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Stereoselective Synthesis of 2,6-Disubstituted Piperidine Alkaloids via $TiCl_4$ Induced Iminium Ion Cyclization of α-Cyanoamines

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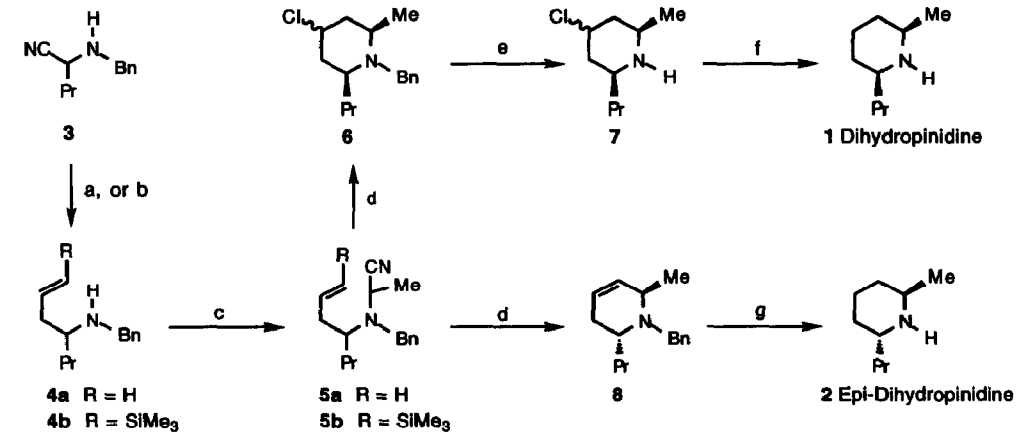
Abstract: The stereoselective cyclization of an α-cyanoamine containing a vinyl group induced by $TiCl_4$ in a methylene chloride solution, produces cis 2,6-dialkylpiperidine; whereas a similar reaction of an α-cyanoamine containing a silyl substituted vinyl group gave the corresponding trans isomer only.

The piperidine ring is one of the most abundant skeleton in the naturally occurring alkaloids. With proper substitutions, the basic nitrogenous six-membered ring forms a large group of important alkaloids.[1] Therefore, it is important to develop stereoselective routes for the preparation of compounds in this category. The reactions related to the preparation of cis 2,6-dialkylpiperidine species have been extensively studied. In contrast, the trans isomers have relatively rare been mentioned in the literature.[2] In our continued efforts on developing the utility of $TiCl_4$ induced iminium ion cyclization of α-cyanoamines,[3] we found the substituents on the π-nucleophilic double bond not only affected the chemical yields and reaction rates of the cyclization process but also significantly influence the stereochemistry of the cyclized products. We now report the highly stereoselective synthesis of both isomeric piperidine alkaloids, dihydropinidine **1** and epi-dihydropinidine **2**.[4]

Scheme I:



(a) AllylMgBr, THF, r.t.; (b) s-BuLi, $Me_3SiCH_2CH{=}CH_2$, THF, r.t.; (c) KCN, CH_3CHO, 6N HCl, H_2O, r.t.; (d) 1.0M $TiCl_4$ in CH_2Cl_2, r.t.; (e) H_2, MeOH, 5% Pd/C, r.t.; (f) n-Bu_3SnH, AIBN, Benzene, reflux; (g) H_2, MeOH, 5% Pd/C, r.t..

The synthesis began with α-cyanoamine **3** which was prepared from butyroaldehyde, benzylamine, and potassium cyanide under the Robinson-Schopf reaction condition in 95% yield. The treatment of α-cyanoamine **3** with 2.5 equivalents of allylmagnesium bromide gave amine **4a** in 90% yield. Another Robinson-Schopf reaction of amine **4a** gave α-cyanoamine **5a** in 85% yield in a methanolic hydrochloric acid solution in the presence of three equivalents of acetaldehyde and potassium cyanide. The reaction of iminium ion cyclization w as carried out by the addition of α-cyanoamine **5a** into a 1M solution of $TiCl_4$ in methylene chloride at ambient temperature. About 60% of the cis 2,6-dialkylpiperidine **6** and less than 5% of the trans isomer were obtained. Similar to our previous observations , addition of $TiCl_4$ to a methylene chloride solution of α-cyanoamine **5a** gave less than 20% of the cyclized product. This result once again indicated that the addition sequence was crucial for this cyclization.[3b] Finally, the cis cyclic amine **6** was debenzylated through a metal catalyzed hydrogenolysis in 97% yield, and the resulting amine **7** was reduced with *tri-n*-butyltin hydride to yield 90% of dihydropinidine **1**.[3b] (Scheme 1)

On the other hand, the α-cyanoamine **5b** was synthesized in a similar fashion as in the preparation of **5a** except that the starting α-cyanoamine **3** was treated with a mixture of allylsilane with *sec*-butyl lithium to produce amine **4b** in 85% yield.[5] Similarly, amine **4b** was mixed with three equivalents of acetaldehyde and potassium cyanide in acidic methanol to give 85% of α-cyanoamine **5b**. The cyclization of **5b** was carried out in a similar manner as **5a** to yield 80% of the trans cyclic amine **8** as the only isolated product. The final target was furnished by the catalytic hydrogenation to provide 95% of *epi*-dihydropinidine **2**. It is worth mentioning that this $TiCl_4$ induced cyclization was carried out at very low temperature. We believe that the reaction is a kinetically controlled process rather than being a thermodynamic equilibrium, as reported by Overman, in which the reaction was usually run at 100°C for more than 20 hours.[6]

In conclusion, the $TiCl_4$ induced cyclization of α-cyanoamines is a highly stereoselective route to either isomer of the 2,6-dialkylpiperidine. However, the detailed mechanistic account for the stereoselectivity of this reaction still remains to be elucidated.

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