The preparation of stable aziridinium ions and their ring-openings†

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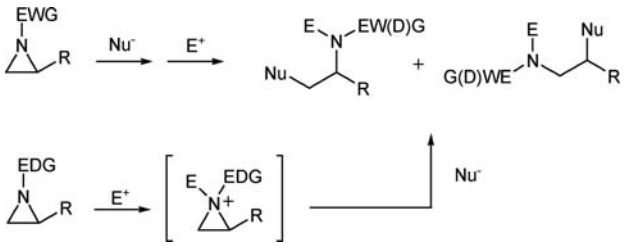
The reaction of enantiomerically pure 2-substituted 1-phenylethyl-aziridine with methyl trifluoromethanesulfonate generated a stable methylaziridinium ion, which was reacted with various external nucleophiles, including nitrile, to yield synthetically valuable and optically pure acyclic amine derivatives in a completely regio- and stereoselective manner.

Small-ring compounds, including cyclopropane, oxirane and aziridine, are valuable, not only because they are the constituents of a number of important molecules, but because they are good synthetic intermediates in the synthesis of acyclic molecules *via* ring-opening reactions. Compared with cyclopropane and oxirane, the chemistry of aziridine depends on the characteristics of the substituent on the ring nitrogen, as well as the ring carbon.[1] When the aziridine ring nitrogen has an electron withdrawing substituent (EWG), such as a carbonyl or sulfonyl group, the ring becomes less stable and more reactive towards nucleophiles with respect to ring-opening.[2] However, when the ring nitrogen has an electron donating substituent (EDG), such as phenylethyl, the aziridine becomes more stable and less reactive than that bearing a hydrogen or an electron withdrawing substituent. Therefore, an aziridinium intermediate is always involved prior to nucleophilic ring-opening reactions (Scheme 1).

Since we successfully prepared both (2*R*)- and (2*S*)-*N*-α-methylbenzylaziridine-2-carboxylates on a multi-kilogram scale, and in optically pure forms, we have been able to synthesize various cyclic and acyclic nitrogen-containing molecules with ring-opening or ring-expansion as a key step.[3] However, there is always the drawback that the ring nitrogen needs to be activated by a suitable electrophile to generate an aziridinium ion prior to the nucleophilic ring-opening reactions. Therefore, the source of applicable nucleophiles is limited to reagents that can provide the necessary electrophiles, such as carboxylic acids,[4] acid chlorides[5] and trimethylsilyl azide.[6] These reagents provide proton, acyl and trimethylsilyl electrophiles, respectively, to yield the corresponding aziridinium ions prior to ring-opening by the anionic counter-nucleophiles, carboxylate, chloride and azide. To overcome the drawback



Scheme 1 ring-opening reactions of aziridines.

of the limited range of applicable nucleophiles, we needed a reliable method to generate an aziridinium ion that was stable enough to survive in the presence of a counter-anion until the addition of external nucleophiles for ring-opening.

One of the best counter-anions, with poor nucleophilicity after the generation of an electrophilic aziridinium ion, is the sulfonate anion, which is not reactive enough to break down the aziridinium ions. This was tested by reacting methyl trifluoromethanesulfonate with the substrate, 2*R*-[(1*R*)-phenylethyl]methoxymethylaziridine in CH_3CN, leading to the methylation of the aziridine ring nitrogen to provide the corresponding aziridinium ion. We observed that all of the peaks of the starting aziridine in the ^{1}H NMR spectrum had shifted downfield 10 min after adding methyl trifluoromethanesulfonate, from δ 2.51, 1.66, 1.62 and 1.45 to δ 4.02, 3.56, 3.47 and 2.94, with coupling constants originating from the unique aziridine ring conformer. Generation of the aziridinium ion by methylation was also possible with 2*R*-[(1*R*)-phenylethyl]aziridine-2-carboxylate, with ^{1}H NMR peaks shifted downfield from 2.61, 2.26, 1.92 and 1.61 to 4.28, 3.51, 3.41 and 2.97, with a slight change in the coupling constants. The peak positions in the ^{1}H NMR spectrum arising due to the aziridinium ions were unchanged after up to 10 h at room temperature under nitrogen. The configuration of the *N*-methylaziridinium ions is speculated to be that of **2**, on the basis of the crystalline structure of dicyano{[(1*S*)-(1-phenylethyl)aziridin-2-yl]methanolato-k^2*N*,*O*}boron, showing that the ring nitrogen has a tetrahedral geometry, without much torsional change to the aziridine ring (Scheme 2).[7]

2*R*-[(1*R*)-Phenylethyl]methoxymethylaziridine (**1A**) was treated with methyl trifluoromethanesulfonate, followed by reaction with NaN_3, to yield a single regioisomer of ring-opening product **3Aa** in 89% yield (entry 1, Table 1). This led us towards further development with other external nucleophiles, including acetate, morpholine and benzylamine, to give the corresponding 3-acetyloxymethyl- (**3Ab**), morpholin-4-ylmethyl- (**3Ac**) and 3-benzylaminomethyl- (**3Ad**) 2-aminopropanes, respectively (entries 2–4, Table 1).

