Aziridinium Salts

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Stable Aziridinium Salts as Versatile Intermediates: Isolation and Regio- and Stereoselective Ring-Opening and Rearrangement**

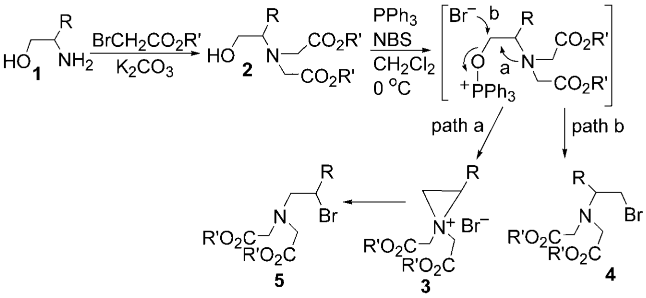
*Hyun A. Song, Mamta Dadwal, Yeseul Lee, Emily Mick, and Hyun-Soon Chong**

A variety of aziridinium cations have been generated in situ as precursors of enantiomerically pure organic compounds and biological active agents. Several aziridinium cations have been proposed as intermediates in the reaction of nitrogen mustards with interstrand cross-linked DNA.[1] The ring-opening of substituted aziridinium cations has been recognized as an efficient synthetic route to chiral 1,2- and 1,3-diamines, 3,4-diamino nitriles, nitrogen-containing heterocycles, and α,β-diamino esters.[2] The synthetic methods to generate quaternary aziridinium cations as reactive intermediates involve N-alkylation of aziridines,[3] intramolecular substitution of β-amino halides,[4] and mesylation of β-amino alcohols.[5] Research efforts have been made to characterize aziridinium salts, and formation of several aziridinium salts was induced by using heavy counter anions such as fluoroborate or perchlorate.[6]

Herein, we describe the synthesis and characterization of a series of aziridinium salts obtained from the bromination of *N,N*-dicarboxymethylated β-amino alcohols. To our knowledge, this is the first report on the isolation of a series of stable aziridinium cations prepared directly from β-amino alcohols under mild conditions. We also report regioselective and stereoselective ring-opening and unprecedented regiospecific rearrangement of aziridinium cations to generate useful organic molecules such as α,β-unsaturated amino esters, and C-functionalized oxomorpholine in excellent yield.

Table 1 shows the aziridinium cations **3** that have been isolated by reaction of *N,N*-dicarboxymethylated β-amino alcohols **2** with *N*-bromosuccinimide (NBS) and triphenylphosphine (PPh_3). We initially wanted to prepare *N,N*-dicarboxymethylated β-amino ethyl bromide **4** as a precursor molecule of a macrocyclic ligand. In a typical bromination reaction, β-amino ethanol **2** (1 equiv) in CH_2Cl_2 was treated with a mixture of NBS (1.2 equiv) and PPh_3 (1.2 equiv) at 0 °C. However, instead of providing the desired S_N2 product **4**, the reaction led to the aziridinium bromide salt **3** from an intramolecular rearrangement as evidenced by ^1H and ^{13}C NMR spectroscopic and high-resolution mass spectral data. As a potential mechanism shown in Table 1, the reaction of **2** with phosphonium salt formed by reaction of NBS and PPh_3 affords the substitution product, which then rearranges to form the aziridinium cations **3** by attack of the nucleophilic nitrogen atom followed by removal of triphenylphosphine oxide.

Table 1: Formation of aziridinium cations **3** and ring-opened compounds **4** and **5**.



Entry	Substrate	R	R′	Product	Yield [%]
1	**2a**	H	*t*Bu	**4a**	86
2	**2b**	H	Bn	**4b**	85
3	**2c**	(*S*)-methyl	*t*Bu	**3c**	44
4	**2d**	*rac*-benzyl	*t*Bu	**3d**	51
5	**2e**	(*S*)-4-nitrobenzyl	*t*Bu	**3e**	55
6	**2f**	*rac*-4-nitrobenzyl	*t*Bu	**3f**	67
7	**2g**	3-(4-nitrophenyl)propyl	*t*Bu	**3g**	66
8	**2h**	(*S*)-CO_2CH_3	*t*Bu	**5h**	23

