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Synthesis of 1,3-Amino Alcohol Derivatives via a Silicon-Mediated Ring-Opening of Substituted Piperidines

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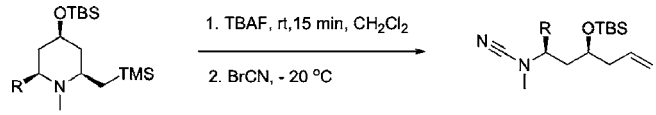
ABSTRACT



Multisubstituted piperidines containing a trimethylsilylmethyl group at C-2 can be opened regioselectively with TBAF and cyanogen bromide. The ring-opened products contain synthetically useful cyanamide and terminal alkene functional groups. This method is useful for the stereoselective synthesis of alkylamine derivatives containing multiple chiral centers.

In our recently published work involving the ring-opening of chiral 2-phenyl-*N*-methylpiperidines,[1] we reported that various piperidines of this type could be stereo- and regioselectively converted to their acyclic counterparts using the von Braun tertiary amine cleavage reaction.[2] While this methodology is efficient and potentially useful, it requires the use of a phenyl substituent at the C-2 position to activate the bond for selective cleavage. This process results in ring-opened products containing a phenyl group in the alkylamine chain. To expand this methodology for application to a broader range of chemistry, it was desirable to have functionality present in the product that would be more amenable than a phenyl group to diversification.

A search was initiated for a C-2 group that would activate the piperidine ring toward regioselective cleavage, and either be a good synthetic handle in and of itself or result in a useful functionality after ring-opening. It was also desirable to be able to insert the group into the ring system using known dihydropyridone substitution methodology.[3] Many plans were considered but the most promising conceptually was the placement of a trimethylsilylmethyl group at the C-2 position.

Since the von Braun cyanoammonium salt intermediates are positively charged,[2] we anticipated that a β-elimination through the trimethylsilylmethyl group would give a ring opened product containing a terminal olefin. The pioneering work done by Carey on the elimination of the esters of β-(hydroxyalkyl)trimethylsilanes,[4] and the cleavage of 2-(trimethylsilyl)ethyl sulfides with cyanogen bromide reported by Decout,[5] provided an indication that this proposed transformation might proceed as desired.

The synthesis of our model system began with a copper-mediated conjugate addition of the trimethylsilylmethyl group to racemic *N*-acyl-2-methyl-1,4-dihydropyridone **1**[6] (Scheme 1). This gave **2** as a mixture of *cis* and *trans* isomers that could not be completely separated by chromatography. The

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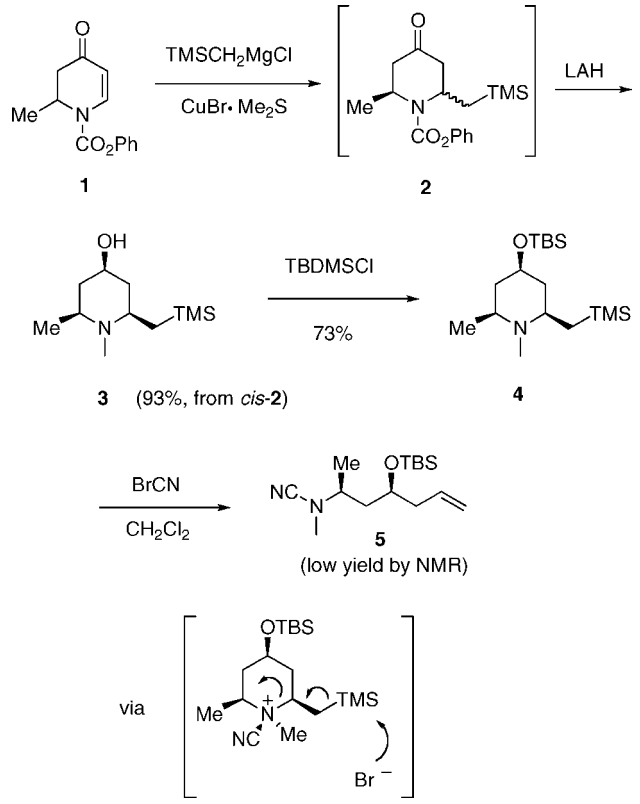
Scheme 1



1 **2** **3** (93%, from *cis*-**2**) **4** **5**

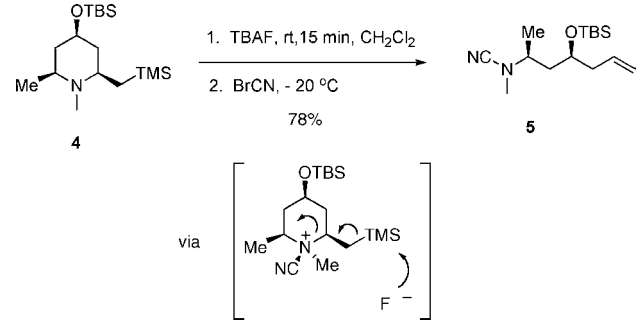
mixture (5/1, *cis*/*trans*) was taken on and subjected to reduction with LAH. Upon purification, the major isomer **3** was isolated with all substituents in a *cis* orientation. The piperidinol was protected as the TBS ether to give **4** which was subjected to our standard von Braun conditions.[1] It was hoped that the bromide ion would attack the trimethylsilyl group of the cyanoammonium salt intermediate and effect ring-opening to give cyanamide **5**. The reaction gave a very complex mixture of mostly indiscernible products. The H^1 NMR spectrum of the crude product did provide some encouragement, as terminal olefin resonances were present indicative of the desired alkene **5**. This gave hope that the reaction could be optimized.

