Tetrahedron Letters, Vol. 34, No. 8, pp. 1265-1268, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Stereoselective Synthesis of (±)-*trans*-Cycloalkanopiperidines and Cycloalkanopyrrolidines via Hydroboration

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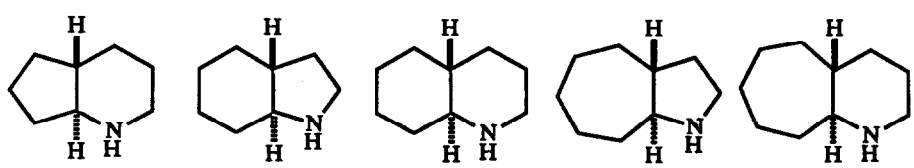
Abstract: *A highly stereoselective synthesis of trans-cycloalkanopiperidines and cycloalkanopyrrolidines has been achieved via hydroboration of bromocycloalkenes with dichloroboranes. The intermediate bromocycloalkylboronic acids were converted into azidocycloalkylboronates. Addition of two equivalents of boron trichloride in dichloromethane generated dichloroboranes which, by an intramolecular cyclisation gave intermediates II. These can be readily hydrolyzed to get the corresponding important nitrogen heterocycles in good yields and excellent stereochemical purities.*

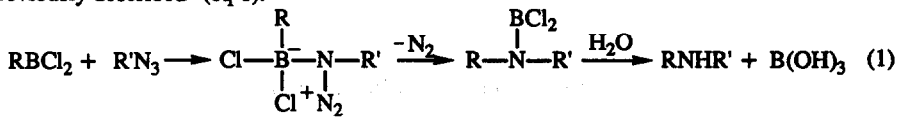
Nitrogen heterocycles incorporated in mono- and polycyclic systems are important structural features of innumerous naturally occurring substances. Therefore any new synthetic approach complementing the existing methodologies is highly desirable. Cycloalkanopiperidines and cycloalkanopyrrolidines are important nitrogen heterocycles because they possess the common skeletal features in several alkaloid families.[2] Decahydroquinolines possess the basic structure similar to that of Pumiliotoxin C alkaloids [2] while the octahydroindole moiety is common to many of the *Amaryllidaceae* family alkaloids.[3] Decahydroquinolines are pharmacologically important since the decahydroquinolinoalkyl benzoates are in general more satisfactory anesthetics than cocaine while the toxicities are considerably less than that of cocaine.[4] Similarly derivatives obtained from compounds **1**, **3** and **5** (Chart I) were found as local anesthetics in rat and antiarrhythmic in dogs.[5]

Chart I



These nitrogen heterocycles (Chart I) are in general prepared by catalytic hydrogenation of the corresponding imines.[6] Catalytic hydrogenation of quinoline normally leads to the *cis* products, or at best

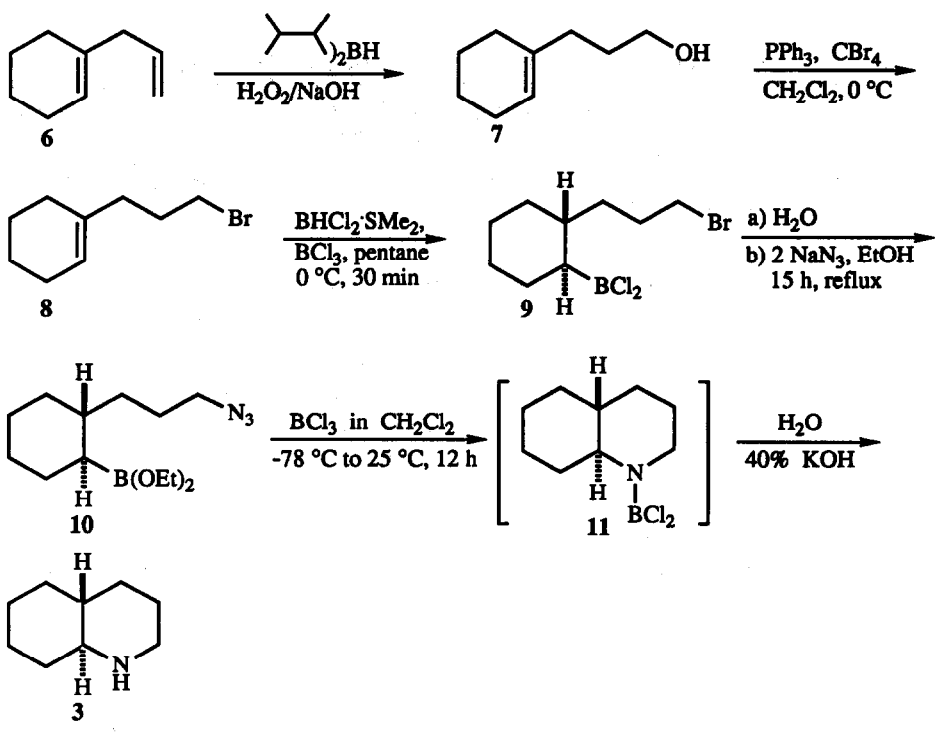
(under special conditions) to mixture in which the *trans* isomer may predominate.[6a] Although several syntheses of these nitrogen heterocycles have been reported in the literature, they generally lack stereoselectivity[6] and/or efficiency. The lack of simple and efficient procedures for the synthesis of these nitrogen heterocycles and the structural similarities they possess with many alkaloid families, has led us to investigate a general method for the construction of such skeletons. The reaction of dichloroboranes with azides to form secondary amines has been previously described[7] (eq 1).



