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Oxidative Rearrangement of Spiro Cyclobutane Cyclic Aminals: Efficient Construction of Bicyclic Amidines

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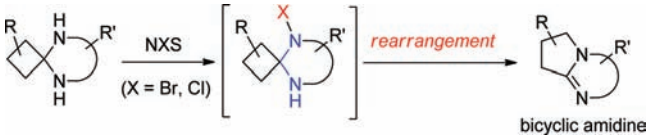
ABSTRACT



A new rearrangement reaction of spirocyclic cyclobutane *N*-halo aminals is described. This process, promoted by treatment of the aminals with *N*-halosuccinimides (NXS, X = Br or Cl), efficiently produces bicyclic amidines by a pathway involving initial *N*-halogenation of one of the aminal nitrogens followed by cyclobutane ring expansion through 1,2-C-to-N migration with simultaneous N−X bond cleavage.

Reactions involving 1,2-carbon migration to a nitrogen center comprise an important family of synthetically useful transformations. Noteworthy examples include the Schmidt[1] and Beckmann rearrangement[2] reactions, which are traditionally utilized as efficient methods to generate a wide array of heterocyclic compounds. In these respective processes, azide (N−N_2) and hydroxylamine derivatives (N−OX, X = H, Ts, etc.) are used as latent electrophilic nitrogen centers at which new N−C bonds are formed by 1,2-carbon migration processes. In contrast, *N*-halo amines have been relatively less well explored as latent electrophilic nitrogens in rearrangement reactions. Only a few reports exist describing rearrangement reactions that are activated by treatment of *N*-chloroamines with silver salts.[3] Recently, the utility of *N*-chloroamines as an electrophilic nitrogen source has attracted attention in the context of useful intramolecular aromatic amination reactions catalyzed by various metals, such as Ni, Cu, and Ti.[4]

These recent observations have stimulated our interest in exploring the potential utility of *N*-halo amines in rearrangement reactions that can be applied to the preparation of interesting heterocyclic compounds. In the study described below, we uncovered a previously unreported oxidative rearrangement reaction of spirocyclic cyclobutane aminals, promoted by treatment with *N*-halosuccinimides, that produces bicyclic amidines.

In a recent investigation,[5] we explored novel one-pot reactions of aminals, formed from aldehydes and 1,2-diamines and promoted by treatment with NBS, that lead to the efficient formation of imidazolines (Scheme 1(1)).[5a] In this context, we envisaged that a new rearrangement process might occur with haloaminals **i** that derive from spirocyclic

(1) (a) Wolff, H. *Org. React.* **1946**, 307. (b) Koldobskii, G. I.; Tereshchenko, G. F.; Gerasimova, E. S.; Bagal, L. I. *Russ. Chem. Rev.* **1971**, *40*, 835. (c) Koldobskii, G. I.; Ostrovskii, V. A.; Gidaspov, B. V. *Russ. Chem. Rev.* **1978**, *47*, 1084. (d) Grecian, S.; Aube, J. *Organic Azides: Syntheses and Applications*; John Wiley and Sons: New York, 2010; p 191.

(2) (a) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1. (b) Gawly, R. E. *Org. React.* **1988**, *35*, 1. (c) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; p 1415.

(3) (a) Schell, F. M.; Smith, A. M. *Tetrahedron Lett.* **1983**, *24*, 1883. (b) Schell, F. M.; Ganguly, R. N. *J. Org. Chem.* **1980**, *45*, 4069. (c) Gassman, P. G.; Carrasquillo, A. *Tetrahedron Lett.* **1971**, *12*, 109. (d) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26.

(4) (a) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (b) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (c) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325. For transition-metal free conditions using TMEDA, see: (d) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

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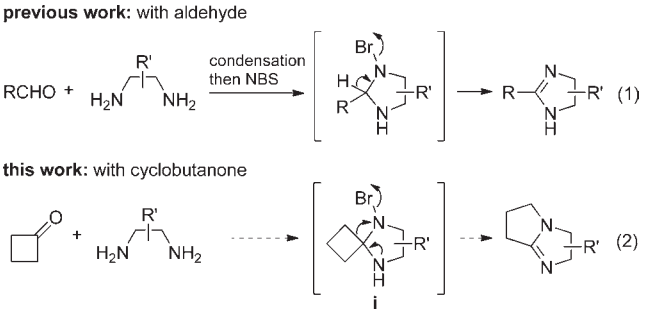
cyclobutane aminals (Scheme 1(2)). Owing to the absence of hydrogen on the spirocyclic aminal carbon of these intermediates, elimination of HBr should not be possible and, instead, a rearrangement reaction involving ring strain induced cyclobutane ring expansion by C-to-N migration might occur to yield bicyclic amidines.[6−8] A further driving force for the 1,2-carbon migration would be provided by the neighboring nitrogen, which stabilizes positive charge development at carbon center from which 1,2-migration takes place in a manner that is similar to the driving force for the Schmidt reaction.

