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Intramolecular Schmidt Reaction Involving Primary Azidoalcohols under Nonacidic Conditions: Synthesis of Indolizidine (−)-167B

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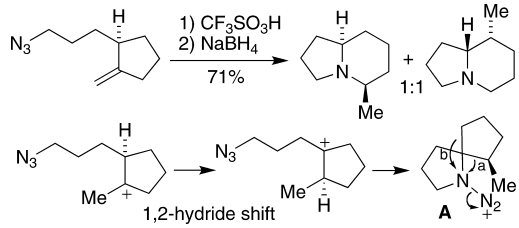
In the early 1990s, Aubé and Pearson independently reported the intramolecular Schmidt rearrangement reaction of alkyl azides with ketones[1] and tertiary carbocations[2,3] generated from alkenes and alcohols under acidic reaction conditions. This reaction rapidly proved to be a powerful tool for the rapid assembly of complex nitrogen containing heterocycles.[4] From a mechanistic point of view, the reaction takes place between an alkyl azide with either an oxocarbenium ion (obtained by protonation of a ketone, acid catalyzed opening of a ketal, etc.) or a secondary/tertiary carbenium ion (obtained by protonation of an alkene or acid promoted heterolysis of a secondary/tertiary alcohol). The synthesis of 5-phenylindolizidine represents a typical example of the carbocationic rearrangement.[3] However, when the same approach was attempted for preparation of 5-methylindolizidine (Scheme 1), a model system for several natural products such as indolizidine 209D and 167B, a 1:1 mixture of regioisomers is obtained due to a rapid rearrangement of the intermediate carbenium ion followed by a nonselective 1,2-migration (**A**, pathways (a) and (b)).[6] Different strategies to overcome this lack of regioselectivity have been investigated but are still relying on acidic reaction conditions.[6−8]

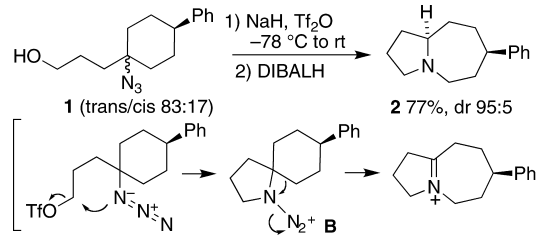
Scheme 1



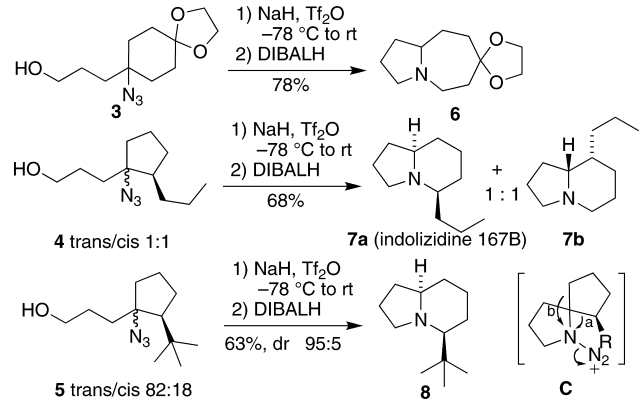
As part of our ongoing research program directed toward the synthesis of various biologically active alkaloids, we recently developed a method for the radical carboazidation of alkenes.[9−12] This process represents a unique source of γ-azidoesters and, after ester reduction, of primary 4-azidoalcohols. We report here a modified version of the intramolecular Schmidt reaction involving such primary azidoalcohols. This process is run under nonacidic conditions, and it allows resolution of the regioselectivity problems caused by rearrangement of carbenium ions described in Scheme 1. The utility of the method is demonstrated by a concise synthesis of dendrobate alkaloid (−)-indolizidine 167B.

The 4-azidoalcohol **1** was chosen as a model system for the development of the Schmidt reaction with a primary alcohol. Compound **1** is easily prepared from 4-phenylmethylenecyclohexane via carboazidation and reduction of the intermediate azidoester with $LiBH_4$ (see Supporting Information). Activation of the alcohol with triflic acid according to Pearson's conditions[3] as well as conversion to the corresponding iodide, tosylate, and nosylate followed by heating failed to give the desired rearranged product. Gratifyingly, when the alcohol was converted into the corresponding triflate by treatment with triflic anhydride and sodium hydride at −78 °C and allowed to warm up to room temperature, nitrogen extrusion was observed, and after addition of diisobutylaluminum hydride (DIBALH), clean formation of the octahydropyrroloazepine **2** was observed (77% yield, dr 95:5) (Scheme 2). The use of $NaBH_4$ or $NaBH_3CN$ instead of DIBALH afforded **2** in similar yields but with lower diastereoselectivities (dr ≤70:30). The reaction involves likely a nucleophilic substitution of the triflate by the azide leading to the intermediate aminodiazonium **B** followed by a 1,2-alkyl migration leading to the iminium ion that is finally reduced by the hydride. To the best of our knowledge, this is the first example of an intramolecular Schmidt reaction involving a primary electrophilic carbon center.

