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New Insights into NIS-Promoted Aminocyclization. Synthesis of Decahydroquinolines from 2-Allylcyclohexylamines[‡]

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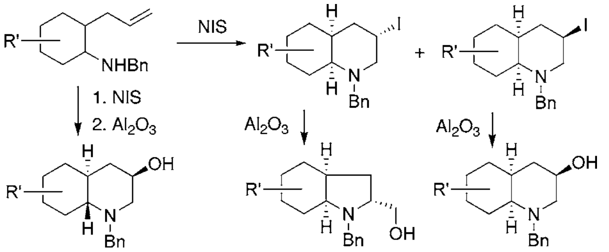
ABSTRACT



Bishomoallylic secondary amines embodying the 2-allyl-*N*-benzylcyclohexylamine unit react with NIS to undergo cyclization through 6-endo processes in either the cis or trans series. Nevertheless, when the resulting *cis*-3-iododecahydroquinolines are treated with Al_2O_3, the exo derivatives evolve into octahydroindoles and the endo derivatives keep the same backbone, the configuration being retained in the generated alcohols.

The formation of functionalized nitrogen-containing rings is a constant endeavor in synthetic organic chemistry, giving access to building blocks that allow new approaches to many naturally occurring and biologically interesting compounds. Halocyclization of unsaturated derivatives with an intramolecular nucleophilic center plays an important role in the stereoselective construction of cyclic structures[1] and thus constitutes a suitable tool for the synthesis of azacyclic compounds. However, iodoaminocyclization of cyclic alkenylamines to build azabicyclic motifs using iodine(I) reagents[2,3] has received limited attention, even starting from N-protected derivatives[4] or anilines.[5] In contrast, the reaction upon noncyclic alkenylamines[6] and the corresponding N-protected derivatives (amides or carbamates)[7] has been profusely studied, usually resulting in five-membered rings through 5-endo and 5-exo cyclization processes.

In this work, we describe the results observed in the NIS-promoted cyclization in bishomoallylic secondary amines embodying the 2-allyl-*N*-benzylcyclohexylamine unit (Scheme

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[‡] Dedicated to Prof. Miguel Yus on his 60th birthday.

(1) (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408. (b) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354−362.

(2) Using iodine: (a) Tanner, D.; Sellén, M.; Bäckvall, J.-E. *J. Org. Chem.* **1989**, *54*, 3374−3378. (b) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275−1294. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891−2897.

(3) Using NIS: (a) Blough, B. E.; Mascarella, S. W.; Rothman, R. B.; Carroll, F. I. *J. Chem. Soc., Chem. Commun.* **1993**, 758−760. (b) Faltz, H.; Bender, C.; Liebscher, J. *Synthesis* **2006**, 2907−2922. (c) Beshore, D. C.; Smith, A. B., III *J. Am. Chem. Soc.* **2007**, *129*, 4148−4149.

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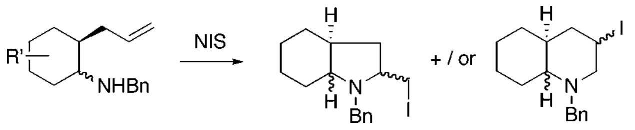
(5) (a) Francis, C. L.; Ward, A. D. *Aust. J. Chem.* **1994**, *47*, 2109−2117. (b) Gataullin, R. R.; Minnigulov, F. F.; Khakimova, T. V.; Kazhanova, T. V.; Fatykhov, A. A.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 456−459. (c) Majumdar, K. C.; Kundu, U. K.; Das, U.; Jana, N. K.; Roy, B. *Can. J. Chem.* **2005**, *83*, 63−67.

