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Efficient Synthesis of Functionalized Aziridinium Salts

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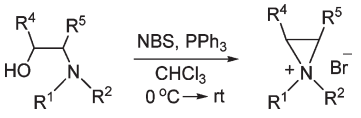

Various aziridinium salts were efficiently prepared from bromination of a series of backbone substituted *N*,*N*-bisubstituted β-amino alcohols and isolated via flash column chromatography. The effect of *C*-substitution, *N*-substitution, solvent, leaving group, and counteranions on formation of the isolable aziridinium salts was investigated.

Aziridinium salts have been utilized as reactive intermediates in asymmetric synthesis of 1,2- and 1,3-diamines, 3,4-diamino nitriles, α,β-diaminoesters, and complex natural products.[1] In addition, they are involved in the biological activity of nitrogen mustards as cancer drugs. Anticancer activity of chlorambucil (CMB), mechlorethamine, and phosphamide mustards stems from reaction of aziridinium cation intermediate derived from the mustards with guanine residues in DNA to form interstrand cross-link.[2] *N*-alkylation of aziridines,[3] intramolecular substitution reaction of β-amino halides,[4] and mesylation or triflation of β-amino alcohols[5] were reported to produce quaternary aziridinium cations as reactive intermediates in situ or isolable salts[6] containing a non-nucleophilic counteranion such as fluoroborate, perchlorate, or triflate.

Recently, we reported the isolation of a series of stable aziridinium salts containing bromide as a counteranion directly from bromination of β-amino alcohols using various brominating agents under mild conditions.[7] The aziridinium salts reported therein are stable at room temperature and can be stored at −20 °C over years and preserved in an acidic medium during removal of a protecting group. We also demonstrated that the regiospecific ring-opening and intramolecular rearrangement of the aziridinium salts can generate the functionalized organic molecules such as β-amino nitriles, allyl amines, and *C*-functionalized oxomorpholine.

In this paper, we sought to broaden the scope of formation of aziridinium salts using various β-amino alcohols. First, we were interested in exploring the effect of solvent on the formation of aziridinium salts.

Bromination of *N*-(benzyl) and *N*-(*tert*-butoxycarbonylmethyl)-derived β-amino alcohol **1a** was carried out in four different solvents, $CHCl_3$, CH_2Cl_2, CH_3CN, and THF (Scheme 1). Treatment of β-amino alcohol **1a** in a solvent with PPh_3 and NBS at 0 °C for 4 h and warming the solution to room temperature for 1 h resulted in the conversion of **1a** to the desired aziridinium salt **2a**. Among the solvents studied, polar aprotic CH_3CN was found to be the most efficient solvent for the formation of **2a** (76%). The lowest isolated yield of **2a** was obtained from the reaction in THF, possibly due to low solubility of the amino alcohol **1a** in the solvent.

We extended our investigation to the effect of leaving group and counteranion on the formation of aziridinium salts. *N*,*N*-Bisubstituted β-amino alcohol **1b** was reacted with various reagents (Table 1). As expected, azridinium cation **2b** was produced from bromination of **1b** with NBS/PPh_3 in excellent yield (89%, Table 1). Reaction of **1b** with thionyl chloride ($SOCl_2$, Table 1) at room temperature provided an inseparable 1:1 mixture of aziridinium salt (**3b**) and the normal substitution product (**4b**). When the same reaction of **1b** with $SOCl_2$ was carried out under reflux, aziridinium cation **3b** was obtained as the exclusive product (Table 1). Interestingly, the reaction of **1b** with methanesulfonyl chloride (MsCl) provided a mixture of **3b** and **4b**

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SCHEME 1. Solvent Effect on the Formation of Aziridinium Cation

