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Synthesis of the Perhydroindole Nucleus by a Pummerer/Mannich Induced Cyclization Cascade

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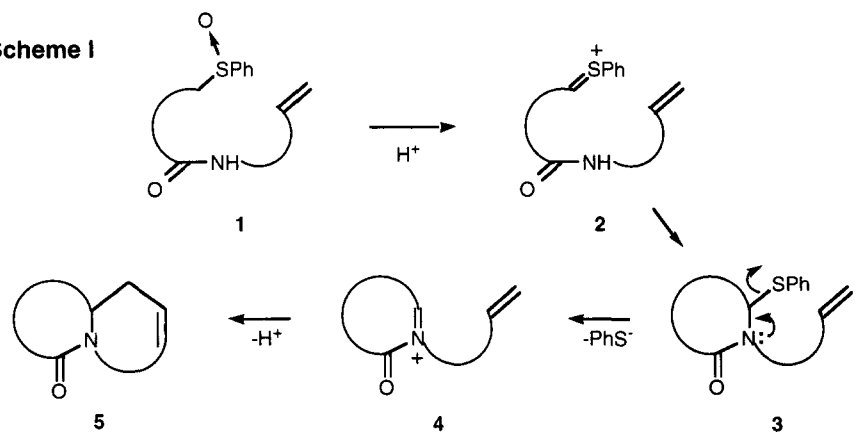
Abstract: The silicon-induced Pummerer reaction of several amido sulfoxides possessing tethered π-bonds proceeds by way of a thionium/*N*-acyliminium ion cascade to provide various azabicyclic ring systems. This cascade sequence was applied toward the synthesis of a member of the protoberberine alkaloid family.

The indolizidine and quinolizidine alkaloids are natural products which have been isolated from plants, fungi, and animal sources.[1] They have aroused considerable interest because of the potent and useful biological activity of certain of its members,[2,3] especially the polyhydroxy derivatives which function as inhibitors of several glycosidases.[4] The common structural feature of these compounds is a six-membered nitrogen heterocycle incorporated into a bicyclic ring. The development of new general methods for the synthesis of these heterocycles remains an area of active investigation.[5,6] An exceptionally viable strategy that has been utilized for the preparation of many five and six-membered nitrogen heterocycles involves the addition of nucleophiles to *N*-acyliminium ions.[7] In particular, the intramolecular reaction of cyclic *N*-acyliminium ions has been successfully employed in the preparation of various azabicyclic ring systems found in natural products.[8]

Our interest in indolizidine/quinolizidine alkaloid synthesis was prompted by the desire to explore the *thionium/N-acyliminium ion cascade* as a key strategy for the assembly of these ring systems. The approach we had in mind was based on our previous success using a tandem Pummerer/Mannich cyclization sequence for synthesis of the erythrinane alkaloid skeleton.[9] We envisioned that thionium ion

Scheme I



2, derived from a Pummerer reaction of sulfoxide **1**, would readily react with the neighboring amido nitrogen atom to provide the 2-thiophenyl substituted lactam **3**.[10] Subsequent elimination of the thiophenyl group should ultimately lead to the azabicyclic lactam **5** *via* cyclization of a transient *N*-acyliminium ion (*i.e.*, **4**). The present communication documents the results of our studies in this area.

