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Novel Synthesis of 3,4-Diaminobutanenitriles and 4-Amino-2-butenenitriles from 2-(Cyanomethyl)aziridines through Intermediate Aziridinium Salts: An Experimental and Theoretical Approach

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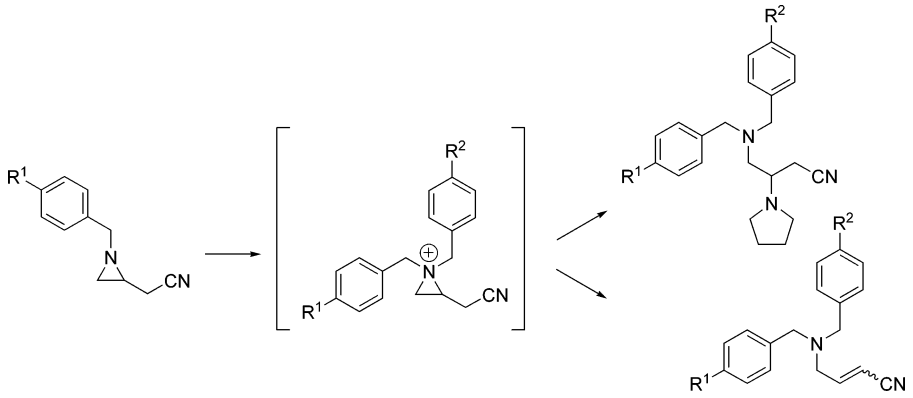

1-Arylmethyl-2-(cyanomethyl)aziridines were transformed into 4-(*N*,*N*-bis(arylmethyl)amino)-3-(pyrrolidin-1-yl)butanenitriles and 4-(*N*,*N*-bis(arylmethyl)amino)-2-butenenitriles via 4-(*N*,*N*-bis(arylmethyl)amino)-3-bromobutanenitriles in high yields and purity. The key steps involve the unprecedented regiospecific ring opening of intermediate 2-(cyanomethyl)aziridinium salts by bromide and pyrrolidine in acetonitrile, exclusively at the substituted aziridine carbon atom. The results were rationalized on the basis of ab initio calculations.

Introduction

The search for new pathways toward amino nitriles as precursors of the corresponding amino acids is an important challenge in organic synthesis.[1] The interesting pharmacological properties of β- and γ-amino acids and their use in the synthesis of the corresponding β- and γ-peptides have, especially in the past decade, renewed the interest of organic chemists.[2] 3-Substituted 4-aminobutyric acids in particular, such as 3-alkyl (anticonvulsant)[3] and 3-hydroxy derivatives (carnitine),[4] have received major interest in recent years because of their broad pharmacological relevance. Furthermore, also β,γ-diaminobutanoic acids comprise an attractive class of amino acids with interesting applications as biologically active compounds. Emericedin **1** has been isolated from the fungus *Emericella quadrilineata* and emeriamine **2** is a strong and specific inhibitor of

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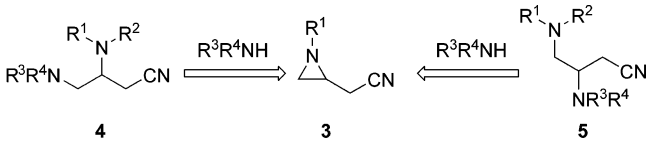
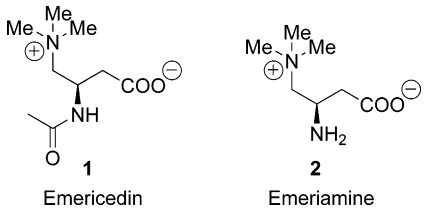
SCHEME 1



carnitine palmitoyltransferase-2.[5] Because of the medicinal relevance of the latter amino acids, a variety of 3,4-diaminobutanoic acid derivatives have been prepared, mostly starting from aspartic acid derivatives,[6] and evaluated as inhibitors of carnitine palmitoyl transferase.[7] However, very little effort has been made toward the synthesis of their nitrile precursors, i.e., 3,4-diaminobutanenitriles, as an alternative approach toward this valuable class of compounds.[8]



Although the preparation of 1,2-diamines from aziridines is known in the literature,[9] no reports are available on the synthesis of 3,4-diaminobutanenitriles starting from suitably substituted aziridine derivatives. From a retrosynthetic point of view, the ring opening of 2-(cyanomethyl)aziridines **3** could offer an easy access to 3,4-diaminobutanenitriles **4** and/or **5** depending on the regioselectivity of this ring opening (Scheme 1).