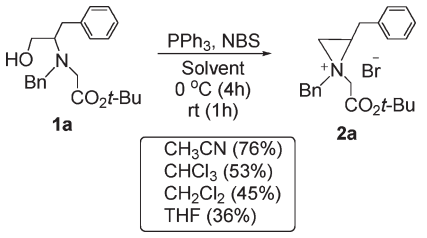
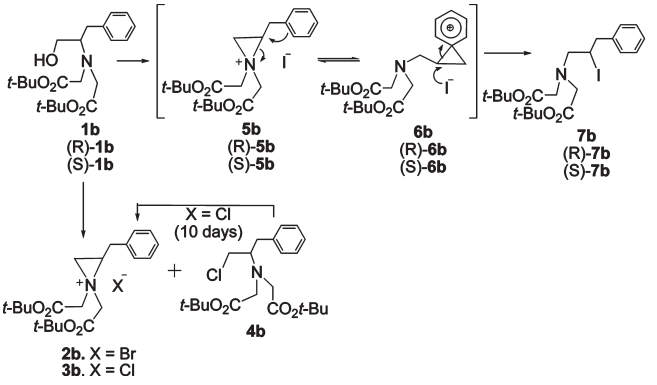


TABLE 1. Effect of Leaving Group and Counter Anion on the Formation and Ring-Opening of Aziridinium Cations



substrate	reagents	solvent	reaction time	X	product[a] (yield, ee[b])
1b	NBS, PPh_3	$CHCl_3$	4 h (0 °C), 1 h (rt)	Br	**2b** (89%)
1b	$SOCl_2$	$CHCl_3$	1d (rt)	Cl	**3b** + **4b** (43%)
1b	$SOCl_2$	$CHCl_3$	0.5 h (reflux)	Cl	**3b** (32%)
1b	MsCl	THF	3d (rt)	Cl	**3b** + **4b** (51%)
1b	I_2, PPh_3	CH_2Cl_2	4 h (0 °C), 1 h (rt)	I	**7b** (32%)
1b	I_2, PPh_3, Imi	CH_2Cl_2	4 h (0 °C), 1 h (rt)	I	**7b** (90%)
(*R*)-**1b**	I_2, PPh_3, Imi	CH_2Cl_2	4 h (0 °C), 1 h (rt)	I	(*R*)-**7b** (97%, 95%)
(*S*)-**1b**	I_2, PPh_3, Imi	CH_2Cl_2	4 h (0 °C), 1 h (rt)	I	(*S*)-**7b** (88%, 100%)
1b	NIS, PPh_3	CH_2Cl_2	4 h (0 °C), 1 h (rt)	I	**7b** (75%)

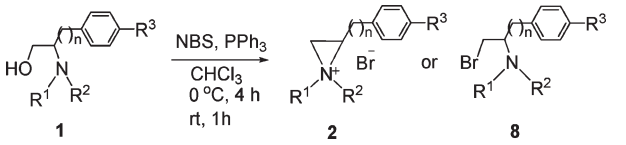
[a]Isolated yield. [b]Determined by chiral-HPLC.

containing chloride, not mesylate as a counteranion (Table 1). ^1H and ^{13}C NMR data of the mixture indicate that the inseparable mixture does not contain the peak corresponding to the mesylate group. It was reasonably concluded that once formed, β-amino mesylate was converted to a mixture of **3b** and **4b** as a result of nucleophilic attack by counteranion chloride. When continuously stirred in $CHCl_3$ for 10 days at room temperature, a mixture of **3b** and **4b** was converted slowly but completely to aziridinium salt **3b** as evidenced by ^1H and ^{13}C NMR analysis (Supporting Information). This experimental result suggests that β-amino chloride **4b** containing a poorer leaving group compared to bromide or iodide was slowly transformed into **3b**, which was inert to intramolecular ring-opening by less nucleophilic chloride. Iodination of β-amino alcohol **1b** was carried out with different iodinating reagents (NIS/PPh_3, I_2/PPh_3, or I_2/PPh_3/imidazole). Surprisingly, none of the iodination reactions studied provided aziridinium salt **5b**, and the secondary amino ethyl iodide **7b** was isolated as the exclusive product (Table 1). The formation of **7b** suggests that the reaction initially produced the aziridinium salt **5b**, which was converted to **7b** by subsitition reaction with iodide at the electron deficient methine carbon. The best synthetic yield of **7b** (90%) was obtained from the reaction with I_2/PPh_3/imidazole.