Scheme 2



Scheme 3



The reaction of primary 4-azidoalcohols **3**−**5** was examined next (Scheme 3). The acid sensitive acetal **3** gave the expected octahydropyrroloazepine **6** in 78% yield. The 1-azido-2-propylcyclopentane **4** gave a 1:1 mixture of the two indolizidines **7a** and **7b**. Compound **7a** can be obtained in an analytically pure form by further chromatography and is identical to the known alkaloid indolizidine 167B, a natural product isolated from the skin the frog *Dendrobates speciosus*.[13−15] The lack of regioselectivity of this rearrangement is reminiscent of the reaction reported by Pearson described in Scheme 1.[3,16] Remarkably, the 2-*tert*-butyl-substituted azidocyclopentane **5** afforded a single regio- and diastereomer of 5-*tert*-butylindolizidine **8** in 63% yield.[17]

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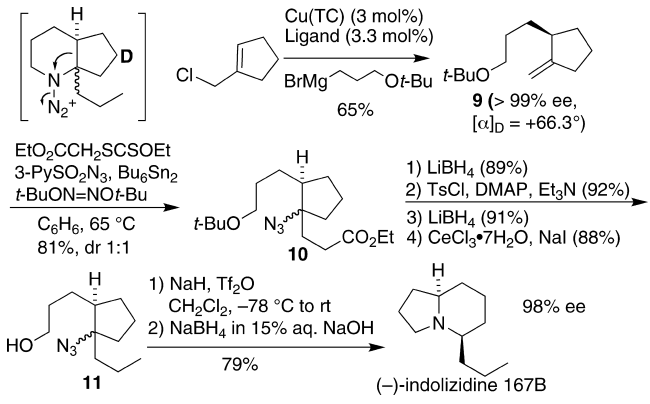
Since the 4-azidoalcohol **4** affords a mixture of **7a/7b**, another approach for selective synthesis of indolizidine 167B was envisaged. As proposed by Pearson,[3] a piperidinodiazonium salt of type **D** should lead to the desired product with high regioselectivity (Scheme 4). However, Pearson's approach did not afford the desired product due to the unexpected carbocationic rearrangement. Interestingly, activation of the primary carbon atom of 5-azidoalcohol **11** should lead exclusively to the piperidinodiazonium salt **D** and therefore to a fully regioselective synthesis of indolizidine 167B. The synthesis of (−)-indolizidine 167B is depicted in Scheme 4. The starting methylenecyclopentane **9** was readily prepared from 1-chloromethylcyclopentene in 65% yield and 99% ee using Alexakis enantioselective copper(I) catalyzed allylic substitution.[18] The carboazidation of **9** afforded the azidoester **10** in 81% yield as a 1:1 mixture of diastereomers. Since both diastereomers of **10** are expected to give the desired product, no separation was performed. The propyl side chain was installed by reduction of the ester to the primary alcohol with $LiBH_4$ followed by tosylation and, finally, reduction of the primary tosylate with $LiBH_4$. After removal of the *tert*-butyl protecting group with cerium(III) chloride in the presence of NaI,[19] the primary 5-azidoalcohol **11** was obtained in 65% overall yield from **10**. The azidoalcohol **11**, as a 1:1 mixture of diastereomers, was treated with triflic anhydride in the presence of sodium hydride at −78 °C, and the reaction mixture was allowed to warm up to room temperature overnight. The intermediate iminium ion was reduced in situ with $NaBH_4$ (7 equiv) to afford (−)-indolizidine 167B in 79% yield as a single regio- and diastereomer. The optical purity of the final product (ee ≥ 98%) matches the one of the starting material. (−)-Indolizidine 167B has been synthesized in 7 steps and 27% overall yield starting from 1-chloromethylcyclopentene and 42% overall yield from methylenecyclopentane **9**.[20] Remarkably, even if the carboazidation reaction delivers a 1:1 mixture of diastereoisomers, the whole process is fully stereoselective and takes place with complete retention of the absolute configuration.

Scheme 4



In conclusion, we have developed a powerful intramolecular Schmidt reaction starting from primary azidoalcohols. This approach involves a nonacidic activation of the alcohol via triflation and is complementary to the rich chemistry mediated by secondary and tertiary carbocations developed by Pearson. The synthetic advantages offered by the mild reaction conditions were unambiguously demonstrated by the regio- and stereoselective synthesis of (−)-indolizidine 167B.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The reaction was reapeated with diastereomercially pure *cis*-**4** and *trans*-**4** and both diastereomers gave the same 1:1 mixture of **7a/7b**.
(17) The regioselectivity may be due to a favorable conformation of the aminodiazonium salt or to a higher inherent migration ability of the *tert*-butyl substituted carbon atom.
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(20) Shorter syntheses of indolizidine 167B are reported; however, they rely on starting material containing either the pyrrolidine or the piperidine rings. See for instance ref 14h and 14j. Our synthesis compares well with syntheses where both heterocycles are synthesized; see for instance ref 14e (11 steps from cycloheptadiene) and ref 14i (25% overall yield from a noncommercially available starting material).

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