Communications

New Application of the Pummerer Reaction of Imidosulfoxides for the Generation of Mesoionic Dipoles†

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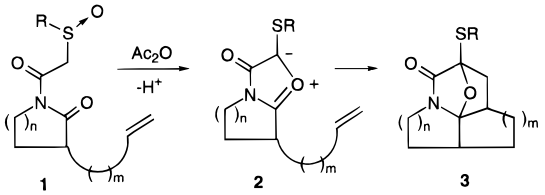
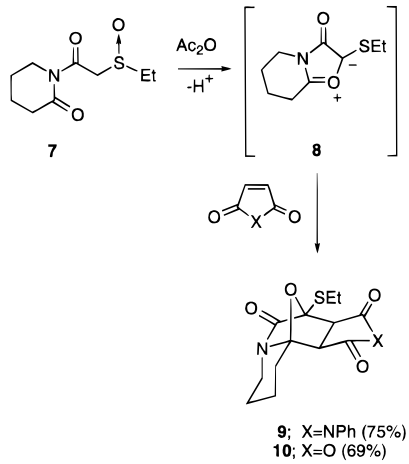
α-Acyl thionium ions generated from α-acyl sulfoxides under Pummerer conditions are powerful electrophiles, reacting efficiently with a variety of nucleophilic species.[1−3] Bimolecular addition of these types of cations to carbon−carbon double bonds is well known.[3] In the realm of natural product synthesis, most success has been achieved using intramolecular Friedel−Crafts cyclization of the Pummerer thionium ion intermediate.[4−12] Recent publications from these laboratories have described the internal trapping of the Pummerer thionium ion by adjacent carbonyl groups as a method for generating reactive dienes for subsequent use in Diels−Alder chemistry.[13] The combination of a sequence of individually powerful methods often has a value significantly greater than the sum of the individual reactions and is of current interest to the synthetic organic community.[14] In the context of our studies dealing with the tandem chemistry of thionium ions, we have discovered that the Pummerer reaction can also be utilized for generating mesoionic dipoles[15] of type **2** (Scheme 1). Herein we report details of this new reaction and provide an application of the process to the formal synthesis of lupinine (**4**) and anagyrine (**5**), two members of the lupinine family of alkaloids.[16]

Scheme 1



Scheme 2



Imidosulfoxide **7** was easily prepared from 2-piperidone in two steps (85%) by heating the lactam with (ethylsulfenyl)acetyl chloride (**6**),[17] followed by sodium periodate oxidation. Slow addition of **7** to a refluxing mixture of toluene, acetic anhydride (10 equiv), *N*-phenylmaleimide (1.3 equiv), and *p*-toluenesulfonic acid (1 mol %) led to the formation of cycloadduct **9** in 75% yield. An analogous process occurred using maleic anhydride as the trapping agent to afford cycloadduct **10** in 69% yield. The isolation of these compounds supports the intermediacy of dipole **8**, formed by thionium ion cyclization followed by a subsequent deprotonation (Scheme 2).

The ability of imidosulfoxides to undergo intramolecular dipolar cycloaddition leading to complex nitrogen polyheterocycles was demonstrated by exposure of **11** to acetic anhydride in refluxing toluene to provide **12** in 61% isolated yield (Scheme 3). Two additional examples that illustrate the scope and variety of systems that can be employed in this *cyclization−deprotonation−cycloaddition* sequence are outlined below. Exposure of **13** to the standard Pummerer conditions afforded acetoxypyridone **15** in 52% yield. The initially formed cycloadduct **14** was not isolated as it readily underwent oxybridge cleavage, presumably promoted by the nitrogen atom lone pair. Subsequent reaction of a transient 5-hydroxypyridone intermediate with additional acetic anhydride furnished **15**. In a related fashion, imidosulfoxide **16** produced a mixture of cycloadduct **17** (29%) and pyridone **18** (41%), thereby demonstrating that a tethered alkene attached to the sulfoxide can also be used in these Pummerer-induced cycloadditions. Further heating of **17** in toluene with a trace of *p*-toluenesulfonic acid resulted in dehydration to form pyridone **18** in quantitative yield.

Our interest in establishing imidosulfoxide **7** as a useful building block for indolizidine alkaloid synthesis

† Dedicated to my research mentor, Cheves Walling, on the occasion of his 80th birthday.