In the present report, an elegant and straightforward approach toward novel 4-(*N*,*N*-bis(arylmethyl)amino)-3-(pyrrolidin-1-yl)-butanenitriles and 4-(*N*,*N*-bis(arylmethyl)amino)-2-butenenitriles from 1-arylmethyl-2-(cyanomethyl)aziridines is described via regiospecific ring opening of intermediate aziridinium salts. The exclusive attack of bromide and pyrrolidine at the more hindered aziridine carbon atom in the ring opening of 2-(cyanomethyl)-aziridinium salts is rationalized on the basis of ab initio calculations. At present, very few in-depth theoretical studies on the ring opening of aziridinium salts are available.[10] From the computational viewpoint the system under study is challenging, as the solvent might be crucial for predicting the correct reaction preference. To validate the importance of the incorporation of the molecular environment, the reaction route was modeled at various levels of theory: in the gas phase, with inclusion of explicit solvent molecules, and by embedding in a continuum characterized by a dielectric constant which is characteristic for the solvent. The latter was found to be important in other studies to capture the bulk electrostatic effects.[11]

Results and Discussion

The synthesis of 1-arylmethyl-2-(cyanomethyl)aziridines **6** as suitable synthons in organic chemistry has been reported previously by treatment of 1-arylmethyl-2-(bromomethyl)-aziridines,[12] a peculiar yet promising class of β-halo amines, with 1 equiv of potassium cyanide in DMSO and heating at 60−70 °C for 3 h.[13] The combination of an aziridine moiety and a cyano group in these unexplored substrates enables the preparation of a variety of functionalized amino nitriles through ring opening reactions of the constrained ring.

Only a limited number of reports are available on the regioselective ring opening of 2-substituted aziridinium salts (different from 2-aryl or 2-acyl substitution) at the more hindered aziridine carbon atom.[14] This unique feature offers a useful tool in targeted organic synthesis and is considered as an important synthetic advantage of nonactivated 2-substituted aziridines with regard to their activated counterparts.

Treatment of aziridines **6** with 1 equiv of an arylmethyl bromide in acetonitrile afforded novel 4-amino-3-bromobutanenenitriles **8** in good yields after several days at room temperature (Scheme 2, Table 1). In this transformation, the arylmethyl bromide is responsible for both the activation of the aziridine ring toward an aziridinium intermediate and the delivery of the nucleophilic bromide anion which induces ring opening of the aziridinium ion. Since only one similar compound has been reported in the literature, i.e., *N*-(2-bromo-3-cyanopropyl)-succinimide,[15] the presented methodology offers an elegant approach toward this new class of versatile substrates **8** suitable for further elaboration because of the presence of a γ-amino nitrile moiety and a β-bromo amine in one structural entity.

In accordance with the previously observed reactivity of 2-(bromomethyl)-, 2-(aryloxymethyl)-, and 2-(alkanoyloxymethyl)aziridines toward arylmethyl bromides in acetonitrile,[16] a regioselective ring opening of the intermediate 2-(cyanomethyl)aziridinium salts **7** by bromide occurred at the more hindered