The stereochemistry of ring-opening of **5b** was investigated by using enantiomerically rich substrate (*R*)-**1b** and (*S*)-**1b**, which were prepared starting from (*R*)-phenylalanine and (*S*)-phenylalanine, respectively (Supporting Information). Iodination of (*R*)-**1b** and (*S*)-**1b** provided (*R*)-**7b** and (*S*)-**7b** resulting from double inversion in excellent ee, respectively (Table 1). The result demonstrates that ring-opening of (*R*)-**5b** and (*S*)-**5b** occurred by nucleophilic attack of the neighboring aryl group at the methine carbon to produce the phenonium ion intermediates (*R*)-**6b** and (*S*)-**6b**. Opening of the three-membered ring at the methine carbon of (*R*)-**6b** and (*S*)-**6b** by nucleophilic iodide provided (*R*)-**7b** and (*S*)-**7b**, respectively.

Next, we turned to examining the effect of *N*-substitution on the formation of aziridinium salts (Table 2). β-Amino alcohols substituted with various functional groups including benzyl, allyl, *p*-nitrobenzyl, 2,4-dimethoxylbenzyl (DMB), and carboxylate ester (CO_2R) were reacted with NBS/PPh_3 in $CHCl_3$. *N*,*N*-Bisubsituted β-amino alcohols **1** were prepared from the reaction of the corresponding β-amino alcohols with alkylating agents (Supporting Information). Aziridinium salts shown in Table 2 were obtained from reaction of **1** with NBS/PPh_3 in $CHCl_3$ in good to excellent isloated yield, and no attempt was made to optimize the synthetic yield of the new aziridinium salts reported. Azridinium cation **2c** substituted with *N*,*N*-*tert*-butyl acetate was prepared from **1c** by a modification of the procedure as previously reported by our group (entry 1).[7] We noted that the isolated yield of **2c** can be improved when **1c** in the reaction mixture was continuously stirred for 1 day at room temperature or kept in the freezer for several days (75−95% vs. 54%). *N*,*N*-Bis(benzyl acetate)-derived

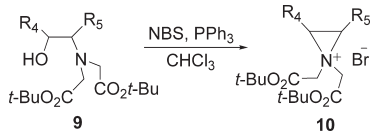
TABLE 2. Synthesis of *N*-Substituted Aziridinium Cations



entry	substrate	R^1	R^2	R^3	n	product (yield)[a]
1	**1c**	CH_2CO_2t-Bu	CH_2CO_2t-Bu	NO_2	1	**2c** (75%)[b]
2	**1d**	CH_2CO_2Bn	CH_2CO_2Bn	NO_2	3	**2d** (84%)
3	**1e**	H	BOC	H	1	**8e** (47%)
4	**1f**	allyl	CH_2CO_2t-Bu	H	1	**2f** (87%)
5	**1g**	*p*-NO_2-Bn	CH_2CO_2t-Bu	H	1	**2g** (92%)
6	**1h**	allyl	allyl	H	1	**2h** (78%)
7	**1i**	Bn	Bn	H	1	**2i** (87%)
8	**1j**	allyl	DMB	H	1	**2j** (25%)[b]

[a]Isolated yield. [b]Reaction was carried out at 0 °C for 4 h and continuous stirring at room temperature overnight.

TABLE 3. Synthesis of *C*-Substituted Chiral Aziridinium Cations



Starting material	Product	Yield[a]
(9a)	(10a)	62%
(9b)	(10b)	75%
(9c)	(10c)	60%
(9d)	(10d)	38%
(9e)	(10e)	45%
(9f)	(10f)	41%

[a]Isolated yield.

