] derived from the reaction of thioamides such as **1** with bromoacetyl chloride and triethylamine[9] showed that the reaction proceeds by the initial formation of a thio *N*-acyliminium ion (*i.e.*, **2**). Proton abstraction from the activated α-position occurs readily in the presence of base to furnish the mesoionic betaine **3** which undergoes subsequent dipolar-cycloaddition with added dipolarophiles.[8-10] Thio *N*-acyliminium ions such as **2** have received very little attention as potential electrophilic partners in cationic π-cyclizations despite the ease with which they can be formed. By incorporating an activated π-nucleophile as a tether on the thioamide, cyclization followed by further manipulation of the resulting *S,N*-acetals allows for the construction of the skeletal framework of several classes of alkaloids. The present communication documents the results of our studies in this area.

Scheme I



1 **2** **3** **4** **5**

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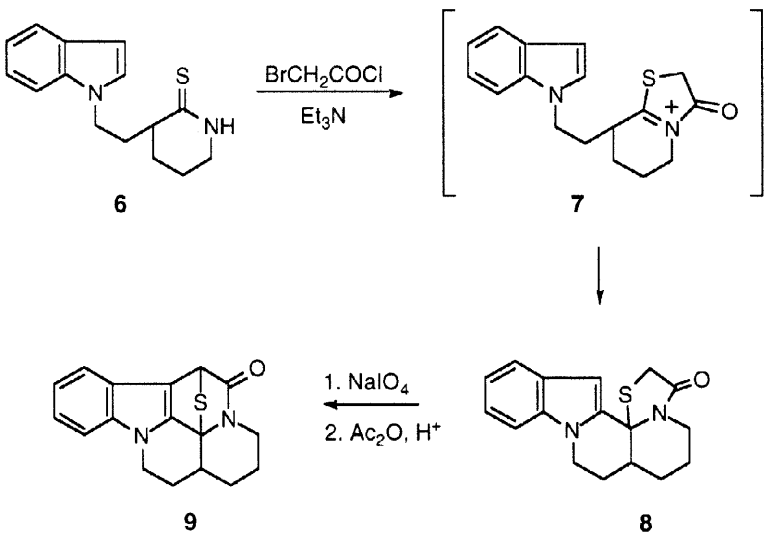
Although a vast amount of information is available concerning the reactivity of heteroaromatics in cycloadditions where the heterocycle functions as the $4\pi_s$ component,[11] a study of their dipolarophilic activities has not been extensively examined.[12] Cycloaddition of thioisomünchnone dipoles across the pendant indole π-system would represent an attractive route toward the pentacyclic skeleton found in the eburnamenine alkaloids.[13] With this in mind, thiolactam **6** was treated under the standard conditions for dipole formation and cycloaddition. However, no product of dipolar-cycloaddition across the indole π-bond was detected in the reaction mixture. Instead, *S,N*-acetal **8** was isolated in 85% yield. Compound **8** is derived by cyclization of the dipole precursor **7** onto the 2-position of the indole ring. Apparently, attack by the nucleophilic π-bond onto the reactive *N*-acyl iminium ion present in **7** occurs faster than dipole

