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Stereoselective Synthesis of 2,5,6-Trisubstituted Piperidines

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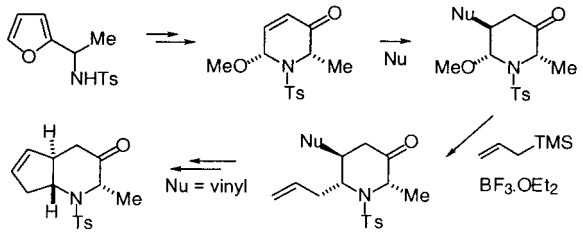
ABSTRACT



A short and efficient synthesis of 2,5,6-trisubstituted piperidines was achieved by a combination of an aza-Achmatowicz oxidation of a furyl benzenesulfonamide, conjugate addition to the resulting 2*H*-pyridinone, and subsequent addition of various nucleophiles to a transient *N*-sulfonyliminium ion. The steric bulk of the tosyl group directs attack of the nucleophile from its opposite side, thereby leading to the formation of *cis*-substituted products.

Piperidine ring systems exhibit a variety of biological activities and are found in numerous therapeutic agents.[1] The related indolizidine structure forms the skeleton of many naturally occurring alkaloids[2] and presents a worthy target for new synthetic methodology.[3] Accordingly, novel strategies for the stereoselective synthesis of six-membered aza-heterocycles continue to receive attention from the synthetic community.[4] In the past, addition of organometallic reagents to *N*-acyl pyridinium salts,[5] hetero Diels−Alder reactions of imines,[6] Lewis acid or electrophile induced cyclizations of imines or iminium ions,[7] and reactions of bicyclo cyano piperidines and lactams[8] have been employed for this purpose. Most of the known indolizidine alkaloids are either 3,5- or 5,8-substituted.[9]

A critical problem in the total synthesis of various indolizidine alkaloids involves setting the stereocenters in the piperidine ring. We envisioned an approach to systems

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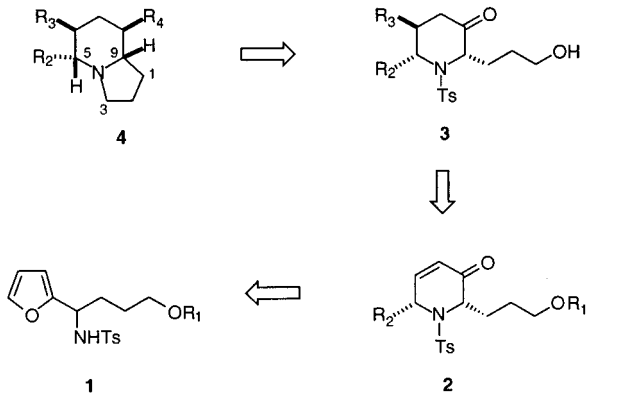
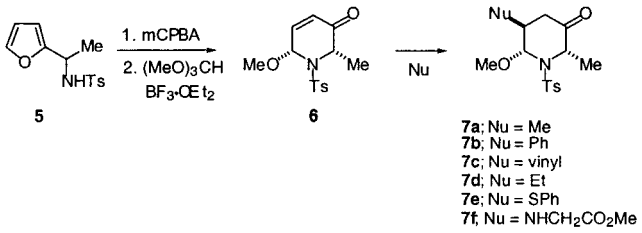
Scheme 1



Scheme 2[a]



7a; Nu = Me
7b; Nu = Ph
7c; Nu = vinyl
7d; Nu = Et
7e; Nu = SPh
7f; Nu = $NHCH_2CO_2Me$

entry	nucleophile (Nu)	yield %
1	$Me_2Cu(CN)Li$	90[a]
2	$Ph_2Cu(CN)Li$	90[b]
3	$(vinyl)_2CuMgBr$	87[c]
4	$(Et)_2CuMgBr$	85[d]
5	PhSH	85[e]
6	$H_2NCH_2CO_2Me$	60[f]

such as **4** (Scheme 1) that is based on the aza-Achmatowicz reaction, a process defined as the conversion of furylamides such as **1** into 1,6-dihydro-2*H*-pyridin-3-ones (i.e., **2**).[10] This novel rearrangement has been used for the synthesis of azasaccharides,[11] izidine structures, β-lactam intermediates, and unusual amino acids and, we believe, possesses significant potential for the preparation of a variety of piperidine-based alkaloids. The successful application of this approach for the stereocontrolled synthesis of various 2,5,6-trisubstituted piperidines is the subject of this communication.

To test our strategy for the eventual synthesis of indolizidines such as **4**, we needed to evaluate the stereochemical aspects of the 1,4-conjugate addition to the dihydro-2*H*-pyridone intermediate. 6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (**6**) was prepared from furyl sulfonamide **5** in two steps and in 72% overall yield (Scheme 2). The stereochemical assignment of **6** as the *cis*-isomer is based on NMR spectroscopic analysis (1D NOE). The exclusive formation of **6** can be rationalized by assuming that $A^{1,3}$-strain between the two substituents and the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation. It should be noted that this stereochemistry (vide infra) does not follow from previous literature results with related systems.[12,13] The earlier reports either have suggested that the *trans*-dihydropyridinone isomer results from the oxidative cyclization[12] or have not unequivocally elucidated the configuration of the product.[13]

Treatment of 2*H*-pyridinone **6** with various cuprate reagents (entries 1−4) proved to be remarkably stereospecific, providing the Michael adducts (**7a**−**d**) in pure diastereomeric form and in high yield (Scheme 2).