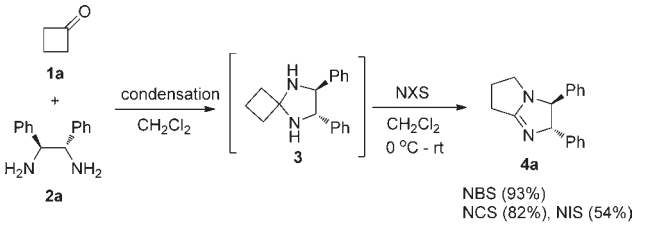
Scheme 1. Reactions of Aminals



Bicyclic amidines are an important class of organic bases, as is exemplified by the utilzation of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in promoting a variety of synthetically useful organic transformations.[9] Existing methods for the preparation of bicyclic amidines, involving cyclization reactions of lactam derivatives, most often require several steps and harsh reaction conditions.[10] Consequently, a new method for the efficient preparation of these substances is an important goal.

Initial studies to explore this proposal were conducted using the reaction of cyclobutanone (**1a**) with 1,2-diphenyl ethylenediamine (**2a**). Reaction of these substances in dichloromethane for 1 d followed by solvent removal leads to the isolation of spirocyclic aminal **3** in nearly quantitative yield. Treatment of the crude product mixture containing **3** with NBS promotes formation of bicyclic amidine **4a** in a 93% yield (Scheme 2). When NCS is employed in place of NBS as the halogen source, the reaction proceeds to give a comparable yield of **4a**, while NIS promotes a lower yielding reaction. The rearrangement reaction of **3** occurs spontaneously even at room temperature and in the absence of additives, such as silver salts.[3]

Scheme 2. Test Reaction



Following this study, which demonstrates the feasibility of the new bicyclic amidine forming rearrangement reaction of *N*-halo intermediates generated from spirocyclic aminals, we carried out experiments designed to explore the substrate scope of the process. A one-pot procedure was employed for these processes, involving initial condensation of the cyclobutanone with the selected diamine followed by oxidative rearrangement promoted by treatment with NBS. As the results displayed in Table 1 demonstrate, reaction takes place to produce a bicyclic amidine in excellent yield when 1,2-diphenyl ethylenediamine (**2a**) and 2,2-dimethyl-1,3-diaminopropane (**2b**) are used for spirocyclic aminal formation. The presence of substituents at C-3 of the cyclobutane substrate was found to have no effect on the efficiency of this process (Table 1, entries 2, 4, 6, and 7). In addition, reaction of the aminal derived from diamine **2a** and 3-phenylcyclobutanone (**1b**) generates amidine **4b** as a 3:1 mixture of diasteromers. Sterically bulky 3,3-disubstituted cyclobutane derivatives also undergo this reaction to give the corresponding bicyclic amidines in high yields (Table 1, entries 3 and 5). Furthermore, substrates possessing BocN, BnO, and TBDPSO groups also react under the NBS promoted reaction conditions to produce products in equally high yields (Table 1, entries 5−7). However, the aminal derived from condensation of cyclopentanone with diamine **2a** does not undergo the rearrangement reaction under the conditions. This finding suggests that ring strain present in the cyclobutane ring serves as an important driving force for the rearrangement process.

The reaction of aminal **5a**, derived by condensation of *o*-aminobenzylamine (**2c**) was next investigated. The reaction of the aminal **5a** is of interest because two products can possibly be produced by a difference in the reaction course. Specifically, 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (**6a**)

(6) For a review on the reactions of cyclobutanes, see: Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740.

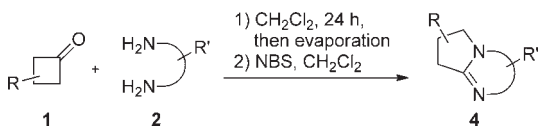
(7) For our studies on the reaction of cyclobutanols with hypervalent iodine reagents, see: (a) Fujioka, H.; Komatsu, H.; Miyoshi, A.; Murai, K.; Kita, Y. *Tetrahedron Lett.* **2011**, *52*, 973. (b) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun.* **2010**, *46*, 4133.