Scheme II



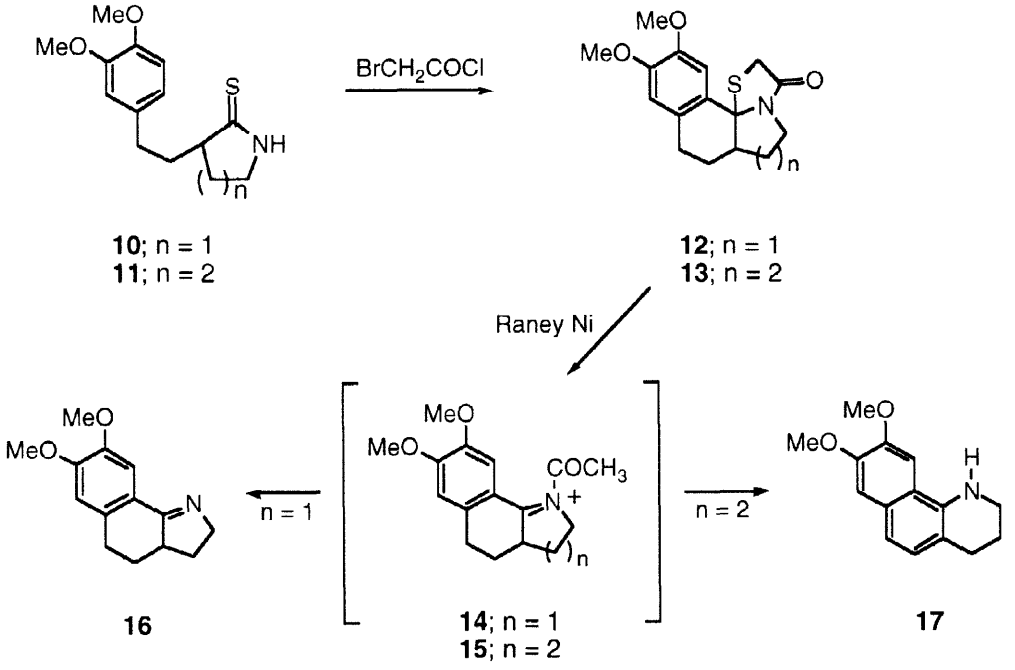
6 **7** **9** **8**

formation even in the presence of triethylamine. By taking advantage of the newly formed and highly functionalized *S,N*-acetal **8**, we were able to indirectly effect the desired 1,3-dipolar cycloaddition in a stepwise fashion. Thus, oxidation of **8** to the corresponding sulfoxide followed by a Pummerer[14] induced cyclization gave the thio-bridged compound **9** in 65% overall yield. Compound **9** is formally the product derived from cycloaddition of a thioisomünchnone across the indole π-bond but in a higher oxidation state.

To further study the *N-acyliminium ion generation/π-cyclization sequence*, both the 5-(**10**) and 6-membered (**11**) cyclic thiolactams containing a 3,4-dimethoxyphenethyl tether were prepared. In the absence of Et_3N, treatment of either **10** or **11** with bromoacetyl chloride provided the cyclized *S,N*-acetals **12** or **13** in 88% and 95% yields, respectively. Reductive cleavage of the sulfur bridge using Raney nickel gave imine **16** (91%) (starting from **12**) and amine **17** (90%) from *S,N*-acetal **13**. Both products can be rationalized by sulfur atom extrusion to first produce the *N*-acylated iminium ions **14** and **15**. Deacylation of **14** provides **16** whereas the deacylation of **15** was followed by a further oxidation to form the fully aromatic tetrahydroisoquinoline **17**.

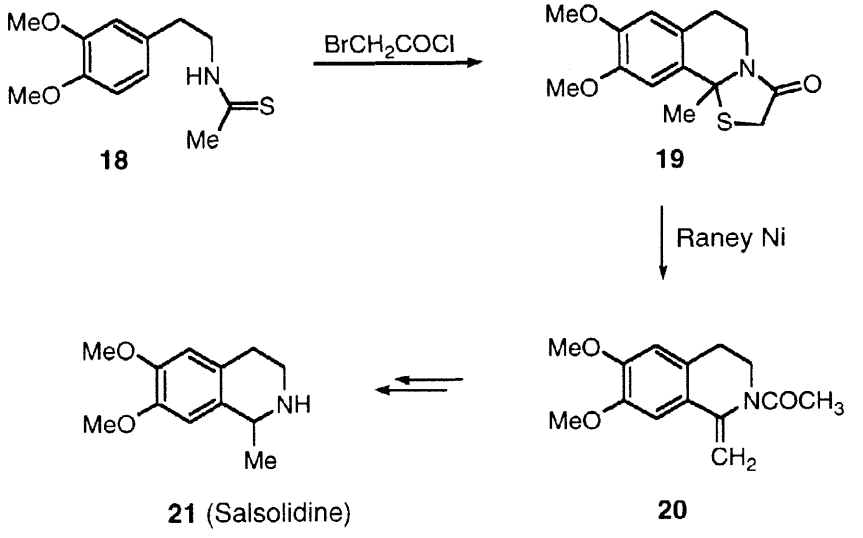
The tetrahydroisoquinoline skeleton is widely represented in various plant families and provides a challenging target for synthesis.[15] The great majority of the published syntheses are plagued by the harsh experimental conditions necessary for ring closure which limit their use with precursor compounds containing sensitive functional groups.[16] The π-cyclization procedure outlined above represents an efficient and mild approach toward this important class of nitrogen heterocycles. To highlight this new

Scheme III



strategy, the synthesis of the alkaloid salsolidine **21** was undertaken. When thioamide **18** was treated with bromoacetyl chloride, the cyclized *S,N*-acetal **19** was obtained in 98% yield. Removal of the sulfur atom with Raney nickel gave **20** (71%). This represents a formal synthesis of salsolidine (**21**), as alkene **20** had been previously hydrogenated in an enantioselective manner and deacetylated to produce **21**.[17]

Scheme IV



In conclusion, π-cyclization of activated aromatic rings onto thio *N*-acyliminium ions represents a highly efficient method for the synthesis of various polycyclic nitrogen containing heterocycles. Work to extend these discoveries to the total synthesis of a number of natural products is in progress, and the results of these investigations will be reported in due course.

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