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SCHEME 2

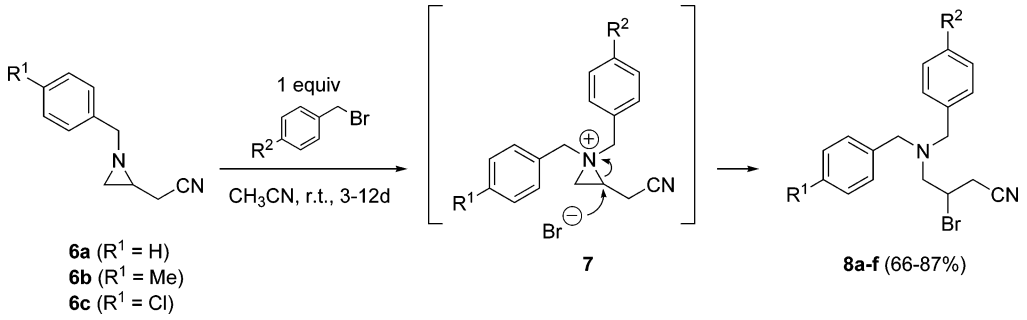
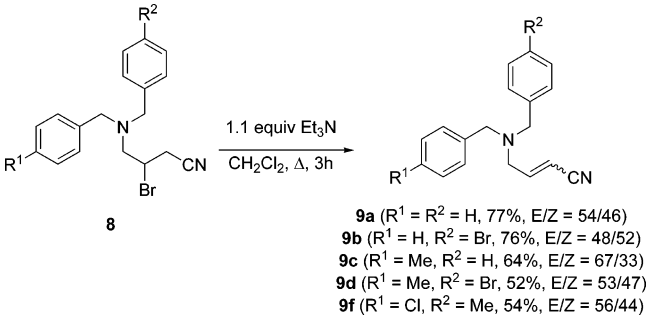


TABLE 1. Synthesis of 4-Amino-3-bromobutanenitriles 8 Starting from 1-Arylmethyl-2-(cyanomethyl)aziridines 6

entry	R^1	R^2	time (d)	compd	yield (%)[a]
1	H	H	10	**8a**	66
2	H	Br	10	**8b**	74
3	Me	H	3	**8c**	80
4	Me	Br	5	**8d**	87
5	Me	Me	12	**8e**	77
6	Cl	Me	4	**8f**	74

[a] Yields after column chromatography

SCHEME 3



aziridine carbon atom, affording β-bromo amines **8** as the sole reaction products in high purity. Detailed spectral analysis confirmed the structural identity of these novel *N*-(2-bromo-3-cyanopropyl)amines **8**, excluding the formation of the corresponding regioisomers. The regiospecific ring opening of 2-(cyanomethyl)aziridinium salts **7** by bromide in acetonitrile at the more hindered position was further validated by performing ab initio calculations (see section Ab Initio Calculation Results).

It should be remarked that upon heating of aziridines **6** in the presence of an arylmethyl bromide under reflux for 5 h, the reaction mixtures were contaminated with reasonable amounts of the corresponding 4-amino-2-butenenenitriles **9** (15−50%) because of the acidity of the α-proton with respect to the cyano group, whereas no dehydrobromination occurred at room temperate (although longer reaction times of 3−12 days were required to drive the reaction to completion). The selective preparation of 4-amino-2-butenenenitriles **9** as mixtures of *E*/*Z*-isomers could be accomplished by a simple base treatment of 4-amino-3-bromobutanenitriles **8** with 1.1 equiv of Et_3N in refluxing CH_2Cl_2 for 3 h (Scheme 3). Other base/solvent combinations, such as KO*t*Bu/Et_2O and NaH/THF, appeared to be less successful, resulting in complex reaction mixtures. Two main reasons can be adduced for the relevance of γ-aminobutenenitrile derivatives such as **9**, the first being the general interest in structural (in casu unsaturated) analogues of the neurotransmitter γ-aminobutyric acid (GABA), and the second the manifold efforts reported in the literature for the production of L-carnitine from crotonobetaine.[17]

Another useful elaboration of 4-amino-3-bromobutanenitriles **8** comprises their transformation into β,γ-diaminobutanenitriles as precursors for the corresponding amino acid derivatives. Treatment of β-bromoamines **8** with 2 equiv of pyrrolidine in refluxing acetonitrile afforded 3,4-diaminobutanenitriles **10** as the sole reaction products in good yields after 3 h (Scheme 4). This reaction can be explained considering the formation of an intermediate aziridinium salt **7**, followed by nucleophilic ring opening of the latter by pyrrolidine at the more hindered aziridine carbon atom (Scheme 4). The structural identity of 4-(*N*,*N*-bis(arylmethyl)amino)-3-(pyrrolidin-1-yl)butanenitriles **10** (and not the regioisomers) was determined by detailed spectroscopic analysis and confirmed by comparison with literature data of 3-(*N*,*N*-dibenzylamino)-4-(pyrrolidin-1-yl)butanenitrile.[8b]