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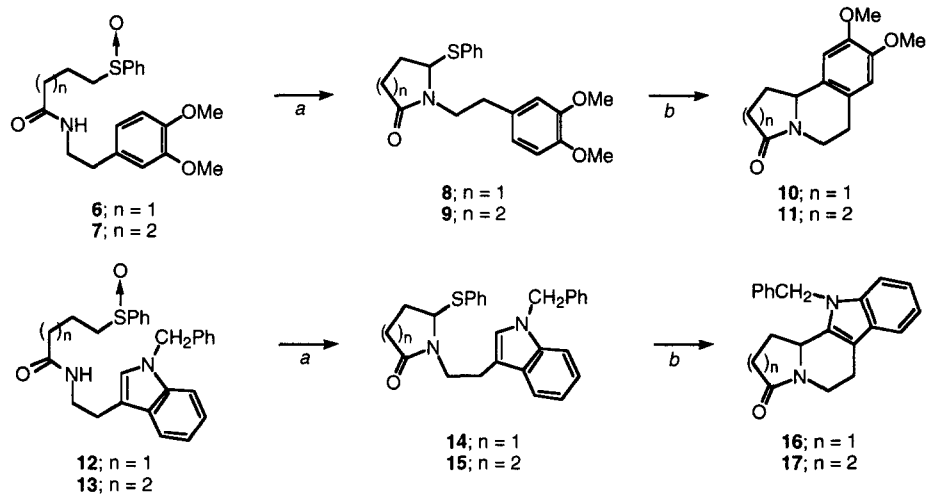
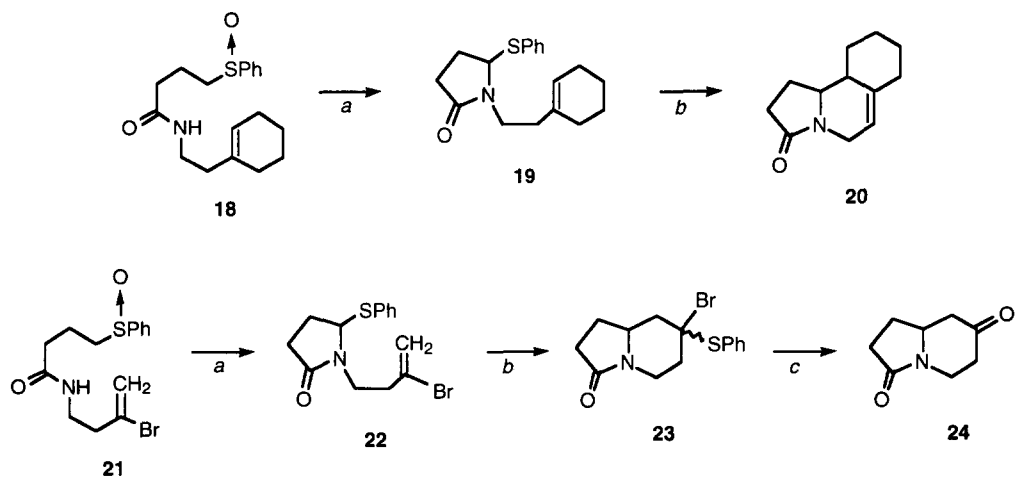
Amido sulfoxides **6** and **7** were easily prepared by addition of thiophenol to the appropriate alkenoic acid π-bond, and this was followed by reaction of the *in situ* generated acyl chloride with 3,4-dimethoxyphenethyl amine. The silicon-induced Pummerer reaction of these amido sulfoxides was carried out using 1-(dimethyl-*tert*-butylsiloxy)-1-methoxyethylene in dry acetonitrile in the presence of a catalytic amount of ZnI_2 as described by Kita[11] and led to the very clean formation (>90%) of 2-thio substituted lactams **8** and **9**. Iminium ion-aromatic π-cyclization was readily accomplished by treatment of **8** or **9** with 1.2 equiv of BF_3•2AcOH in CH_2Cl_2 at 25 °C to provide bicyclic lactams **10** or **11** in 98% and 79% yield, respectively. A related set of reactions occurred using the indolyl substituted amido sulfoxides **12** and **13** which afforded indoles **16** and **17** in excellent yield from the initially formed Pummerer products **14** and **15**.



Reagents: (a) TBDMSOC(OMe)=CH_2, ZnI_2; (b) BF_3•2AcOH

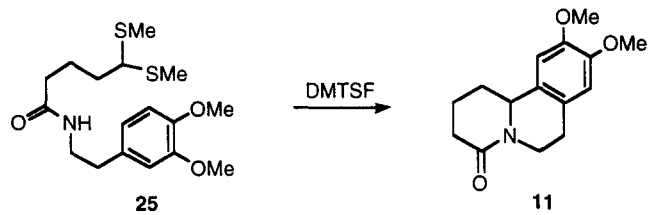
Since the previous examples involve aromatic π-bond cyclization, we decided to study several systems which possess a simple olefinic tether. We found that treatment of the cyclohexenyl substituted amidosulfoxide **18** with the *t*-butyl O-silylated ketene acetal caused an intramolecular Pummerer-type



