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GENERATION AND CYCLIZATION OF NITRILIUM IONS FROM AMIDES. ASYMMETRIC SYNTHESIS OF FUSED AZABICYCLICS

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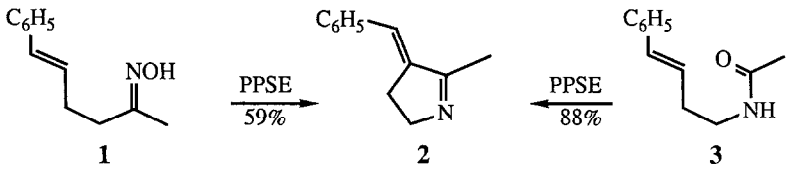
Abstract: Treatment of 2° amides with PPSE affords nitrilium ions which may be cyclized onto appropriate terminators. The conditions are compatible with esters in the molecule, and further elaboration to pyrrolizidine and indolizidine rings is possible via asymmetric reduction.

Nitrilium ions generated from oximes or their derivatives have recently been shown to be useful initiators in cationic cyclization reactions for both carbocycle and heterocycle synthesis.[1] Although utilization of this reaction within the context of an alkaloid synthesis has been demonstrated for systems containing no functional groups,[1b] the presence of functional groups as unreactive as ethers served to minimize yields which otherwise seemed quite promising.[1a] The generation of these ions by Beckmann rearrangement[2] is stereospecific. In the absence of a stereoselective synthesis of oxime stereoisomers, utilization of oximes as nitrilium ion precursors necessitates either using a mixture of both diastereomers and throwing away the unwanted products from the "wrong" isomer or undertaking what is usually a tedious and unreliable chromatographic separation.

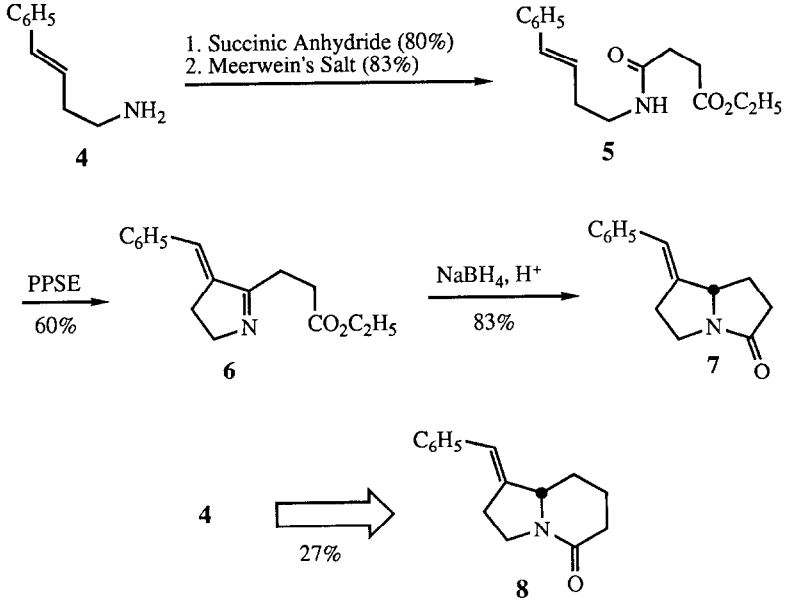
During the course of our investigation into the "oxime rearrangement cyclization" reaction,[1a] we noticed that if a reaction did not go to completion, a mixture of starting material, cyclization product, and a secondary amide (Beckmann product) were obtained. Subjecting this mixture to the reaction conditions a second time effected complete conversion. This observation indicates (at least qualitatively) that the nitrilium ion (or imidate[1a,2]) is accessible from the 2° amide as well as from the oxime. We hoped that nitrilium ion generation from amides would alleviate the oxime stereoisomer problem and might possibly get around the poor cyclization yields observed for functionalized substrates. We now report that this is indeed the case.



1 2 3

Cyclization of oxime 1 (which is 70% E) with trimethylsilylpolyphosphate (PPSE) in refluxing carbon tetrachloride afforded pyrroline 2 in 59% yield.[1a] Since the reaction is stereospecific, this constitutes an 84% conversion. Treatment of amide 3 with the same reagent afforded 2 in 88% yield. Thus the nitrilium ion cyclization is slightly more efficient from an amide than from an oxime.

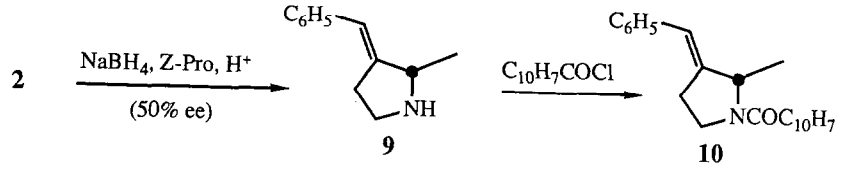
In order to test the compatibility of a functional group with the cyclization, we decided to prepare a precursor containing an ester, because esters are reportedly stable to PPSE.[3] Amine 4 was acylated with succinic anhydride (80%) and esterified [$(C_2H_5)_3OBF_4$, triethylamine, methylene chloride,[4] 83%]. Treatment of the amide ester 5 with PPSE afforded pyrroline ester 6 in 60% yield, constituting the first example of a functionalized nitrilium ion undergoing cationic cyclization.



4 5 6 7 8

This system seemed ideally suited to further elaboration, in particular to generation of the pyrrolizidine ring system. Some 25 years ago,[5] Meyers showed that sodium borohydride reduction of similar systems proceeds in a 1,2-fashion, and that appropriately placed electrophiles facilitate intramolecular alkylation of the resultant amine. Along the same lines, sodium borohydride reduction of pyrroline ester **6** proceeded with concomitant cyclization, giving benzylidinepyrrolizidinone (±)-**7** in 83% yield (33% from **4**). Utilization of glutaric anhydride in a similar strategy afforded indolizidinone (±)-**8** equally readily (26% from **4**).

Pyrrolizidines and indolizidines are available by cationic cyclization of N-acyliminium ions,[6] but in the absence of a stereogenic center in the molecule,[7] the chiral amines produced are racemic. Because the products of nitrilium ion cyclization are achiral, we felt that asymmetric reduction of the cyclization products in sequences such as those outlined above would afford an interesting alternative to the production of racemic amines via iminium ion cyclizations. To demonstrate the process, we first subjected pyrroline **2** to asymmetric reduction using the benzyloxycarbonylproline (Z-Pro) modified sodium borohydride reagent reported by Iwakuma.[8] Acylation of the resultant amine, **9**, with 1-naphthoyl chloride and Pirkle column analysis[9] of the resultant naphthamide **10** indicated an optical yield of 50%ee. Absolute configuration was assigned S based on the order of elution from the Pirkle column.



Treatment of **6** and and its homolog afforded (-)-**7** ($[\alpha]_D$ -39, EtOH) and (-)-**8** ($[\alpha]_D$ -40, EtOH). The absolute configuration and optical purity of these latter two compounds are not known with certainty, but are presumed to be as drawn, by analogy with **9**.

Applications of the protocol described in this Letter to the asymmetric synthesis of some pyrrolizidine and indolizidine alkaloids is in progress, and will be reported in due course.

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