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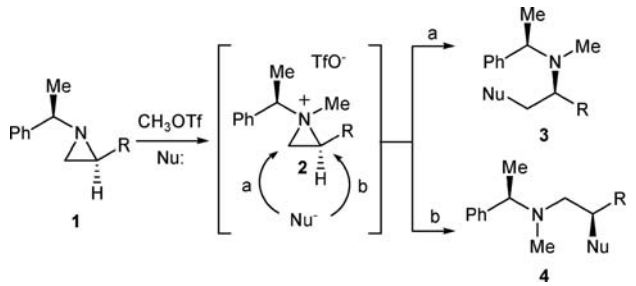


Scheme 2 Reactions of (1*R*)-phenylethyl-2-substituted aziridine.

Once we had observed the successful ring-opening reactions with various external nucleophiles, we applied a carbon nucleophile (nitrile) to the activated aziridinium ion **2**. The addition of NaCN provided ring-opening product **3Ae** in 80% yield (entry 5, Table 1). This reaction is the first example of an aziridine ring-opening reaction with an external nucleophile to lead to an alkyl substituent at the ring nitrogen (Table 1). This is also the first case in which a carbon nucleophile has been introduced in the ring-opening of an aziridinium ion intermediate. Further development was achieved by using 2-benzyloxymethylaziridine as a substrate, which could yield an alcohol if necessary under the same conditions as those used to remove the α-methylbenzyl group on the ring nitrogen.[8] The reactions with nucleophiles, including N_3^-, AcO^- and CN^-, provided the corresponding ring-opening products (**3Ba**, **3Bb** and **3Bc**) as single regio- and stereoisomers in 76, 79 and 81% yield, respectively (entries 6–8, Table 1).

Reductive ring-opening by hydride derived from $NaCNBH_3$ afforded product **3Bd** in 57% yield (entry 9, Table 1). Having observed these regioselective ring-opening reactions with 2-alkyl-substituted aziridines, we applied the same procedure to aziridines containing different substituents at C2, including aziridine-2-carboxylate and 3-aziridin-2-ylacrylate. The same ring-opening reaction of **1C** with azide yielded product **4Ca** as a single isomer in 87% yield (entry 1, Table 2). On the basis of our earlier observation, ring-opening occurred with the cleavage of the bond between C2 and the ring nitrogen of the aziridine, to yield the β-amino compound. This pathway was confirmed by comparison of the diamino compound, **5**, with the compound derived from the ring-opening product of starting aziridine **3Aa**. The azide and carboxylate functional groups in product **4Ca** were sequentially reduced, followed by methylation of the hydroxyl group to give **5**, which is a different diamine originating from **3Aa** (Scheme 3).

Table 1 ring-opening at C3 of the aziridine following pathway a in Scheme 2 towards compound **3**

Entry	Substrate	R	Nu:[a]	Product	Yield (%)[b]
1	**1A**	CH_2OMe	N_3^-	**3Aa**	89
2	**1A**	CH_2OMe	AcO^-	**3Ab**	75
3	**1A**	CH_2OMe	Morpholine	**3Ac**	41
4	**1A**	CH_2OMe	NH_2Bn	**3Ad**	32
5	**1A**	CH_2OMe	CN^-	**3Ae**	80
6	**1B**	CH_2OBn	N_3^-	**3Ba**	76
7	**1B**	CH_2OBn	AcO^-	**3Bb**	79
8	**1B**	CH_2OBn	CN^-	**3Bc**	81
9	**1B**	CH_2OBn	H^-	**3Bd**	57

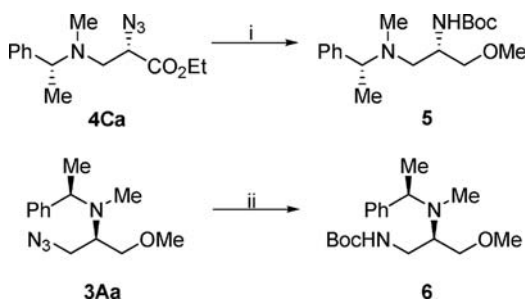
[a] The reagents used for the generation of the anionic nucleophiles were NaN_3, NaOAc, NaCN and $NaCNBH_3$. [b] The isolated yield was not optimized.