Reagents: (a) TBDMSOC(OMe)=CH_2, ZnI_2; (b) BF_3•2AcOH; (c) $Hg(OAc)_2$, HCO_2H

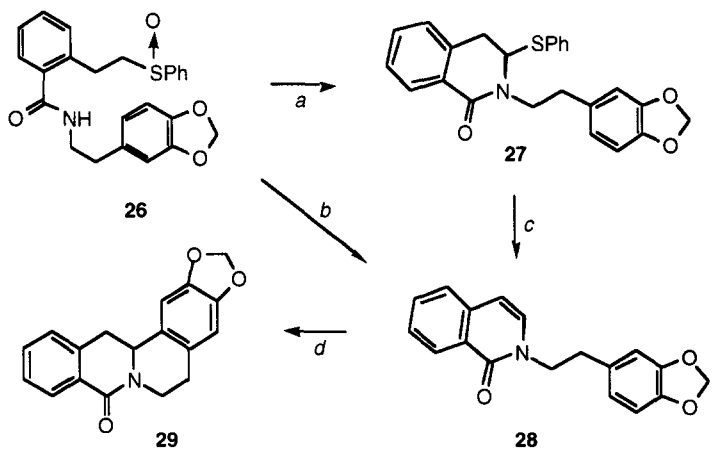
reaction to give α-thiolactam **19** which was subsequently converted to **20** upon treatment with BF_3•2AcOH in 50% overall yield. Extension of the two-step sequence to the bromoalkenyl substituted amide **21** was investigated next. When **21** was subjected to the typical Kita Pummerer conditions,[11] the desired 2-thiolactam **22** was isolated in 80% yield. Further reaction of **22** with BF_3•2AcOH furnished the novel bromo-thiophenyl substituted indolizidone **23** which was hydrolyzed to ketolactam **24** in good yield.

Initial attempts to induce a *"one-pot"* tandem cascade of the starting amidosulfoxides failed to produce the cyclized product. However, the desired domino cascade sequence could be induced by using a dithioacetal substituted amide as the thionium ion precursor. Thus, treatment of amide **25** with dimethyl-(methylthio)sulfonium fluoroborate (DMTSF), as described by Trost,[12] initiated a one-pot cascade sequence to deliver hexahydroisoquinolinone **11** in near quantitative yield.



25 **11**

Our interest in establishing amidosulfoxides as useful building blocks for heterocyclic synthesis prompted us to use the Pummerer methodology for the preparation of a member of the protoberberine alkaloid family.[13] The protoberberines are a large class of natural products typically characterized by a tetracyclic ring skeleton with an isoquinoline core. Considerable efforts have been expended in the study of these molecules for both their synthetic and biological significance.[13] Most of the synthetic approaches are generally plagued by the non-availability of starting materials, multi-step procedures, and moderate to poor yields.[14] A short synthesis of the berberine derivative **29** was carried out as depicted below. Subjection of amidosulfoxide **26** to TMSOTf/NEt_3 as the Pummerer initiator afforded 2-thiophenyl lactam **27** in 64% yield. In contrast, when the Kita silicon conditions[11] were used to trigger the Pummerer reaction, only enamide **28** (85% yield) was obtained. The reaction of **27** with Lewis acids such as ZnI_2 did result in the formation of **28**. When **28** was exposed to acidic conditions, it was transformed into **29** in 55% yield (unoptimized).[15]



Reagents: (a) TMSOTf/NEt_3; (b) TBDMSOC(OMe)=CH_2, ZnI_2; (c) ZnI_2; (d) H^+

In conclusion, this study has demonstrated that the *thionium/N-acyliminium ion cyclization sequence* of amido sulfoxides represents a highly efficient method for the synthesis of azabicyclic ring systems. The further utilization of this cyclization cascade for the stereocontrolled synthesis of perhydroindole alkaloids is under current investigation.

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