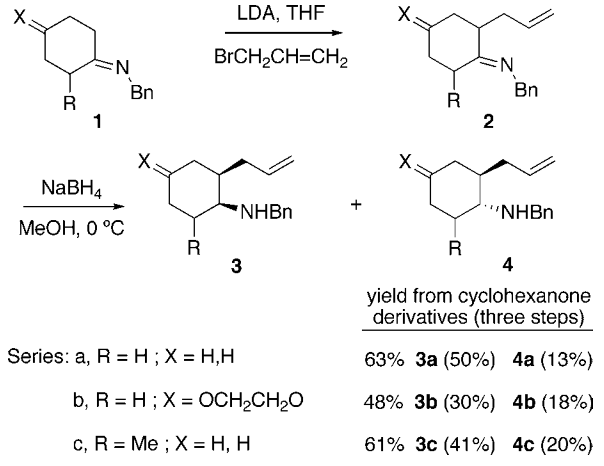
10.1021/ol070770g CCC: $37.00

Scheme 1. Possible Regio- and Stereochemical Outcomes for Cyclization



1). Curiously, the iodoaminocyclization of 2-alkenylcyclohexylamines has not been studied so far, the only related precedent being the iodocyclization of a homoallylic sulfonamide.[4b] Thus, the regio- and stereoselectivity of the iodine(I)-promoted aminocyclization of the cyclic starting materials reported here would give new insights into this classical reaction and, in turn, open new perspectives for the synthesis of decahydroquinoline derivatives.

Scheme 2. Synthesis of 2-Allylcyclohexylamines



The starting materials were prepared from the appropriate cyclohexanone according to the following three-step sequence: (i) imine formation; (ii) α-allylation; and (iii) reduction (Scheme 2). In series **a** and **b**, the imine was formed by reaction of benzylamine with cyclohexanone and the monoethyleneacetal of 1,4-cyclohexanedione, respectively, at room temperature in CH_2Cl_2 solution. In series **c**, the reaction starting from 2-methylcyclohexanone required heating under Dean–Stark conditions for the preparation of **1c**. Imines **1** were allylated using LDA as a base in THF at −78 °C, and the resulting imines **2** were reduced with $NaBH_4$ to give a mixture of secondary amines **3** and **4** (4:1 to 2:1 according to the series; see Scheme 2).[8] At this point, improving the diastereoselectivity of the reduction[9] was not a priority because the availability of all the diastereomers would help evaluate the scope and limitations of the NIS-promoted cyclization process. To our knowledge, the protocol reported here for the synthesis of α-alkylated cyclohexylamines by alkylation of a cycloalkylimine and subsequent reduction of the imine is unprecedented because this type of compound (i.e., **3**, **4**) is usually prepared by reductive amination of the corresponding α-alkylated cyclohexanone.[10]

Treatment of *cis*-alkenylamine **3a** with NIS in CH_2Cl_2, using K_2CO_3 as the base, gave after filtration on a silica gel pad the decahydroquinolines **5a** and **6a**. If the reaction mixture was heated, the imide **7**[11] (42%) was isolated together with **6a** (27%), but when **5a** was heated in CH_2Cl_2 and NaI, it did not give the corresponding 2-iodomethyl derivative and was recovered.[12] Interestingly, when compounds **5a** and **6a** were eluted separately through Al_2O_3, alcohols **8a** and **9a** were isolated, respectively. Although it is well documented that nucleophilic substitution of 3-halopiperidines and 2-halomethylpyrrolidines proceeds stereospecifically through an aziridinium salt intermediate[11a,13] with retention of configuration, to our knowledge, the stereospecific Al_2O_3-promoted formation of alcohols is unprecedented.

Having established the optimal conditions for the cyclization, we were ready to do a one-pot procedure. Treatment of amino alkene **3a** with NIS in CH_2Cl_2 followed by column chromatography upon alumina allowed the isolation of alcohols **8a** (43% for the two steps) and **9a** (29% for the two steps), constituting a 72% overall yield for the cyclization and interconversion of the functional group (Scheme 3). The ^{13}C NMR data[14] (see Supporting Information) of these

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(6) (a) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287–291. (b) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925. (c) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991–1994. (d) Bubnov, Y. N.; Misharin, M. A.; Ignatenko, A. V. *Tetrahedron Lett.* **1997**, *38*, 6259–6262. (e) Hügel, H. M.; Hugues, A. B.; Khalil, K. *Aust. J. Chem.* **1998**, *51*, 1149–1155. (f) Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598–9603. (g) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901–903. (h) Kim, J. H.; Long, M. J. C.; Deo, W. D.; Ryu, Y. B.; Yang, M. S.; Park, K. H. *J. Org. Chem.* **2005**, *70*, 4082- 4087. (i) Fiorelli, C.; Marchioro, C.; Martelli, G.; Monari, M.; Savoia, D. *Eur. J. Org. Chem.* **2005**, 3987–3993.

