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Stereoselective Synthesis of Acyclic Amino Alcohols via von Braun Ring Opening of Chiral Piperidines

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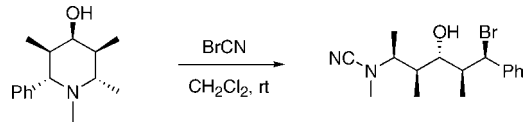
ABSTRACT



Multisubstituted piperidines containing a phenyl group at C-2 can be opened regio- and stereoselectively with cyanogen bromide. The ring-opened products contain useful cyanamide and benzylic bromide functional groups. This methodology is useful for the stereoselective synthesis of uniquely substituted alkylamine derivatives containing multiple chiral centers and various functionality.

Chiral amino alcohols are very important compounds in the realm of organic synthesis and medicinal chemistry. They are useful as chiral ligands, found in peptidomimetic compounds, and act as building blocks for the synthesis of many naturally occurring molecules. Numerous antiviral compounds, such as the HIV (human immunodeficiency virus) protease inhibitors ritonavir and lopinavir, contain chiral amino alcohol fragments.[1] In addition, functionalized 1,3-diols have received much attention from the synthetic community,[2] as have methodologies for synthesizing "skip" 1,3-dimethyl compounds with stereocontrol.[3]

An effort to extend our known synthetic methodology based on the 2,3-dihydro-4-pyridone ring system to the synthesis of chiral acyclic amino alcohols was recently initiated. Through total synthesis projects on various enantiopure alkaloids over the years, we have developed methods to substitute every center about the piperidine ring with absolute and relative stereocontrol.[4] It occurred to us that by using the rigidity inherent in the *N*-acyl-2,3-dihydropyridone ring system to set stereochemistry, followed by a stereoselective opening of the ring, novel chiral acyclic amine derivatives with multiple chiral centers could be prepared. This type of strategy for stereocontrolled synthesis of acyclic compounds is common via carbocycles and lactone rings, but it has seldom been extended to the piperidine ring system to yield open-chain amines.[5] Described herein is application of our methodologies for substituting dihydropyridone rings with stereocontrol to the construction of acyclic amino alcohols by using a selective von Braun tertiary amine cleavage reaction of substituted piperidines.

The von Braun cyanogen bromide reaction has been known for over a century[6] and has been widely used for

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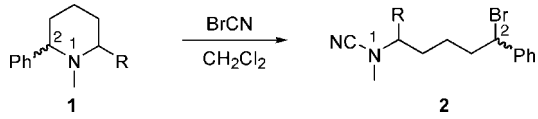
demethylation of tertiary amines. Due to the indiscriminate cleavage of many tertiary amines, it has found little use in rational designed synthesis of complex molecules. It was recently discovered in our group that the von Braun reaction could be performed on *N*-methyl-2-phenylpiperidines of type **1** to give solely the ring-opened product **2** via C-2 bond cleavage (Scheme 1). This regioselective ring opening is due

Scheme 1



to activation of the C−N bond at C-2 by the phenyl substituent. Although ring-opening of piperidines was observed during early studies on the von Braun reaction,[6b,7] the yields were generally low and the method appeared to have limited synthetic value. We set out to determine the scope of this ring opening and to explore if the von Braun reaction could be carried out with stereo- and regiocontrol on more complex piperidines.

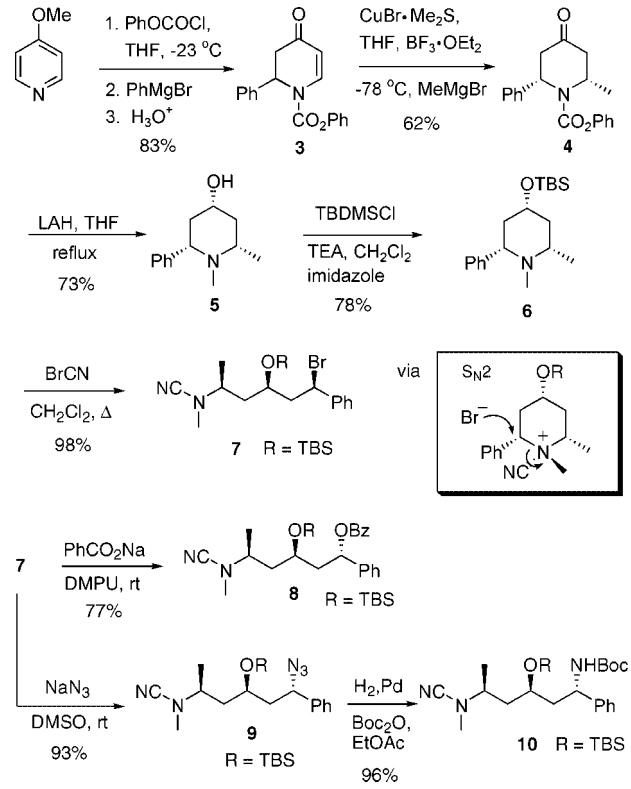
Our initial racemic model system was designed to contain, for simplicity, only three stereocenters. The synthesis commenced using our known *N*-acylpyridinium salt chemistry to convert 4-methoxypyridine to dihydropyridone **3** in 83% recrystallized yield.[8]