This unexpected result prompted us to explore the scope of the reaction using various backbone-substituted *N,N*-dicarboxymethylated β-amino alcohols. In particular, we wanted to understand the effect that substituents in **2** have on the formation of the strained aziridinium cation. It appears that the steric hindrance of any R substituent on the β-amino alcohol backbone prevents S_N2 attack of bromide at the less hindered methylene carbon. All backbone-substituted β-amino ethanols **2** including **2c**, which has the sterically less demanding methyl group, were transformed to aziridinium salts by intramolecular rearrangement (Table 1, entry 3). It should be noted that the reaction of **2a** (R′ = *t*Bu) and **2b** (R′ = Bn), which contain no backbone substitution, led to the intermolecular substitution products **4a** and **4b**, respectively, and no aziridinium salts were formed (Table 1, entries 1 and 2). This experimental result proves that steric hindrance caused by substitution of the backbone in **2** resulted in the formation of the aziridinium salts. All aziridinium salts were readily purified by flash silica gel chromatography and fully characterized by ^1H and ^{13}C NMR, HRMS, and/or CHN analysis (see the Supporting Information). No peak corresponding to the CH_2Br unit in the normal

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[*] H. A. Song, M. Dadwal, Y. Lee, E. Mick, H.-S. Chong
Chemistry Division
Biological, Chemical, and Physical Sciences Department
Illinois Institute of Technology, Chicago, IL (USA)
E-mail: chong@iit.edu

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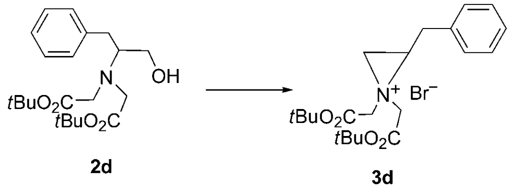
substitution product **4** was present in ^{1}H and ^{13}C NMR spectra of the aziridinium salts. Interestingly, no aziridinium cation was obtained from the substrate **3**, which has a methyl ester group, and bromination of **3** produced the secondary aminoethyl bromide **5h** (Table 1, entry 8). It appears that the attack of the counter anion bromide at the electron-deficient methine carbon in the aziridinium cation generated in situ led to the formation of **5h**.

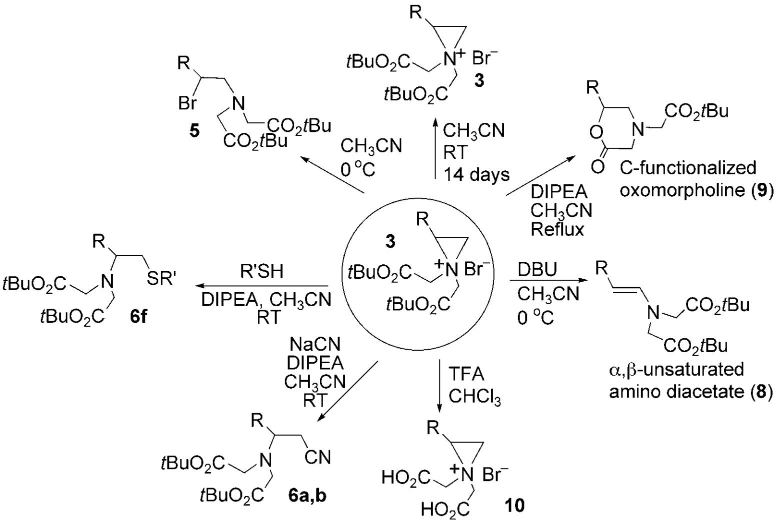
Bromination of amino alcohol **2d** using different reagents was attempted (Table 2). Among the brominating reagents studied, CBr_4/PPh_3 was found to be the best and it smoothly converted **2d** to the desired product **3d** in 89 % yield (Table 2, entry 4). Reaction of **2d** with $SOBr_2$ proceeded very slowly, providing **3d** in poor yield (12 %; Table 2, entry 2). No reaction was observed between **2d** and PBr_3 in CH_2Cl_2 (Table 2, entry 3).

Table 2: Formation of aziridinium bromide salt **3d** by bromination using various reagents.



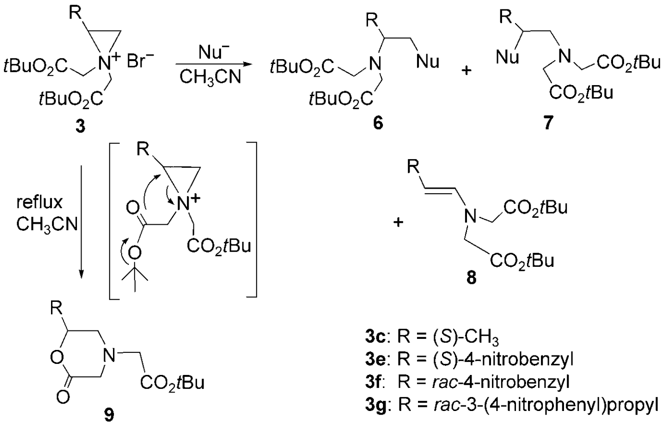
Entry	Reagents	Solvent	*T*	Reaction time	Yield [%]
1	NBS, PPh_3	CH_2Cl_2	0°C–RT	4 h	51 %
2	$SOBr_2$	$CHCl_3$	RT	5 h	8 %
3	PBr_3	CH_2Cl_2	RT		no reaction
4	CBr_4, PPh_3	$CHCl_3$	RT	3 h	89 %