From a synthetic point of view, the ring opening of aziridinium salts by nitrogen nucleophiles constitute a powerful method for the preparation of 1,2-diamino derivatives,[18] although very little reports on this type of chemistry are available in the literature. Recently, the synthesis of methyl α,β-diaminocarboxylates by treatment of methyl 3-phenyl-2-(trifluoromethanesulfonyloxy)propenoate with secondary amines has been reported, in which ring opening of the intermediate aziridinium salts occurred at the benzylic position.[19] However, elimination toward the corresponding enamines appeared to be a common side-reaction in this type of transformations. This side-effect was avoided by means of a *N*,*N*-dibenzyl-protected serine methyl ester, leading to chiral α,β-diamino esters via ring opening of intermediate aziridinium salts by amines.[20] Other rare examples of the ring opening of aziridinium salts by amines include the reaction of a 2-(trifluoromethyl)aziridinium salt with *N*-benzyl-*N*-methylamine and butylamine, affording the corresponding 1,2-diamines through ring opening at the less hindered aziridine carbon atom.[21] In another report, the ring opening of 2-substituted 1,1-dibenzylaziridinium salts by methylamine has been evaluated, showing a preferential (yet never exclusive) attack at the less hindered carbon atom for 2-methyl-, 2-benzyl-, and 2-isopropylaziridinium salts, and opening at the benzylic position

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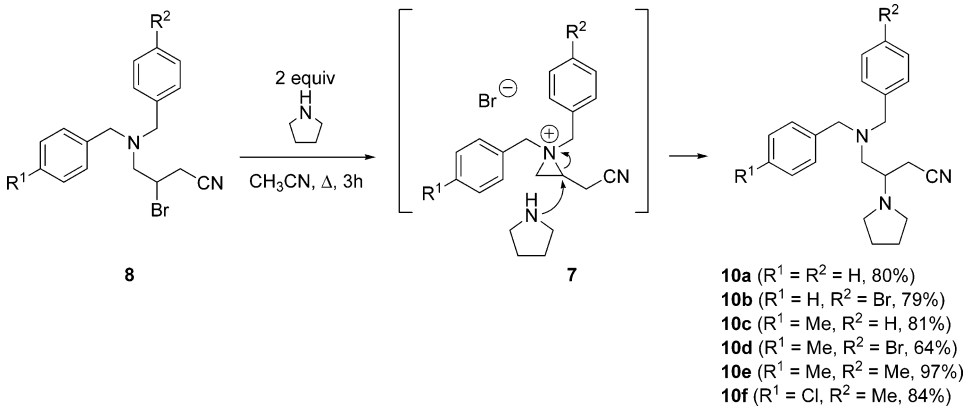
SCHEME 4



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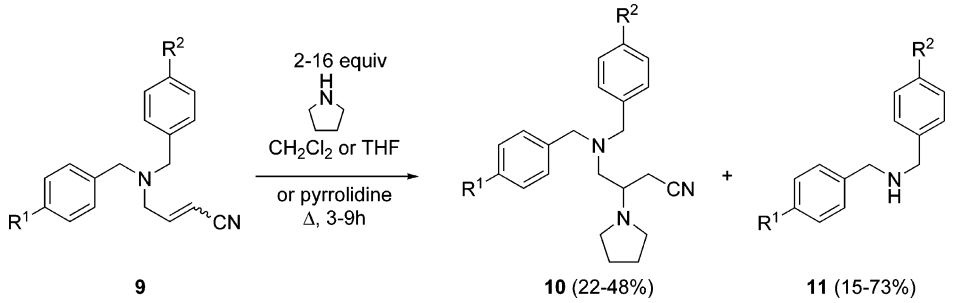

in the case of 2-phenyl substitution.[22] The present work comprises the first report of the regiospecific ring opening of 2-substituted aziridinium salts **7** by a secondary amine (pyrrolidine) at the more hindered aziridine carbon atom in an elegant and straightforward approach. This new and valuable synthetic methodology was further supported on the basis of ab initio calculations (see section Ab Initio Calculation Results).