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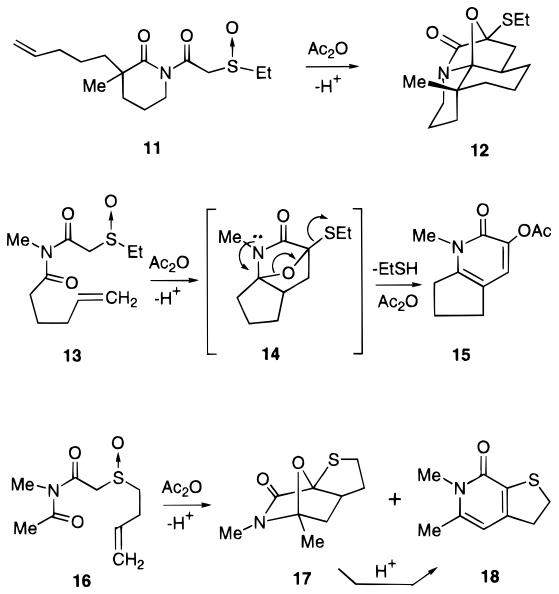
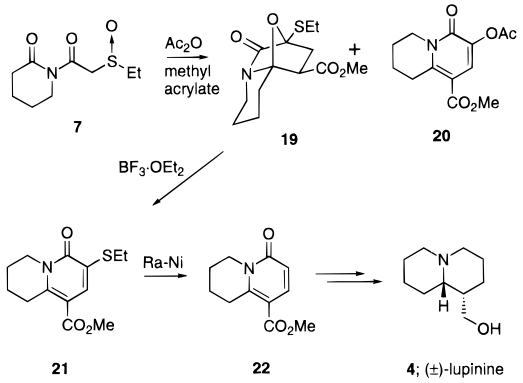
Scheme 3

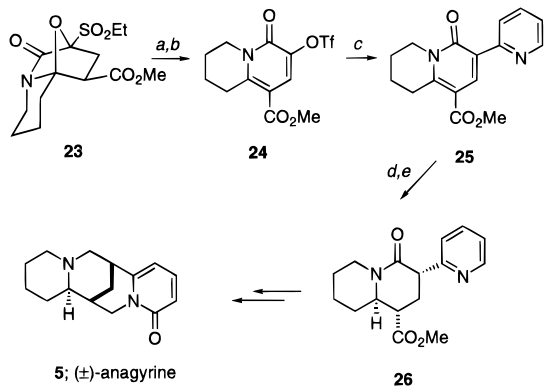


Scheme 4



prompted us to use the above methodology for the preparation of (±)-lupinine (**4**). A short synthesis of this alkaloid was carried out as depicted in Scheme 4. The Pummerer-induced reaction of **7** with methyl acrylate gave rise mainly to cycloadduct **19** (61%) together with lesser quantities of pyridone **20** (10%). Interestingly, treatment of **19** with $BF_3{\cdot}OEt_2$ furnished the ethylthio-substituted pyridone **21** (62%), which upon Raney-nickel reduction provided the desulfurated pyridone **22** (85%). The preparation of **22** constitutes a formal synthesis of (±)-lupinine (**4**), as Boekelheide had previously reported the conversion of **22** into **4**.[18]

Scheme 5[a]



[a] Reagents: (a) $BF_3{\cdot}OEt_2$; (b) $(TfO)_2NPh$; (c) 2-(tri-*n*-butylstannyl)pyridine, $Pd_2(dba)_3$, TFP; (d) H_2, PtO_2; (e) NaOMe, MeOH.

As shown in Scheme 5, cycloadduct **19** may also be used for a short synthesis of (±)-anagyrine (**5**). Oxidation of **19** with $NaIO_4/RuCl_3$ furnished sulfone **23** (91%), which, when treated with $BF_3{\cdot}OEt_2$ followed by reaction with *N*-phenyltrifluoromethanesulfonamide,[19] gave triflate **24** in 80% overall yield. Stille cross-coupling[20] of **24** with (tri-*n*-butylstannyl)pyridine provided **25** in 70% yield. Catalytic hydrogenation of **25** over PtO_2 followed by a base-induced equilibration delivered **26** in 85% isolated yield. The present sequence constitutes a formal synthesis of (±)-anagyrine, based on the successful conversion of lactam **26** into **5** by Goldberg and Lipkin.[21]

In conclusion, this study has demonstrated that the Pummerer reaction of imidosulfoxides represents a highly efficient method for the synthesis of azapolycyclic ring systems. The further utilization of this tandem *cyclization−deprotonation−cycloaddition* sequence for the stereocontrolled synthesis of other alkaloids is under current investigation.

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Supporting Information Available: Experimental details for the preparation of, as well as spectroscopic data for, all new compounds (18 pages).

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