(8) Although cyclobutane ring is strained, the rearrangement reaction of cyclobutyl amine was reported to need treatment of silver salt. See ref 3.

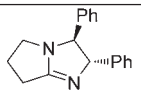
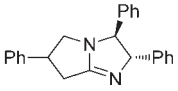
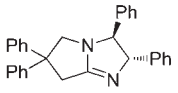
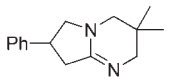
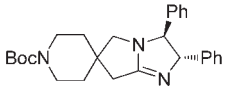
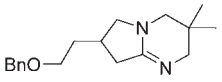
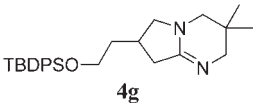
(9) For examples, see: (a) Ghosh, N. *Synlett* **2004**, 574. (b) Taylor, J. E.; Jones, M. D.; Williams, J. M. J.; Bull, S. D. *Org. Lett.* **2010**, *12*, 5740. (c) Miura, M.; Toriyama, M.; Kawakubo, T.; Yasukawa, K.; Takido, T.; Motohashi, S. *Org. Lett.* **2010**, *12*, 3882. (d) Price, K. E.; Larrivée-Aboussafy, C.; Lillie, B. M.; McLaughlin, R. W.; Mustakis, J.; Hettenbach, K. W.; Hawkins, J. M.; Vaidyanathan, R. *Org. Lett.* **2009**, *11*, 2003. (e) Baidya, M.; Mayr, H. *Chem. Commun.* **2008**, 1792. (f) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2006**, *9*, 37. (g) Shieh, W.-C.; Dell, S.; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188. (h) K. Aggarwal, V.; Mereu, A. *Chem. Commun.* **1999**, 2311.

(10) For synthesis of DBU and DBN type bicyclic amidines, see: (a) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 478. (b) Ostendorf, M.; Dijkink, J.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 115. (c) Kotsuki, H.; Sugino, A.; Sakai, H.; Yasuoka, H. *Heterocycles* **2000**, *53*, 2561. (d) Dijkink, J.; Eriksen, K.; Goubitz, K.; van Zanden, M. N. A.; Hiemstra, H. *Tetrahedron: Asymmetry* **1996**, *7*, 515. (e) Convery, M. A.; Davis, A. P.; Dunne, C. J.; MacKinnon, J. W. *Tetrahedron Lett.* **1995**, *36*, 4279 and ref 9f.

Table 1. Synthesis of Bicyclic Amidines[a]



1 2 4

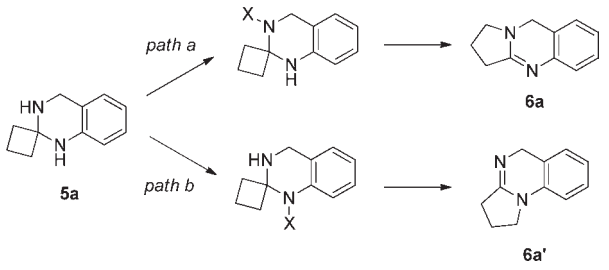
entry	1	2	product	yield
1	**1a**	**2a**	 **4a**	93%
2	**1b**	**2a**	 **4b**	93% (dr = 3:1)
3	**1c**	**2a**	 **4c**	73%
4	**1b**	**2b**	 **4d**	75%
5	**1d**	**2a**	 **4e**	88%
6	**1e**	**2b**	 **4f**	87%
7	**1f**	**2b**	 **4g**	85%

[a] 1) Conditions: **1** (1.1 equiv), **2** (1 equiv), NBS (1.1 equiv), CH_2Cl_2 (0.1 M). 2) Substrates: **1b**, 3-phenylcyclobutanone; **1c**, 3,3-diphenylcyclobutanone; **1d**, 7-tosyl-7-azaspiro[3.5]nonan-2-one; **1e**, 3-(2-(benzyloxy)ethyl) cyclobutanone; **1f**, 3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclobutanone; **2b**, 2,2-dimethyl-1,3-diaminopropanes.

and 1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinazoline (**6a′**) can be produced depending on which nitrogen is more rapidly halogenated (Scheme 3).

