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THE INTRAMOLECULAR CYCLOADDITION OF AZIDES WITH ω-CHLOROALKENES. A FACILE ROUTE TO (-)-SWAINSONINE AND OTHER INDOLIZIDINE ALKALOIDS

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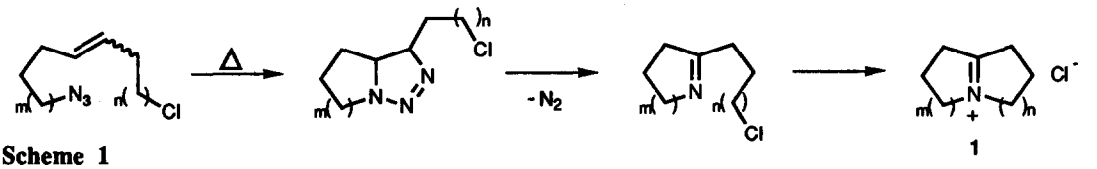
ABSTRACT: A potentially general route to the 1-azabicyclo[n.m.0]alkane skeleton of various alkaloids is embodied in the intramolecular 1,3-dipolar cycloaddition of aliphatic azides with ω-chloroalkenes. Cycloaddition is followed by rearrangement and intramolecular N-alkylation, affording bicyclic iminium ions 1 in one operation. The application of this method to the synthesis of (±)-δ-coniceine 6, (1S,2R,8aR)-indolizidine-1,2-diol 13 and (-)-swainsonine 15 is described.

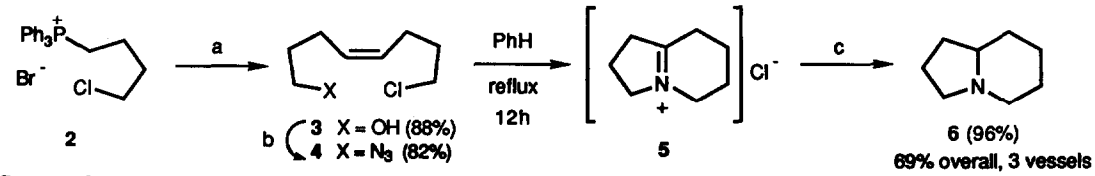
Bicyclic saturated heterocycles such as the pyrrolizidine, indolizidine and quinolizidine alkaloids are widespread in nature. We have been interested in developing general methods for the construction of such skeleta. Recently, we reported that the intramolecular 1,3-dipolar cycloaddition of aliphatic azides with certain types of electron rich 1,3-butadienes produces pyrrolizidines and indolizidines in one operation.[1] To extend this type of strategy, we have examined the intramolecular cycloaddition of azides with other types of functionalized alkenes. Herein we report that alkenes bearing ω-chloroalkyl groups are excellent dipolarophiles in azide cycloadditions, and lead to useful bicyclic iminium ions by a rearrangement / alkylation sequence. This technique allows the assembly of bicyclic nitrogen containing heterocycles in one operation, and is illustrated by short and efficient syntheses of three indolizidine alkaloids, δ-coniceine **6**, (1S,2R,8aR)-indolizidine-1,2-diol **12**, and (-)-swainsonine **15**.[2]

The strategy is outlined in Scheme 1. Intramolecular 1,3-dipolar cycloaddition[3] of an aliphatic azide onto an ω-haloalkene should generate a thermally labile triazoline, which may undergo ring opening and a well-precedented 1,2-hydrogen shift[4] with nitrogen loss to produce a 1-pyrroline. Intramolecular alkylation of the imine nitrogen of this pyrroline[5] would then generate a bicyclic iminium ion **1**, which may then be subjected to a number of further transformations. Ideally, the entire sequence would proceed in one vessel.