Thiophenol and glycine methyl ester also furnished 1,4-addition products **7e** and **7f** in high yield.[14] The stereochemistry of the Michael addition products were unambiguously assigned on the basis of NMR spectroscopic analysis as well as an X-ray crystal structure of compound **7a**. The stereochemistry of the conjugate addition product is the result of axial attack from the face opposite the diaxial substituents at C_2 and C_6. This may be attributed to steric hindrance between the pseudoaxially oriented 2,6-substituents and the equatorially approaching nucleophile, thereby leading to the exclusive formation of the kinetically favored axial 1,4-adduct.[15] It should be noted that related conjugate additions in the literature using dihydropyranulosides as substrates generally led to the formation of a mixture of diastereomers.[16] More than likely, the absence of a tosyl group makes the molecule more flexible, thereby permitting attack from both sides of the π-bond.[17]

Stereoselective functionalization of the pyridinone ring at the 6-position was accomplished by treating the heterocyclic system with allyl trimethylsilane under the influence of $BF_3{\cdot}OEt_2$ at 0 °C (Scheme 3). For example, the reaction of compound **6** with $CH_2{=}CHCH_2SiMe_3$ and $BF_3{\cdot}OEt_2$ afforded **8** in 85% yield. Similarly, treating **7a** and **7d** with allyl silane under comparable reaction conditions furnished **9** and **10** in 85% yield, respectively. Propenyl acetate reacted with **7a** in the presence of $BF_3{\cdot}OEt_2$ to give ketone **11** in 70% isolated yield. In all of the above examples, a single diastereomer was isolated whose stereochemistry was assigned as the 2,6-*cis*-disubstituted isomer. This assignment rests on literature analogy[18] and also is consistent with a NOE enhancement between the hydrogens on the C_2-methyl group and the methylene hydrogens of the allyl side chain at C_6.

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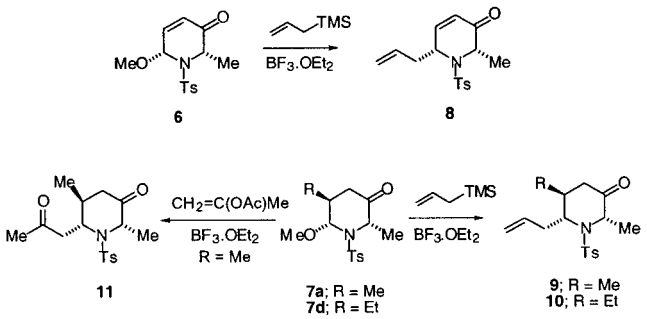
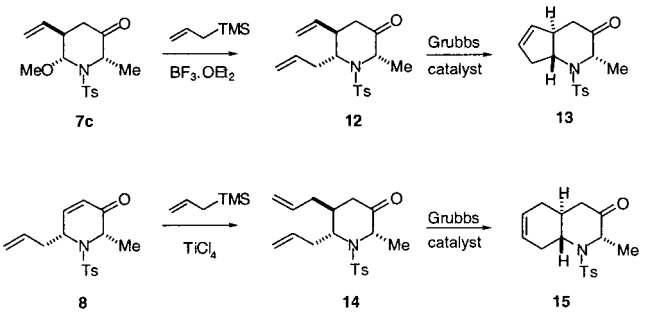
Scheme 3



Scheme 4



As suggested by others,[19] the preference for the 2,6-*cis*-disubstituted product can be rationalized by the $A^{1,3}$-strain present between the tosyl and methyl groups that causes the tosyl group to shield the opposite face of the molecule. The steric bulk associated with the tosyl group directs the attack of the nucleophile on the iminium ion to the side of the C_2-methyl group, leading to the formation of the *cis*-product.

In the past few years, the use of the ring closing metathesis reaction (RCM)[20] for creating heterocyclic systems[21] from acyclic diolefins has increased enormously as a result of the ruthenium alkylidene catalysts that have been developed by Grubbs and co-workers.[20] Prompted by the ease with which pyridinones **12** and **14** can be prepared (Scheme 4), we decided to investigate their ring closing olefin metathesis chemistry. The key cyclization reaction of **12** and **14** was performed with the Grubbs ruthenium benzylidene catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (3 mol %) in CH_2Cl_2 under an atmosphere of nitrogen. Dienes **12** and **14** were completely consumed within 3 h at room temperature furnishing the hexahydro-1*H*-pyrindine and octahydro-quinoline ring systems **13** and **15** in 60% and 80% yield, respectively.

In conclusion, we have shown that 2-methyl-6-methoxy-2,6-dihydro-2*H*-pyridin-3-one (**6**) readily undergoes conjugate addition with various nucleophiles to deliver *cis*-substituted 2,5-piperidines. The resulting products can be further utilized as precursors for *N*-sulfonyliminium ions by reaction with various nucleophiles in the presence of a Lewis acid. The stereochemistry associated with the conjugate additions was established by X-ray analysis and is believed to arise from $A^{1,3}$-strain between the tosyl and adjacent substituents. Further utilization of this method for the stereoselective synthesis of several indolizidine alkaloids is under current investigation and will be reported in due course.

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Supporting Information Available: Complete description of the synthesis and characterization of all compounds prepared in this study and an Ortep drawing for compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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