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Synthesis, characterization, and nucleophilic ring opening reactions of cyclohexyl-substituted β-haloamines and aziridinium ions

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ABSTRACT

Cyclohexyl-substituted β-haloamines and aziridinium ions were prepared and characterized. Stereospecific ring opening of aziridinium ions was applied for efficient synthesis of vicinal amine, β-amino acid, and tetrahydroisoquinoline (THIQ) analogues. Nucleophilic ring opening reactions of aziridinium ions and *N*-protected aziridine analogues were for the first time comparatively studied. The result of nucleophilic reactions clearly indicates that aziridinium ions were significantly more reactive toward nucleophilic ring opening than the aziridine analogues.

Aziridinium ions[1] and aziridines[2] as strained three membered ring systems remain useful entities in asymmetric synthesis of small organic molecules including vicinal amines, amino alcohols, and amino acids. Aziridinium ion contains a positively charged nitrogen and two electrophilic carbons and is expected to rapidly react with various nucleophiles under mild conditions. Biological application of the highly reactive aziridinium ions is well demonstrated in the development of nitrogen mustards such as chlorambucil and mechlorethamine as anti-cancer agents.[3] While aziridines have been extensively utilized in organic synthesis,[2] chemistry of aziridinium ions and their applications as labile electrophilic species for nucleophilic reactions are limitedly reported.[4] To the best of our knowledge, no comparative evaluation on ring opening reactions of aziridinium ions and aziridine analogues has been reported.

In this Letter, we report synthesis and characterization of β-haloamines and aziridinium ions derived from *trans*-1,2-cyclohexylamino alcohol. The cyclohexyl-backboned β-haloamines and aziridinium ions were studied for nucleophilic ring opening reactions for stereospecific synthesis of vicinal diamine, β-amino acid, and tetrahydroisoquinoline (THIQ) analogues. Comparative nucleophilic ring opening reactions of aziridinium ions and aziridines are also described.

Synthesis of cyclohexyl-backboned β-haloamines **4** and aziridinium ions **5** is shown in Scheme 1. *trans*-*N*,*N*-Dibenzyl-β-aminocyclohexanol **1**[5] was used as a model system for the present study. β-Amino alcohol *trans*-**1** was reacted with one of the halogenating reagents, diethylaminosulfur trifluoride (DAST), *N*-halosuccinimide (NXS, X = Cl or Br), or I_2 to provide *trans*-halocyclohexylamine **4a**–**d** as the exclusive product in 60–70% isolated yields. Conversion of *trans*-**1** to *trans*-**4** was completed in 4 h at room temperature as evidenced by TLC analysis during the reactions, and no byproduct was formed during halogenation. However, β-haloamines **4** were obtained in less than quantitative yield, mainly due to hydrolysis of the products during column chromatographic purification. The formation of *trans*-**4** was rationalized based on the mechanism wherein intramolecular rearrangement of phosphonium halide **2** to aziridinium ion **3** and subsequent ring opening of **3** by the halide counter anion proceeded in a S_N2 pathway. *trans*-β-Bromocyclohexylamine **4c** was prepared from reaction of **1** with PPh_3 and NBS for structural determination, and the retained stereochemistry in **4c** was unambiguously confirmed by X-ray crystallography (Scheme 1) and proves the formation and ring opening of aziridinium ion in a S_N2 pathway.

Aziridinium ions **5ca** (X = BF_4) and **5cb** (X = OTf) were directly prepared by treatment of *trans*-**4c** with a halosequestering silver salt containing weakly nucleophilic counteranions, $AgBF_4$ and AgOTf, respectively (Scheme 1). Aziridinium ion **5ca** containing tetrafluoroborate as a counter anion was rapidly formed from