Table 2 Ring-opening at C2 of the aziridine following pathway b in Scheme 2 towards compound **4**

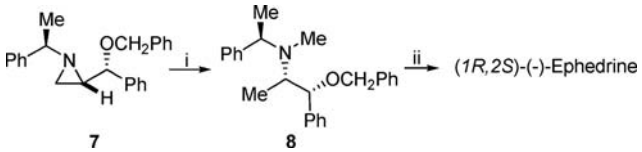
Entry	Substrate	R	Nu:[a]	Product	Yield (%)[b]
1	**1C**	CO_2Et	N_3^-	**4Ca**	87
2	**1C**	CO_2Et	AcO^-	**4Cb**	72
3	**1C**	CO_2Et	Morpholine	**4Cc**	53
4	**1C**	CO_2Et	NH_2Bn	**4Cd**	31
5	**1C**	CO_2Et	CN^-	**4Ce**	86
6	**1D**	$CHCHCO_2Et$	N_3^-	**4Da**	71
7	**1D**	$CHCHCO_2Et$	AcO^-	**4Db**	87
8	**1D**	$CHCHCO_2Et$	CN^-	**4Dc**	72

[a] The reagents used for the generation of the anionic nucleophiles were NaN_3, NaOAc, NaCN and $NaCNBH_3$. [b] The isolated yield was not optimized.

These two compounds show the different regiochemical pathways of the ring-opening reactions. This reaffirmed our earlier observation that the ring-opening reactions proceed by two different pathways, with cleavage occurring *via* either the a or b pathway, depending on the electronic character of the C2 substituent of the aziridine.[5] When acyl or vinyl substituents were present, the bond between C2 and the ring nitrogen was activated towards approaching nucleophiles. Reaction of aziridine-2-carboxylate **1C** with many different nucleophiles, including AcO^-, morpholine and $BnNH_2$, yielded the expected products, **4Cb**, **4Cc** and **4Cd**, in 72, 53 and 31% yields, respectively (entries 2–4, Table 2). Nitrile was also applied as a carbon nucleophile, to give the ring-opening product, β-amino-α-cyanopropionate **4Ce**, which is a valuable chiral synthon for the preparation of various β-amino acids, in 86% yield (entry 5, Table 2). Vinyl substituted aziridine **1D** was reacted with an azide nucleophile in the same manner as above to afford the corresponding δ-amino-γ-azido compound in 71% yield (entry 6, Table 2). Reactions with different nucleophiles, such as AcO^- and CN^-, yielded the expected products, **4Db** and **4Dc**, in 87 and 72% yields, respectively (entries 7 and 8, Table 2). This synthetic method was applied in the preparation of (1*R*,2*S*)-(−)-ephedrine, starting from aziridine **7**, which originated from the commercially available aziridine-2-carboxylate.



Scheme 3 Ring-opening reactions of aziridines. *Reagents and conditions:*(i) (1) $LiAlH_4$, THF (2) $(Boc)_2O$, (3) CH_3I, NaH, rt, 58%; (ii) (1) $LiAlH_4$, THF (2) $(Boc)_2O$, 66%.



Scheme 4 Ring-opening reactions of aziridines. *Reagents and conditions*:(i) (1) MeOTf, (2) $NaCNBH_3$, rt, 53%; (ii) $Pd(OH)_2$, H_2(g) 50 psi, EtOH, rt, 55%.

Reductive ring-opening of the *N*-methyl ammonium salt of **7** with $NaCNBH_3$, as in entry 9 of Table 1, yielded product **8** in 53% yield, and the benzyl protecting groups on both the nitrogen and oxygen were readily removed by catalytic hydrogenation, in 55% yield (Scheme 4).

In this Communication, the formation of stable aziridinium ions by methylation with methyl trifluoromethanesulfonate, and the subsequent regioselective aziridine ring-opening reactions, bearing the phenylethyl group as an electron donating substituent at the ring nitrogen, has been described. Various external nucleophiles, including nitrile, were applied to yield products in a completely regio- and stereoselective manner, depending on the substituents at the C2 position of the aziridine. This procedure offers an efficient route to synthetically valuable *N*-methyl acyclic amines in optically pure forms.[9]

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