Ring-opening of aziridinium cations has been recognized as a useful synthetic route for the generation of 1,2- or 1,3-diamine analogues.[2a,5] Encouraged by the efficient preparation of the aziridinium salts, we wanted to investigate their ring-opening by various nucleophiles (Scheme 1 and Table 3). First, the stability of the aziridinium cation was investigated. The aziridinium cations are stable at room temperature and inert to nucleophilic attack of the counteranion bromide; they can be stored at −20°C for years. When a solutions of the aziridinium salt **3g** in CH_3CN was stirred at room temperature for 14 days, no transformation and no ring-opening by the counteranion bromide was observed (Table 3, entry 5). Aziridinium salt **3g** was stable in acidic media, and the *tert*-butyl groups in **3g** were removed to produce **10** in good yield (Scheme 1). However, when refluxed in CH_3CN in the presence of diisopropylethylamine (DIPEA), **3g** was transformed into the oxomorpholine analogue **9g** by regiospecific opening of the cation at the methine carbon (Table 3, entry 6). The carbonyl oxygen of the *tert*-butyl carboxylate group in **3g** is proposed to attack the more substituted carbon to afford intramolecular cyclization product **9g** (77 %). It is interesting to note that the reaction of **3f** with DBU (diaza(1,3)bicyclo[5.4.0]undecane, 3 equiv) produced the α,β-unsaturated amino diacetate **8f** with exclusive stereospecificity in quantitative yield (Table 3, entry 4). Only the *trans* isomer was isolated from elimination of the methylene proton and opening of the aziridinium cation at the less hindered carbon. When the aziridinium cations **3c**, **3e**, and **3g** (Table 3, entries 1, 2, and 7) were treated with the strong



Scheme 1. Reactions of aziridinium salts. TFA = trifluoroacetic acid.

Table 3: Regioselective ring-opening and rearrangement of aziridinium cations.



3c: R = (*S*)-CH_3
3e: R = (*S*)-4-nitrobenzyl
3f: R = *rac*-4-nitrobenzyl
3g: R = *rac*-3-(4-nitrophenyl)propyl

Entry	Substrate	Nu	Base	*T*	Product (Yield)
1	**3c**	NaCN	DIPEA	RT	**6a** (100 %)
2	**3e**	NaCN	DIPEA	RT	**6b** (84 %)
3	**3e**	NaN_3	DIPEA	RT	**6c** (45 %) **7c** (29 %) **8c** (7 %)
4	**3f**	–	DBU	0°C	**8f** (100 %)
5	**3g**	–	–	RT	**3g** (100 %)
6	**3g**	–	DIPEA	82°C	**9g** (77 %)
7	**3g**	NaCN	DIPEA	RT	**6d** (99 %)
8	**3g**	NaN_3	DIPEA	RT	**6e** (41 %) **7e** (30 %)
9	**3g**	$CH_3(CH_2)_2SH$	DIPEA	RT	**6f** (52 %)

nucleophile cyanide, opening of the aziridinium cations occurred at the less hindered methylene carbon in an S_N2 manner to afford the respective regiospecific ring-opening products **6a**, **6b**, and **6d** as the exclusive regioisomers. Products **6a** and **6d** were obtained from **3c** and **3g**, respectively, in almost quantitative yield, while **6b** arose in slightly lower yield (84%) from the reaction of more hindered **3e**. The reaction of the aziridinium cations **3e** and **3g** with the less nucleophilic azide provided a mixture of the regioisomers **6** and **7** resulting from opening of the cation at both the methine and methylene carbons (Table 3, entries 3 and 8). The regioisomers **6c** (45%) and **6e** (41%) were obtained as the major products from attack of azide at methylene carbon of **3e** and **3g**, respectively. Formation of the regioisomers **7c** (29%) and **7e** (30%) as the minor products from the regioselective opening of the aziridinium cations at the more hindered methine carbon can be explained by the thermodynamic control of the reaction with the more weakly nucleophilic azide.[3a] The reaction of **3e** with azide also provided the elimination product *trans*-**8c** (7%). The ring-opening of **3g** by propanethiol took place at the less substituted carbon, exclusively providing **6f** in 52% yield (Table 3, entry 9).