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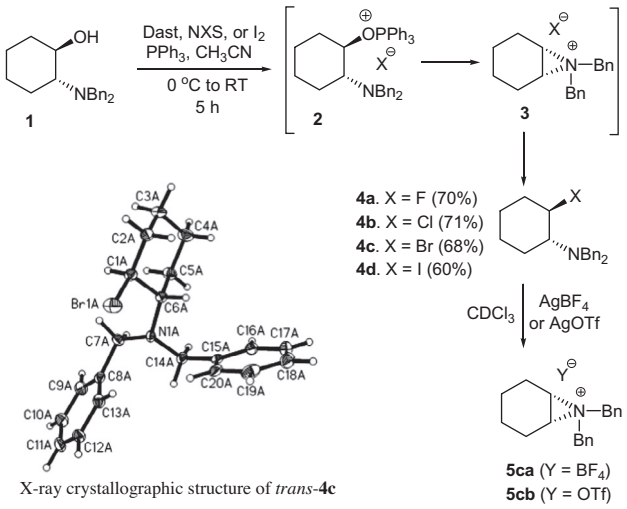
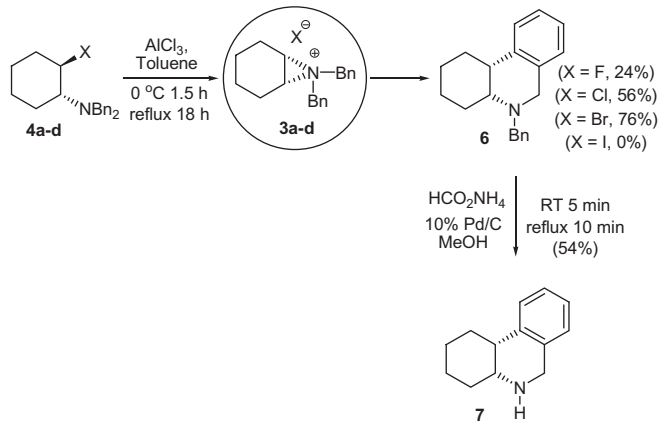


Scheme 1. Synthesis and characterization of cyclohexyl-substituted β-haloamines and aziridinium ions.

β-bromoamine **4c** (13 min), while formation of aziridinium ion **5cb** containing triflate was complete in 2 h. ^{1}H and ^{13}C NMR spectra of aziridinium ions **5ca** or **5cb** were clearly distinguished from those of β-bromoamine **4c** (Supporting information). Aziridinium ions **5ca** and **5cb** have very similar ^{1}H NMR spectra. A slight difference in coupling pattern and resonance frequency of the methylene protons in the cyclohexyl backbone of **5ca** and **5cb** was observed that may be explained by the counter ion effect. The benzylic protons in aziridinium ions resonate as two singlet signals at more deshielded fields (δ 4.2 and 4.4 ppm) than those in β-bromoamine **4c** that appeared as two doublets (δ 3.5 and 3.9 ppm). The methine protons in β-bromoamine **4c** (δ 4.2 ppm) and aziridinium ions **5ca** and **5cb** (δ 4.1 ppm) have similar resonance frequency. Aziridinium ions **5ca** and **5cb** with different counter ions produced the essentially identical ^{13}C NMR signals. The methine carbon (C_2) in β-bromoamine **4c** (δ 56 ppm) was shown to be more deshielded than that of aziridinium **5ca** or **5cb** (δ 49 ppm). The two phenyl rings in aziridinium ions **5ca** and **5cb** were shown to be magnetically non-equivalent giving 8 different signals in ^{13}C NMR.

Utility of cyclohexyl-backboned β-haloamines **4** and aziridinium ions **3** as electrophilic species for nucleophilic substitution reactions was investigated. First, β-haloamines **4a–d** were subjected to intramolecular Friedel–Craft (FC) reaction (Scheme 2).[6] Lewis acid-promoted FC reaction of β-chloroamine **4b** or β-bromoamine **4c** produced *cis*-isomer of cyclohexyl-substituted tetrahydroisoquinoline (THIQ) **6** in the respective isolated yields of 56% and 76%. β-Fluoroamine **4a** containing fluoride as a poor leaving group was not an efficient substrate in producing **6** (24% isolated yield). It appears that the FC reaction of **4c** having bromide as a better leaving group was more efficient than **4a–b** containing chloride and fluoride. Interestingly, the reaction of **4d** containing iodide did not provide the desired THIQ product. Intermolecular nucleophilic reaction of aziridinium ion **3d** with better nucleophilic iodide seems to be favored over the FC reaction. The stereochemistry in **6** was confirmed by converting **6** to the known THIQ analogue **7**.[7] Hydrogenolysis of *cis*-**6** using ammonium formate and 10% Pd/C provided *cis*-**7** in 53% isolated yield. Based on the stereochemistry observed, we propose that the intramolecular ring opening of aziridinium ion **3** by the *N*-aromatic ring occurred in a S_Ni pathway.[8a–d] It is speculated that the intramolecular FC reaction was promoted by the partial positive charge developed at C-1 or C-2 carbon due to a loose C–N bond in the strained aziridinium ion. The retained stereochemistry may be explained by stabilization of the partial positive charge by one of the phenyl ring via cation–π interaction followed by a front side attack of the other aromatic ring on the methine carbon in the aziridinium ion.[8e,f]