The dihydropyridone **3** was subjected to conjugate addition of methyl cuprate at −78 °C in the presence of BF_3•OEt_2.[9] Optimized results for this procedure produced a 5:1 cis/trans ratio of diastereomers which were separable by chromatographic methods. The major isomer **4** was reduced with LAH in THF to give the *N*-methylpiperidinol **5** as the only diastereomer formed. The piperidinol hydroxyl was protected to provide the TBS ether **6** in good yield. A 2-D NOESY experiment was conducted on the acetate of **5** and confirmed the relative stereochemical assignments of the ring-opening precursor **6**. This assignment was needed in order to elucidate the stereochemical course of the von Braun cyanogen bromide reaction.

Piperidine **6** was subjected to standard von Braun conditions to give the ring-opened product **7** in excellent yield. It was predicted from previously published work that the mechanistic pathway of bond cleavage would likely proceed with inversion of configuration.[7] The reaction gave a single diastereomer, and the predicted inverted center at C-2 was confirmed by X-ray analysis of the cyanamide **7**.

The key synthetic handles resulting from the ring-opening reaction are a benzylic bromide and a cyanamide. In addition to acting as an amine protecting group, a cyanamide can be

Scheme 2



converted to several other useful functionalities.[10] The presence of a benzylic bromide offers an opportunity for further elaboration through S_N2 substitution. The stereochemically pure bromide **7** can be substituted with nucleophiles in good to excellent yields allowing the installation of hetereoatoms at the benzylic position with inversion of configuration. The bromide **7** was treated with sodium benzoate to afford the ester **8** in 77% yield. In a similar fashion, reaction of **7** with sodium azide in DMSO at room temperature provided a 93% yield of the azido intermediate **9**. Chemoselective hydrogenation of **9** with Pearlman's catalyst in EtOAc in the presence of Boc_2O gave the Boc-protected amine **10**[11] in 96% yield.

We next explored the possibility of opening a fully substituted piperidine ring. Dihydropyridone **3** was converted to piperidone **12** in two steps using standard procedures. Alkylation of **12** with LiHMDS and methyl iodide afforded compound **13** (Scheme 3). Stereoselective reduction of the keto group with L-Selectride at −78 °C provided the desired alcohol **14** as a single diastereomer.

The phenyl carbamate group was reduced with LAH to give the *N*-methylpiperidinol **15** in near-quantitative yield. Since the von Braun reaction has been observed to occur in

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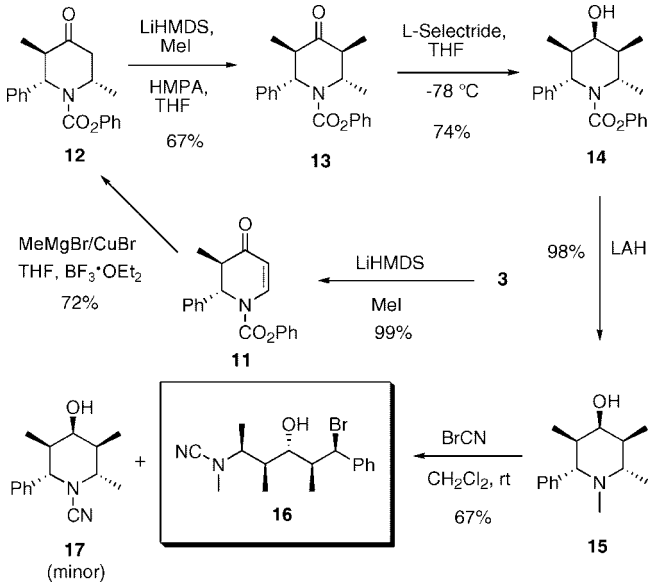
Scheme 3



the presence of hydroxyl groups,[12] the ring-opening reaction was attempted without prior protection. To our delight, the fully substituted piperidine **15** on treatment with cyanogen bromide at room temperature provided the ring-opened product **16** in 67% yield. In addition, a small amount of crystalline cyanamide **17** was isolated as a byproduct and was subjected to X-ray analysis. The results confirmed the stereochemical assignments for **14** and **15**.

(12) Casy, A. F.; Hassan, M. M. A. *Tetrahedron* **1967**, *23*, 2075.

It has been shown by our racemic model study that various substituted piperidine rings may be opened regio- and stereoselectively with cyanogen bromide in the presence of a phenyl activating group at C-2. The reactions presented are high yielding, and the products are open to diversification and further substitution. Although this study used racemic starting materials, the methodology can produce enantiopure products of either antipode by starting with readily available nonracemic dihydropyridones.[13,14] This methodology can be used to stereoselectively synthesize uniquely substituted amine derivatives containing multiple chiral centers and various functionality.

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Supporting Information Available: Experimental procedures and characterization for **4**−**16**, NMR spectra for **4**−**10** and **12**−**16**, and ORTEP plots and X-ray crystal data (CIF) for **7** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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