Given the strong affinity that fluorine has for silicon, it was thought that the presence of excess fluoride ion would help the elimination to occur. Indeed, with the addition of TBAF, the reaction proceeded smoothly and gave the desired terminal olefin **5** as the only product observed (Scheme 2).

In our previously published work, we utilized a phenyl substituent at the C-2 position to activate the *N*-methylpiperidines to selective cleavage during the ring-opening reaction.[1] We were curious as to whether or not we could use a piperidine containing two activating groups and show preference for one type of cleavage over the other. A competition experiment was designed to see if ring-opening could be effected selectively at C-6 in the presence of a C-2 phenyl activating group.

The dihydropyridone **6**[6] was treated with the (TMS)-methylcuprate to again give a mixture of isomers (**7**) that

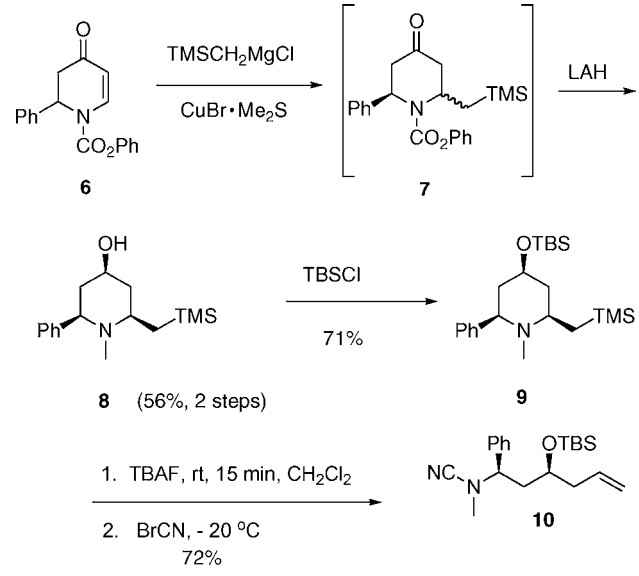
Scheme 2



4 **5**

was taken on and reduced to the piperidinol **8** before purifying by chromatography (Scheme 3). The *cis*- piperi-

Scheme 3



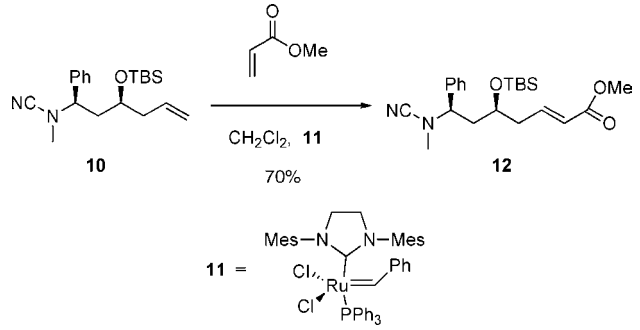
6 **7** **8** (56%, 2 steps) **9** **10**

dinol **8** was protected as the TBS ether **9** and treated under our ring-opening conditions. The reaction again proceeded smoothly to give the terminal olefin **10** as the only observed product. The crude reaction mixture was then taken on and subjected to a Grubbs cross metathesis reaction to determine if the cyanamide function would be tolerated by the catalyst.

To our satisfaction, the cross metathesis reaction gave **12** in good yield (Scheme 4). This homologation not only extended the chain by one carbon but also introduced very useful functionality into the chiral molecule. This illustrates that the terminal alkene of these cyanamides can be easily modified for further elaboration.

We have expanded the scope of our previous piperidine ring-opening methodology by utilizing a new C-2 activating group. A group was chosen that not only can be easily installed using our previously developed dihydropyridone chemistry,[3] but also provides excellent selectivity in the ring-opening while yielding a synthetic handle that may be

Scheme 4



manipulated in various ways for synthetic purposes. Although racemic starting materials were used in this study, the method can produce enantiopure products of either antipode by starting with readily available nonracemic *N*-acyldihydropyridones.[7,8] This chemistry should be applicable to natural product and peptidomimetic syntheses. Investigations are currently ongoing into further developing this methodology as well as its applications in synthesis.

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Supporting Information Available: Experimental procedures and characterization for **2**−**5**, **8**−**10**, and **12**. NMR spectra for **2**−**5**, **8**−**10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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