(7) Inter alia, see: (a) Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 1063–1066. (b) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874–2883. (c) Hashihayata, T.; Sakoh, H.; Goto, Y.; Yamada, K.; Morishima, H. *Chem. Pharm. Bull.* **2002**, *50*, 423–425. (d) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825–2828. (e) Davis, F. A.; Song, M.; Augustine, A. *J. Org. Chem.* **2006**, *71*, 2779–2786.

(8) Of the cyclohexylamines **3a**–**c** and **4a**–**c** here described, only **3a** has been previously reported. This amine has been prepared by an enantioselective reduction of imine **2a**: Ros, A.; Magriz, A.; Dietrich, H.; Ford, M.; Fernández, R.; Lassaletta, J. M. *Adv. Synth. Catal.* **2005**, *347*, 1917–1920.

(9) For a recent example of diastereoselective reduction of 2-substituted iminocyclohexanes, see: Sanderson, J. M.; Findlay, J. B. C.; Fishwick, C. W. G. *Tetrahedron* **2005**, *61*, 11244–11252. For a classic paper in this field: Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412. See also: Knupp, G.; Frahm, A. W. *Arch. Pharm.* **1985**, *318*, 250–257.

(10) For another procedure to achieve 3-alkyl-2-allylcyclohexylamines, starting from 2-cyclohexenone, see: Dijk, E. W.; Panella, L.; Pinho, P.; Naasz, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2004**, *60*, 9687–9693.

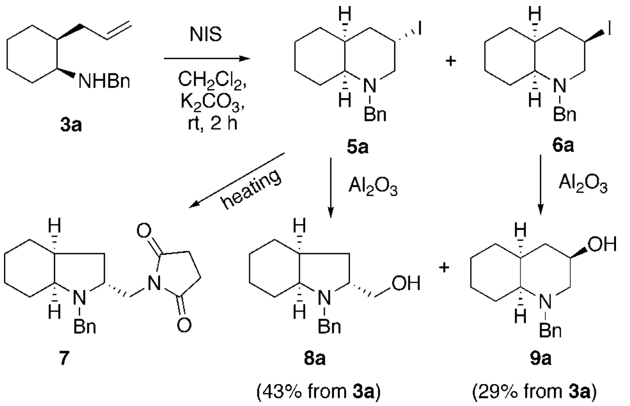
(11) For nucleophilic ring opening of bicyclic aziridinium ions, see: (a) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693–1699. (b) Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966–967.

(12) Hjelmgaard, T.; Tanner, D. *Org. Biomol. Chem.* **2006**, *4*, 1796–1805.

(13) Hammer, C. F.; Weber, J. D. *Tetrahedron* **1981**, *37*, 2173–2180.

(14) For a classical conformational and configurational study on *cis*-decahydroquinolines: Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1977**, *42*, 51–62.

Scheme 3. Aminocyclization of **3a** and Further Transformations

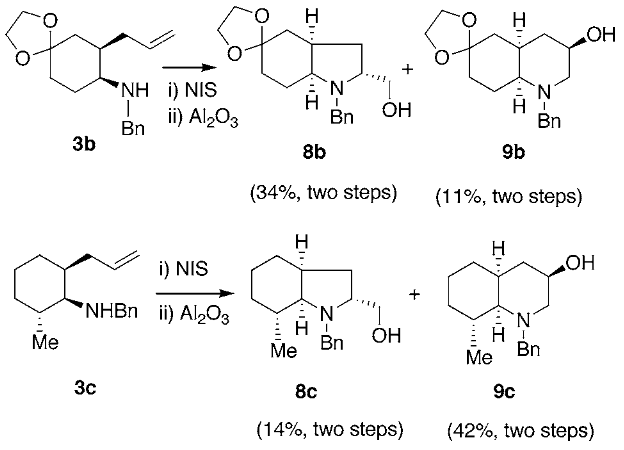


compounds prove that the relative configuration of C-3 in **6a** and **9a** is the same.

Additionally, octahydroindole **8a** was submitted to the reaction conditions developed by Cossy for the ring enlargement of prolinol derivatives (TFAA, Et$_3$N, THF, reflux; then NaOH)[15] to give the corresponding *cis*-decahydroquinoline **10**, the epimer at C(3) of **9a**. This enlargement under thermodynamic reaction conditions clearly indicated that the ring contraction (**5a** → **7**) occurred under kinetic reaction conditions.