β-amino alcohol **1d** was converted to **2d** in 73% isolated yield. It was observed that the carboxyl protection groups (*tert*-butyl *or* benzyl) had no effect on the formation of aziridinium salts (entries 1 and 2). However, when the amino group in **1e** was protected by BOC, the reaction led to the formation of the normal substitution reaction product **8e** (entry 3). β-Amino alcohol **1** containing an *N*-*tert*-butyl acetate group was reacted with allyl bromide or *p*-nitrobenzyl bromide to provide **1f** and **1g** (entries 4 and 5). Bromination of **1f** and **1g** to afford the expected aziridinium cations **2f** and **2g** was accomplished in 87% and 92% isolated yields, respectively. *N*,*N*-Bis(benzyl)- and *N*,*N*-bis(allyl)-derived amino alcohols **1h** and **1i** were converted to aziridinium cation **2h** and **2i**, respectively (entries 6 and 7). Amino alcohol **1j** substituted with *N*-DMB and *N*-allyl groups provided aziridinium cation **2j** (entry 8). It should be noted that the aziridinium cations **2h**−**j** can be converted to diverse organic compounds including vicinal diamines and amino nitriles upon nucleophilic ring-opening followed by removal of the protecting groups.

Finally, asymmetric *C*-substituted aziridinium salts were prepared from bromination of different β-amino alcohols in $CHCl_3$ as shown in Table 3. Amino alcohols **9a** (*n*-propyl), **9b** (isopropyl), and **9c** (phenyl) containing alkyl and aryl groups provided the expected aziridinium salts **10a**−**c** in good yield. Aziridinium salts **10d** (thiobenzyl), **10e** (indole), and **10f** (benzyloxy *tert*-butyl acetate) possessing a functional group were obtained from amino alcohols **9d**−**f**. The functionality was well tolerated during the reaction, and all desired aziridinium salts with structural variation were readily isolated via flash column chromatography.

In summary, we developed an efficient synthetic method to stable aziridinium salts as potential building blocks in asymmetric synthesis and for biological applications. We investigated the scope of the new synthetic method and demonstrated that various aziridinium salts can be prepared from bromination of *C*-substituted or *N*-substituted β-amino alcohols and isolated via purification with use of flash column chromatography in good yields. We also studied that solvent, leaving group, and counteranion play an important role on the formation of the stable aziridinium salts. We noted that the isolated yield of the aziridinium salts can be optimized by varying reaction conditions. Our new synthetic route can be applied to the preparation of numerous aziridinium salts that can be extensively employed in the asymmetric synthesis of various organic molecules including functionalized 1,2 or 1,3 diamines, amino alcohols, β-alkoxy amines, β-amino acids, and β-amino esters as chiral ligands or backbone units of naturally occurring and biologically active compounds.

Experimental Section

General Procedure for the Preparation of Aziridinium Salts via Bromination. To a solution of *N*,*N*-bisubstituted alcohol **1** or **9** (1.0 equiv) and triphenylphosphine (1.2 equiv) in CH_2Cl_2 or $CHCl_3$ was portionwise added *N*-bromosuccinimide (1.2 equiv) at 0 °C over 20 min. The resulting mixture was continuously stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h and evaporated to dryness. The residue was purified via column chromatography on silica gel (60−230 mesh) eluting with 5−10% EtOAc in hexanes.

Sample Procedure and Data of 10b. To a solution of **9b** (166 mg, 0.50 mmol) and PPh_3 (157 mg, 0.60 mmol) in $CHCl_3$ (3 mL) at 0 °C was added NBS (107 mg, 0.60 mmol). The residue was purified by silica gel column chromatography eluted with 5% EtOAc in hexanes to afford colorless oil **10b** (147 mg, 75%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.41 (s, 18H), 2.03 (septet further split into d, J = 6.6, 2.8 Hz, 1H), 3.00 (dd, J = 14.4, 7.1 Hz, 1H), 3.14 (dd, J = 14.4, 7.1 Hz, 1H), 3.35−3.48 (m, 4H), 4.10 (td, J = 7.1, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.99 (q), 21.57 (q), 28.11 (q), 30.67 (d), 56.92 (t), 60.16 (t), 63.95 (d), 81.05 (s), 170.54 (s). HRMS (positive ion FAB) calcd for $C_{17}H_{32}BrNO_4$ [M − Br]$^+$ m/z 314.2331, found [M − Br]$^+$ m/z 314.2315.

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Supporting Information Available: Complete experimental details and characterization of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.