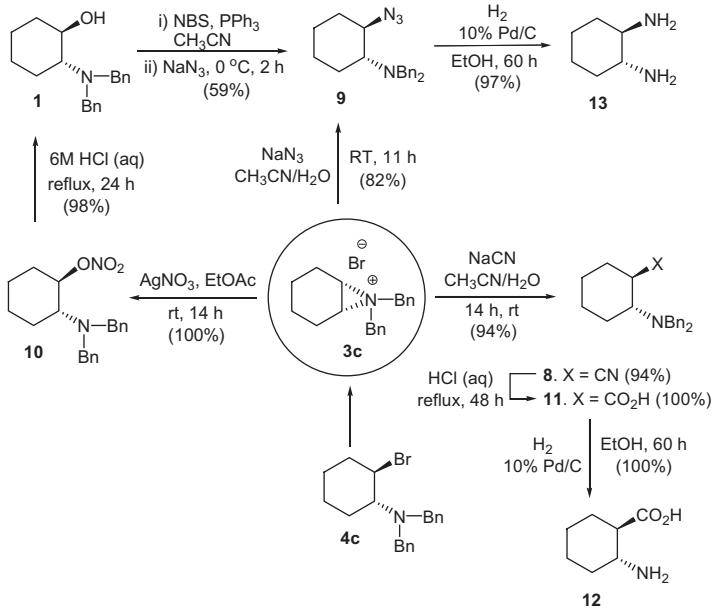


Scheme 2. Ring opening of aziridinium ions: formation of tetrahydroisoquinoline **7** via intramolecular Friedel–Crafts reaction.

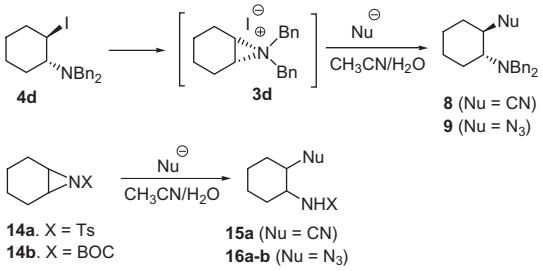
Ring opening reaction of aziridinium ions with nucleophiles was further studied using β-bromoamine **4c** (Scheme 3). Reaction of *trans*-**4c** with NaCN and NaN_3 via formation of aziridinium ion **3c** produced the respective ring opening product of *trans*-**8** and *trans*-**9** in excellent to good isolated yields (94% and 82%, respectively). *trans*-β-Azidoamine **9** was also prepared by convenient one-pot bromination and ring opening reaction of **1**. The retained stereochemistry in **8** and **9** was confirmed by preparing the known compounds, *trans*-γ-amino acid **11** and *trans*-diamine **13** from **8** and **9**, respectively. *trans*-**8** was hydrolyzed using HCl (aq) to produce *trans*-**11** which was subjected to hydrogenolysis to provide **12** in a quantitative yield. Hydrogenation of β-azidoamine **9** afforded vicinal diamine **13** in 97% isolated yield. Interestingly, when *trans*-**4c** was reacted with $AgNO_3$, the reaction provided β-amino nitrate *trans*-**10** in a quantitative yield. For confirmation of stereochemistry in **10**, *trans*-**10** was converted to the known compound *trans*-**1** in 98% isolated yield by acidic hydrolysis of *trans*-**11** under reflux. The retained stereochemistry in C_2 of **8**, **9**, and **10** confirms formation and ring opening of aziridinium ion as the key intermediate in a S_N2 pathway involving a double inversion of the stereochemistry in C_2. The result indicates that ring opening of aziridinium ions can be utilized for highly practical synthesis of γ-aminoacids, vicinal diamines, and β-amino nitrate.

Aziridinium ion **3d** containing iodide and *N*-protected aziridines **14a–b** were compared for nucleophilic ring opening reactions with cyanide and azide at room temperature (Scheme 4). *N*-Protected aziridines **14a** (X = Ts) and **14b** (X = BOC) in the racemic form were prepared as previously reported[9] and reacted with NaCN and NaN_3 in a S_N2 pathway to produce ring opening products **15a** and **16a–b**. Among the substrates tested, aziridinium ion **3d** formed from β-iodoamine **4d** was found to be most reactive with cyanide and azide and provided ring opening products **8** and **9**, respectively (>94% isolated yield, 6 h). Aziridine analogues **14a–b** were significantly slower toward the nucleophilic reactions as compared to aziridinium ions **3d** formed from the corresponding β-haloamines **4d**. Reaction of *N*-Ts protected aziridine **14a**[9] with cyanide and azide was completed in 5 days to provide the corresponding ring opening products **15a**[10] and **16a**[11] in the respective isolated yields of 77% and 95%. Compound **14b**[9] containing the *N*-BOC group was sluggish in reaction with sodium azide to produce **16b**[12] in low isolated yield (59%, 10 days). The results in Scheme 4 clearly indicate that aziridinium ion **3d** was significantly more reactive than *N*-protected aziridines **14a–b**.