Scheme 1

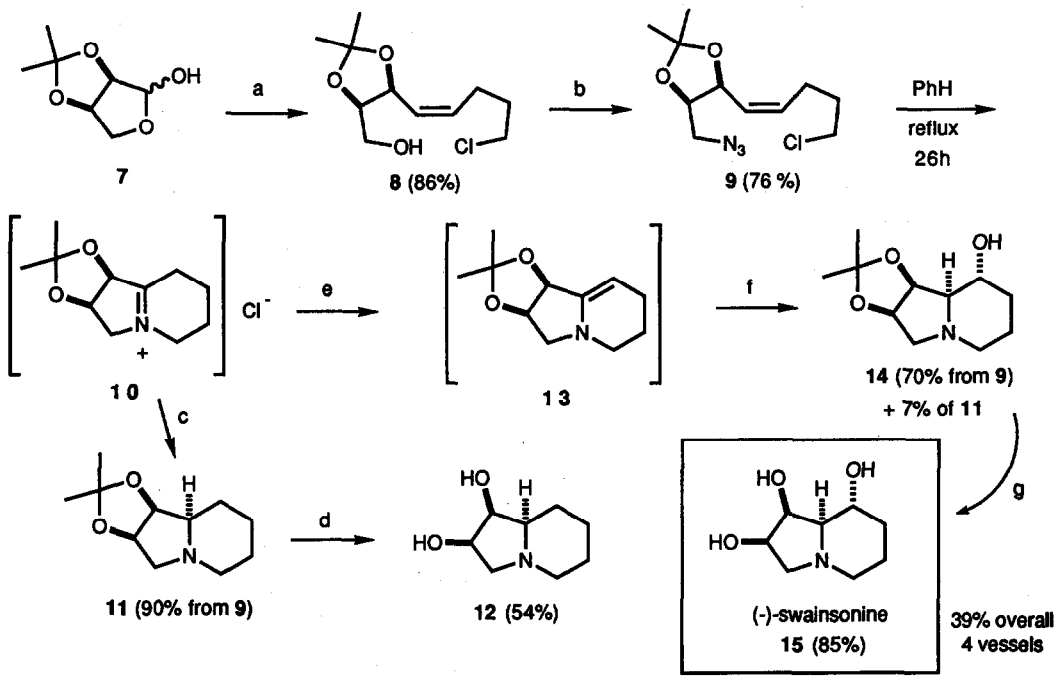
To test this hypothesis, the sequence shown in Scheme 2 was carried out. Wittig olefination of 4-hydroxybutanal with the ylide derived from phosphonium salt **2**[6] provided the chloroalcohol **3** in good yield. Attempted displacement reactions of tosylate, mesylate, or triflate derivatives of **3** with azide ion were unsatisfactory due to competitive displacement of the primary chloride. However, a Mitsunobu reaction with diphenylphosphoryl



Scheme 2 (a) 1.0 eq. $KN(TMS)_2$, THF; 4-hydroxybutanal (0.49 eq.), 0°C, 1h; only Z-isomer of **3** detected. (b) 1.3 eq. $(PhO)_2P(O)N_3$, 1.3 eq. PPh_3, 1.3 eq. $EtO_2CN{=}NCO_2Et$, THF, 23°C, 5h. (c) 1.1 eq. $NaBH_4$, CH_3OH, 0°C, 1h.

azide[7] produced the desired azide **4** directly from **3** in good yield. Heating **4** in refluxing benzene produced the observable bicyclic iminium ion **5**, which was reduced with sodium borohydride to give (±)-δ-coniceine **6**[5d,8] in excellent yield. The three-vessel synthesis of **6** in 69% overall yield from 4-hydroxybutanal clearly illustrates the potential efficiency of this ring forming process.

We then turned our attention to the application of this method to the synthesis of swainsonine **15** (Scheme 3). Swainsonine[9] is an effective inhibitor of lysosomal α-mannosidase,[10] which is involved in the cellular degradation of polysaccharides. It is also an inhibitor of of mannosidase II,[11] which is important in the processing of asparagine-linked glycoproteins. Swainsonine been found to exhibit immunoregulative activity,[12] and most recently is being examined as a candidate for cancer chemotherapy.[13] The interesting biological activity of this alkaloid has led several groups to develop synthetic routes to swainsonine.[2,14] We report below a short and efficient new method to prepare this important compound.