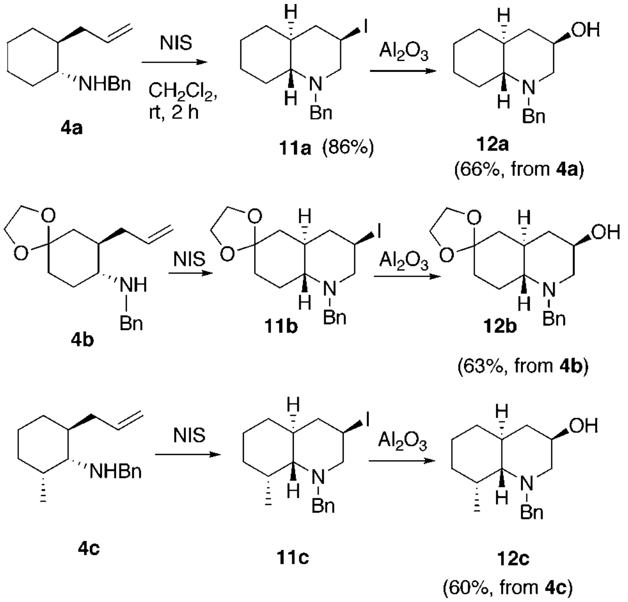
The iodoaminocyclization of **3b** and **3c** was further examined, yielding the results shown in Scheme 4. Although the reaction from **3b** followed the same course as that from **3a**, the diastereoselectivity changed when starting from **3c**, and after treatment with Al$_2$O$_3$, decahydroquinoline **9c** was the main compound.

Scheme 4. Aminocyclization of **3b** and **3c**



Gratifyingly, the iodoaminocyclization of trans derivatives **4a**−**c** with NIS installed a C(3) equatorial iodine atom in the single regio- and diastereomer formed. The decahydroquinolines **11** thus obtained were converted into the corresponding alcohols **12** with good yields (Scheme 5).

Scheme 5. Aminocyclization of Trans Derivatives **4**



Although decahydroquinolines **6**, **9**, and **10** showed the same conformational preference, it is noteworthy that in the 8-methyl-substituted derivatives, **6c** and **9c**, the nitrogen atom lone pair is located equatorially to avoid steric crowding between the C(8)-Me and the *N*-benzyl group.

The regio- and diastereoselectivity observed in the reported reactions from cis (**3a**−**c**) and trans compounds (**4a**−**c**) is consistent with the following envisaged scenario. The intramolecular C−N bond formation arises from the electrophilic activation of the double bond by the iodinating reagent.[16,17] In cis derivatives, the observed diastereoselectivity, i.e., the facial selectivity for the nitrogen atom nucleophile addition to the π-bond, depends on substrate control of the conformationally mobile compounds **3**. As shown in Scheme 6, the coordination in conformation I occurs from the *re* face of the double bond and from the *si* face on conformation II. Each intermediate (A or B) or preassociative complex[17] then undergoes a regioselective attack by the nitrogen atom leading to a 6-endo process.[18]

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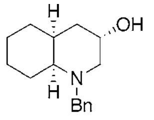
(15) For the application of this protocol to the synthesis of *cis*-decahydroquinolines, see: Mena, M.; Bonjoch, J.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930−5935.