We also investigated the stereochemistry of the nucleophilic opening of the enantiomerically pure aziridinium cations (Table 3, entries 1—3). The stereospecific ring-opening of optically pure **3c** and **3e** by cyanide at the less substituted methylene carbon provided optically pure **6a** and **6b**, respectively. The reaction of **3e** ($[\alpha]_D^{26} = +11.87^\circ$) with azide afforded optically pure **6c** ($[\alpha]_D^{26} = +6.22^\circ$) and **7c** ($[\alpha]_D^{26} = -4.91^\circ$) as the regioselective isomers. The optical rotation data suggest that the ring-opening of the aziridinium cation by cyanide and azide proceeds by a S_N2 displacement.

In summary, the present report describes the potential of aziridinium cations as isolable intermediates to generate various useful organic molecules for asymmetric synthesis and biological applications. We have shown that the stable aziridinium salts can be prepared directly from bromination of β-amino alcohols and purified by flash column chromatography. Regioselective and stereoselective ring-opening and rearrangement of the aziridinium cations produced useful organic compounds including α,β-unsaturated amines and C-functionalized oxomorpholine. We are currently studying the scope of these reactions by using a series of N- and C-substituted β-amino alcohols.

Experimental Section

Typical procedure for the synthesis of **3g**: Portions of NBS (1.2 mmol) were added over 30 min to a solution of **2g** (1 mmol) and PPh_3 (1.2 mmol) in CH_2Cl_2 at 0°C. The resulting mixture was stirred for 3 h at 0°C. The ice bath was removed, and the reaction mixture was warmed to room temperature, stirred for 1 h, and concentrated to dryness. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 10% EtOAc in hexanes to provide **3g** as yellowish oil (4.8 g, 66%). The aziridinium salt **3g** was fully characterized by ^1H and ^{13}C NMR, HRMS, and CHN analysis.

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Keywords: aziridinium ions · rearrangement · regioselectivity · strained molecules

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[1] a) S. M. Rink, M. S. Solomon, M. J. Taylor, S. B. Rajur, L. W. McLaughlin, P. B. Hopkins, *J. Am. Chem. Soc.* **1993**, *115*, 2551–2557; b) B. Ringdahl, C. Mellin, F. J. Ehlert, M. Roch, K. M. Rice, *J. Med. Chem.* **1990**, *33*, 281–286; c) G. B. Jones, J. E. Mathews, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 93–96.

[2] a) D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724–2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; b) S. E. de Sousa, P. O'Brien, P. Poumellec, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1483–1492; c) M. D'hooghe, V. Van Speybroeck, A. Van Nieuwenhove, M. Waroquier, N. De Kimpe, *J. Org. Chem.* **2007**, *72*, 4733–4740; d) H. Chong, B. Ganguly, G. A. Broker, R. D. Rogers, M. W. Brechbiel, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2080–2086; e) M. A. Graham, A. H. Wadsworth, M. Thornton-Pett, C. M. Payner, *Chem. Commun.* **2001**, 966–967; f) J. M. Concellón, E. Riego, J. R. Suárez, S. García-Granda, M. R. Díaz, *Org. Lett.* **2004**, *6*, 4499–4501; g) T. H. Chuang, K. B. Sharpless, *Org. Lett.* **1999**, *1*, 1435–1437; h) J. C. Anderson, H. A. Chapman, *Org. Biomol. Chem.* **2007**, *5*, 2413–2422.

[3] a) M. D'hooghe, V. V. Speybroeck, M. Waroquier, N. D. Kimpe, *Chem. Commun.* **2006**, 1554–1556; b) T. Katagiri, M. Takahashi, Y. Fujiwara, H. Ihara, H. K. Uneyama, *J. Org. Chem.* **1999**, *64*, 7323–7329; c) Q. Liu, M. J. Simms, N. Boden, C. M. Rayner, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1363–1365.

[4] a) K. Weber, S. Kuklinski, P. Gmeiner, *Org. Lett.* **2000**, *2*, 647–649; b) N. Huh, C. M. Thomson, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1551–1554.

[5] a) C. Couturier, J. Blanchet, T. Schlama, J. Zhu, *Org. Lett.* **2006**, *8*, 2183–2186; b) P. O'Brien, T. D. Towers, *J. Org. Chem.* **2002**, *67*, 304–307.

[6] a) N. Leonard, J. Paukstelis, *J. Org. Chem.* **1965**, *30*, 821–825; b) C. Lillocci, *J. Org. Chem.* **1988**, *53*, 1733–1736.