In conclusion, cyclohexyl-backboned β-haloamines and aziridinium ions were prepared and characterized using NMR



Scheme 3. Stereospecific nucleophilic ring opening reactions of aziridinium ion **3c** for synthesis of vicinal diamine and β-aminoacid.



entry	substrate	Nu	temp	reaction time	product	Yield (%)
2	**4d**	NaCN	rt	6 h	**8**	94
3	**4d**	NaN_3	rt	6 h	**9**	98
4	**14a**	NaCN	rt	5 d	**15a**	77
5	**14a**	NaN_3	rt	5 d	**16a**	95
6	**14b**	NaN_3	rt	10 d	**16b**	59

Scheme 4. Nucleophilic ring opening reactions of aziridine and aziridinium analogues.

and/or X-ray crystallography. We demonstrated utility of the cyclohexyl-substituted aziridinium ions as precursor molecules for highly practical stereospecific synthesis of vicinal diamine, β-amino acid, β-amino nitrate, and THIQ analogues. Aziridinium ions were found to be more sensitive toward nucleophilic ring opening than the aziridine congeners. The result indicates that aziridinium ions can be generated from the readily available β-aminoalcohols and applied for stereospecific synthesis of various small organic molecules.

Supplementary data

Supplementary data (experimental details on synthesis, characterization, and ^1H and ^{13}C NMR spectra of compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.101.

References and notes

1. (a) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643–665; (b) Métro, T.-X.; Duthion, B.; Pardo, D. G.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89; (c) Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2009**, *65*, 4310; (d) Guan, H.; Saddoughi, S. A.; Shaw, A. P.; Norton, J. R. *Organometallics* **2005**, *24*, 63582; (e) Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1995; (f) Nagle, A. S.; Salvatore, R. N.; Chong, B. D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011.
2. (a) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881; (b) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199; (c) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662; (d) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126; (e) Moss, T. A.; Fenwick, D. R.; Dixon, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 10076; (f) Rowland, E. B.; Rowland, G. B.; Rivera-Otero, E.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 12084; (g) Yudin, A. K. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006; (h) Mit, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252; (i) Lee, W.-Y.; Salvador, J. M.; Kalavathi, B. *Org. Lett.* **2002**, *2*, 931; (j) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett.* **2002**, *4*, 343.
3. Noll, D. M.; Mason, T. M.; Miller, P. S. *Chem. Rev.* **2006**, *106*, 277.
4. (a) Oxenford, S. J.; Moore, S. P.; Carbone, G.; Barker, G.; O'Brien, P.; Shipton, M. R.; Gilday, J.; Campos, K. R. *Tetrahedron: Asymmetry* **2010**, *21*, 1563; (b) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984; (c) Métro, T.-X.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2007**, *72*, 6556–6561; (d) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183; (e) Andrews, D. R.; Dahanukar, V. H.; Eckert, J. M.; Gala, D.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Tetrahedron Lett.* **2002**, *43*, 6121; (f) Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966; (g) Weber, K; Kuklinski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647; (h) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511–526.
5. Miyano, S.; Lu, L. D. L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350–4360.
6. Yamashita, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1954.
7. Chong, H.-S.; Chen, Y. *Org. Lett.* **2013**, *15*, 5912.
8. (a) Armaroli, S.; Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2000**, *2*, 1105; (b) Davis, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349; (c) Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081; (d) Maas, H.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 17; (e) Yamada, S.; Fossey, J. S. *Org. Biomol. Chem.* **2011**, *9*, 7275; (f) Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M.; Van Speybroeck, V. *J. Org. Chem.* **2010**, *75*, 885.
9. Mordini, A.; Russo, F.; Valacchi, M.; Zani, L.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron* **2002**, *58*, 7153.
10. Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* **2005**, *7*, 3509.
11. Wang, Z.; Cui, Y.-T.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270.
12. Pendem, N.; Douat, C.; Claudon, P.; Laguerre, M.; Castano, S.; Desbat, B.; Cavagnat, D.; Ennifar, E.; Kauffmann, B.; Guichard, G. *J. Am. Chem. Soc.* **2013**, *135*, 4884.