(1)

The successful utilization of intramolecular version of this reaction of the dichloroboranes with azides (eq 1) for the construction of these nitrogen heterocycles is disclosed herein (Scheme I). Similar procedures were utilized for the synthesis of **1**, **2**, **4** and **5**.

Scheme I



The importance of organoboranes for carbon-carbon bond forming reactions is very well documented in the literature. Organoboranes commonly transfer the organyl group to essentially most of the other elements of synthetic interest, including carbon, with complete maintenance of stereochemical integrity.[8]

Several reactions are known involving the transfer of an alkyl group from organoboranes to nitrogen, providing the secondary amine derivatives.[7] The trialkylboranes (R_3B), dialkylchloroboranes (R_2BCl), and monoalkyldichloroboranes ($RBCl_2$) react with variable ease with organic azides to give the intermediates, which are readily hydrolyzed to form secondary amines.[7] Recently Carboni et al.[9] used an intramolecular version of this reaction for the synthesis of pyrrolidine and piperidine ring systems using halogen as non-migrating group while Evans and Webber[10] have used cyclohexyl as a non-migrating group for the same. We are reporting here the development of an intramolecular version of this reaction (eq 1) for the synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines in excellent diastereoselectivity (Table 1).

The dienes needed for this study were prepared according to literature procedure and purified by fractional distillation.[11] The selective hydroboration of the diene **6** with disiamylborane[8] and alkaline peroxide oxidation provided alcohol **7** in very good yields and the usual regioselectivity was observed. The alcohol **7** was converted to the bromocycloalkene **8** using triphenylphosphine and carbon tetrabromide in dichloromethane.[12] The hydroboration of bromocycloalkene **8** with dichloroborane in pentane at 0 °C produced the corresponding bromocycloalkyldichloroborane **9** in quantitative yield and in very high diastereoselectivity.[13] Hydrolysis of **9** gave bromocycloalkylboronic acid. The solid boronic acid was converted to the azidocycloalkylboronate **10** by refluxing in ethanol with two equivalents of sodium azide.[9] The treatment of azidocycloalkylboronate **10** with two equivalents of boron trichloride in dichloromethane at –78 °C generated the dichloroborane[14] which, by an intramolecular cyclisation gave intermediate **11** which can be readily hydrolyzed to decahydroquinoline **3** in 80% isolated yield. As pointed out earlier similar methods were used for the synthesis of **1**, **2**, **4** and **5**.

Table 1. (±)-*trans*-Cycloalkanopiperidines and Cycloalkanopyrrolidines from Bromocycloalkenes.

entry	bromocycloalkenes [a]	amine	yield% [d,e]
1	3-(cyclopent-1'-enyl)propyl bromide	*trans*-octahydro-1-pyridine[c]	80
2	2-(cyclohex-1'-enyl)ethyl bromide	*trans*-octahydroindole[c]	76
3	3-(cyclohex-1'-enyl)propyl bromide	*trans*-decahydroquinoline[b]	80
4	2-(cyclohept-1'-enyl)ethyl bromide	*trans*-perhydrocyclohepta[b]pyrrole[c]	82
5	3-(cyclohept-1'-enyl)propyl bromide	*trans*-perhydrocyclohepta[b]pyridine[c]	82

a) All reactions were carried on 10-15 mmol scale. b) Isomeric purity determined by ^1H NMR (see ref. 6), GC analysis and no *cis* isomer was detectable. c) Isomeric purity was established by comparing the melting points of their appropriate derivatives with literature data (see ref. 6). d) Yields are based on the bromocycloalkylboronic acid. e) All compounds gave satisfactory spectral data.

In conclusion, the method described in this communication represents a convenient and versatile procedure for the construction of these nitrogen heterocycles. This is a truly general and simple approach for the synthesis of *trans*-decahydroquinoline and *trans*-octahydroindole alkaloids, with complete control of stereochemistry. Since a wide variety of enantiomerically pure boronic esters are available by asymmetric

hydroboration or homologation,[15] the synthesis of these nitrogen heterocycles should be possible in optically active form with complete control of stereochemistry.

Currently we are working on the synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines in optically active form using optically active boronic esters. These results will be reported in the near future.

Acknowledgment:
We wish to thank Office of Naval Research for the financial support of this research.

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(Received in USA 12 October 1992; accepted 8 December 1992)