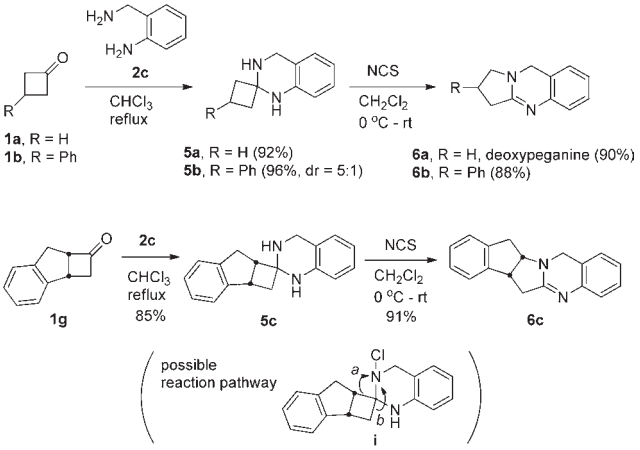
Aminal **5a** is readily prepared by condensation of cyclobutanone with *o*-aminobenzylamine (**2c**) in refluxing $CHCl_3$ and purified by using silica gel column chromatography. Although NBS is an ideal promoter for reactions of aminals generated from aliphatic diamines, this halogen donor is not suitable for reaction of **5a** owing to the fact that a complex product mixture is produced as a result of competitive aromatic ring bromination processes. However, NCS was found to be an excellent oxidant for promotion of the reaction of **5a**, which selectively produces the 3,4-dihydroquinazoline

Scheme 3. Possible Reactions of Aminal **5a** Derived from *o*-Aminobenzylamine and Cyclobutanone



6a (deoxypeganine)[11] in 90% yield (Scheme 4). Importantly, the amidine **6a′** was not detected in the product mixture. This observation suggests that the rearrangement reaction of **5a** is initiated by selective chlorination of the more nucleophilic aliphatic amine rather than the less nucleophilic aniline nitrogen (Scheme 3, path a). When a 5:1 mixture of diastereomeric aminals **5b** is used as substrate, a rearrangement reaction occurs with the same efficiency to yield 3,4-dihydroquinazoline **6b**, formed by initial aliphatic amine chlorination. Furthermore, the structurally interesting ring-fused pentacyclic amidine **6c** can be prepared in high yield by reaction of the aminal **5c**, arising by condensation of cyclobutanone derivative **1g** with *o*-aminobenzylamine. The reaction of **5c** showed a selectivity trend of this transformation: the secondary alkyl carbon migration was substantially preferred rather than primary alkyl carbon migration from the possible intermediate **i** (Scheme 4, a vs b in intermediate **i**).

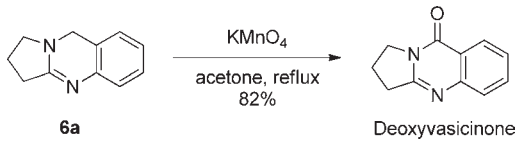
Scheme 4. Synthesis of 3,4-Dihydroquinazolines



Interestingly, amidine **6a** can be readily transformed to quinazolinone alkaloid, deoxyvasicinone, by oxidation with

(11) (a) Khashimov, K. N.; Telezhenetskaya, M. V.; Yususov, S. Y. *Khim. Prir. Soedin.* **1969**, *5*, 456. For examples of biological studies, see: (b) Doetkotte, R.; Opitz, K.; Kiianmaa, K.; Winterhoff, H. *Eur. J. Pharmacol.* **2005**, *522*, 72. (c) Jaén, J. C.; Gregor, V. E.; Lee, C.; Davis, R.; Emmerling, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 737.

Scheme 5. Oxidation of 3,4-Dihydroquinazoline **6a**



$KMnO_4$[12] (Scheme 5). Quinazolinone and related alkaloids have attracted recent interest owing to their biological activities, and a number of studies have been conducted probing the synthesis of important members of this family.[13] Thus, the route utilizing oxidative rearrangement reactions of cyclobutane aminals represents a new strategy for the preparation of these alkaloids.

In conclusion, the studies described above have led to the development of an efficient method for the synthesis of bicyclic amidines that relies on a previously unreported rearrangement reaction of *N*-halo aminals. In addition, the biologically important dihydroquinazolinone alkaloids were prepared in this effort. Investigations exploring the full scope of the new rearrangement reaction and its applications are currently underway.

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Supporting Information Available. Experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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