Scheme 3 (a) 2.5 eq. 2 + 2.4 eq. $KN(TMS)_2$, 0°C, THF, 40 min, then add **7** at -78°C, warm to 23°C, 2h; only *Z*-isomer of **8** detected. (b) 1.2 eq. $(PhO)_2P(O)N_3$, 1.3 eq. PPh_3, 1.3 eq. $EtO_2CN{=}NCO_2Et$, THF, 23°C, 1h. (c) 1.1 eq. $NaBH_4$, CH_3OH, 0°C, 1h. (d) 6N HCl, THF, 23°C, 12h. (e) 1.1eq. $tBuNH_2$; 1.1 eq. $KN(TMS)_2$. (f) 3.3 eq. BH_3·THF, 23°C, 10h; NaOAc, CH_3OH, H_2O_2, 23°C, 12h. (g) 6N HCl, THF, 23°C, 12h; IRA-400 ion exchange chromatography.

Wittig reaction of 2,3-*O*-isopropylidene-D-erythrose **7**[15,16] with the phosphorane derived from **2** proceeded smoothly to give **8**. A Mitsunobu reaction was again found to be the most effective way to introduce the azide functionality, providing the key intermediate **9**. Cyclization of **9** in refluxing benzene produced the observable (^1H NMR) bicyclic iminium ion **10**. Sodium borohydride reduction produced **11** as a single diastereomer, which was deprotected by acid hydrolysis to provide (1S,2R,8aR)-indolizidine-1,2-diol **12**. This diol has been of interest in biosynthetic studies, where Harris found that it is efficiently converted to swainsonine by *R. leguminicola*.[17] However, it is the 8a-epimer of **12** (not shown) that is considered to be the the natural intermediate in the biosynthesis of swainsonine from lysine.[18]

To complete the synthesis of swainsonine, regioselective formation of enamine **13** followed by hydroboration was required. Initial attempts to generate the enamine **13** from **10** with common bases (hydroxide, carbonate, etc.) led to multiple byproducts. The use of t-butylamine was most effective, producing a clean solution of **13** and t-butylamine hydrochloride. Direct hydroboration of this material was attempted, which led to the reduced product **11** in good yield after alkaline hydrogen peroxide workup, apparently as a result of protonolysis of the intermediate borane. Believing the t-butylamine hydrochloride to be responsible, stronger bases were added (e.g., $KN(TMS)_2$) to reduce the chance of protonolysis, but **11** was still the major product of the hydroboration. Attempted isolation or aqueous workup of **13** led to considerable decomposition. While hydroboration of enamines to β-aminoalcohols using a sodium hydroxide and hydrogen peroxide oxidative workup has good precedent in the literature,[2,19] competing protonolysis of the borane is also a precedented process. Schultz[20] found that the use of sodium acetate rather than sodium hydroxide was a viable solution to this problem. This simple modification led to a 70% overall isolated yield of the acetonide **14** from the azide **9**, accompanied by a small amount of **11**. It was still necessary to use a two-base system to generate the enamine **13** for best results. The use of t-butyl amine followed by $KN(TMS)_2$ was empirically found to be best after examination of a number of bases. Direct treatment of the iminium ion **10** with $KN(TMS)_2$ led to undesired byproducts.

With an efficient route to the acetonide **14** in hand, aqueous acid hydrolysis afforded (-)-swainsonine **15** which matched all of the literature data, including optical rotation.[2] The conversion of azide **9** into swainsonine acetonide **14** was carried out in one vessel in 70% yield, demonstrating the potential of this cyclization / rearrangement / alkylation method. Overall, **7** was converted into swainsonine **15** in four separate vessels in an overall yield of 39%, and may thus provide a practical access to this important compound. The use of this method for the synthesis of other alkaloids will be reported in due course.

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