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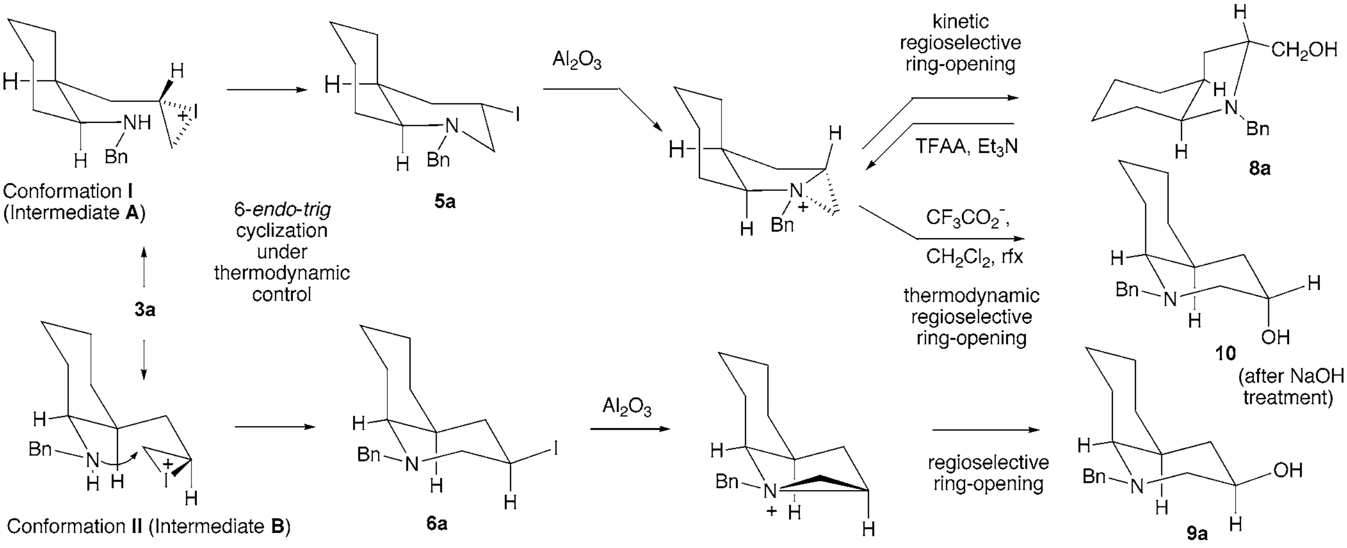
(16) For a semiempirical MO approach to the mechanism of the NIS-mediated nucleophilic addition, see: Mota, A. J.; Castellanos, E.; Alvarez de Cienfuegos, L.; Robles, R. *Tetrahedron: Asymmetry* **2005**, *16*, 1615−1629.

(17) For the sake of clarity, we have drawn the iodonium species in Scheme 6 as intermediates, although they might not actually have been formed.

(18) Interestingly, the aminocyclization of 2-allyl-*N*-tosylcyclohexylamines promoted by MCPBA oxidation always gives octahydroindole derivatives irrespective of the cis or trans relationship of the bishomoallylic amine used: Nuhrich, A.; Moulines, J. *Tetrahedron* **1991**, *47*, 3075−3088.

Scheme 6. Reaction Pathway of Compound **3a**



Thus, the major compounds isolated from **3a** and **3b**, whose preferred conformation was I, were decahydroquinolines **5**,[19] which would then evolve into octahydroindole derivatives **8**, whereas **3c**, whose preferred conformation was II according to the NMR data, primarily gave decahydroquinoline **6c** evolving into **9c**. The process in the trans series is highly regio- and stereoselective,[20] according to the thermodynamic control in the cyclization step and the kinetically controlled ring opening at the methine carbon in the aziridinium intermediate formed during the Al_2O_3-promoted functional exchange (I → OH).

In conclusion, both *cis*- and *trans*-2-allyl-*N*-benzyl-cyclohexylamine derivatives undergo 6-endo cyclizations leading to 3-iododecahydroquinolines, but the resulting cis derivatives behave differently. Thus, although the exo derivatives **5** with Al_2O_3 easily form aziridinium ions that evolve through a kinetic-controlled ring opening to octahydroindoles **8**, the endo derivatives **6** undergo a different regioselective aziridinium ring opening to give decahydroquinolines **9** through a nucleophilic attack at the methine carbon. Under thermodynamic reaction conditions, the ring opening of the aziridinium ion coming from the exo derivative **5a** follows a different regioselectivity, giving the decahydroquinoline **10**.

In summary, the first synthetic approach to decahydroquinolines using a N → π-cyclization promoted by NIS has been reported. We are currently applying this procedure to the synthesis of the marine alkaloid fasicularin.[21]

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Supporting Information Available: Experimental and NMR data for all compounds reported, including tables of ^{13}C NMR chemical shifts of octahydroindoles and decahydroquinolines described. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds as well as COSY and HSQC spectra when available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Unlike **6**, compounds **5** are conformationally heterogeneous at rt and showed very broad signals in their NMR spectra. Sharp and interpretable spectra of **5b** were obtained at −20 °C.

(20) The NIS-promoted oxacyclization of *trans*-2-allylcyclohexanol gives an epimeric mixture of 2-iodomethylperhydrobenzofurane derivatives: Tanikaga, R.; Matsumoto, Y.; Sakaguchi, M.; Koyama, Y.; Ono, K. *Tetrahedron Lett.* **2003**, *44*, 6781−6783.

(21) (a) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531−2549. (b) Schär, P.; Cren, S.; Renaud, P. *Chimia* **2006**, *60*, 131−141.