It is important to note that the Michael addition of pyrrolidine onto 4-amino-2-butenenenitriles **9** does not offer a suitable alternative for the synthesis of 3,4-diaminobutanenitriles **10**, since treatment of butenenitriles **9** with 2−16 equiv of pyrrolidine resulted in all cases in mixtures of 3,4-diaminobutanenitriles **10** (22−48%), *N*,*N*-bis(arylmethyl)amines **11** (15−73%), and sometimes unreacted starting material **9** (0−43%) (Scheme 5). On the contrary, the methodology involving the preparation of 4-amino-3-bromobutanenenitriles **8** followed by treatment with pyrrolidine offers an elegant route toward 3,4-diaminobutanenitriles **10** in good yields. The formation of *N*,*N*-bis(arylmethyl)amines **11** can be rationalized considering a base-assisted migration of the double bond in butenenitriles **9** toward intermediate iminium salts, which are then hydrolyzed affording bis(arylmethyl)amines **11**.

Computational Details. All ab initio calculations were performed with the Gaussian 03 software package.[23] Density Functional Theory (DFT) methods have been shown to be more efficient than wave function based procedures such as highly correlated post-Hatree-Fock methods because of their excellent cost to performance ratio. The MPW1B95/6-31+g(d) level of theory was used for both geometries and energies, which is known to give reliable estimates of these parameters.[24] Moreover, a variety of other electronic levels were tested and the selected methods have been found most suitable. Caution is needed in interpreting the quantitative values for the barriers resulting from DFT calculations, as the absolute values for the energies might vary largely depending on the specific functional that is used.[25] Our main objective in this study is the prediction of qualitative trends that might contribute to a better understanding of the experimental results, and therefore the proposed functional is well suited.

Also the effect of solvent is taken into account, explicitly by surrounding the reactive center of the complexes with two or four acetonitrile molecules and implicitly by embedding all structures in a polarizable medium characterized by a fixed dielectrical constant which is typical for acetonitrile (i.e., $\epsilon = 36.64$). The solvation energy originates from two contributions: the explicit coordination with acetonitrile molecules and the electrostatic effect of the solvent dielectricum. The first effect might be expected to involve the bare bromide ion, as it is an important part of our model system, and it is expected to coordinate explicitly with surrounding solvent molecules. The solvation due to the bulk electrostatic effects is obtained by enclosing the reactive intermediate in a cavity within a continuous dielectricum medium. The CPCM option in Gaussion was applied. A recent study by Kelly, Cramer, and Truhlar on the accurate determination of solvation free energies might be interesting for a more detailed reading on this subject.[26]

Ab Initio Calculation Results. Effect of Solvation on the Intermediate Aziridinium Salts 7. From a molecular modeling viewpoint, the system under study is challenging, as it concerns

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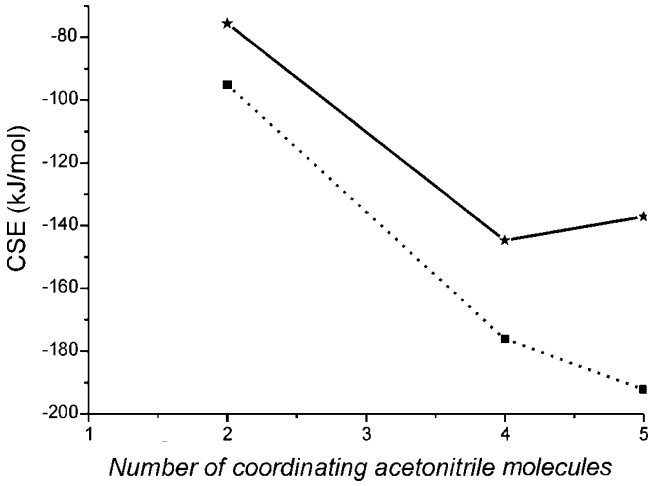

FIGURE 1. The coordination solvation energy (CSE) in terms of a varying number of acetonitrile solvent molecules for the intermediate of the ring opening of the aziridinium salt **7** by bromide (dotted line) and the ring opening of aziridinium salt **7** by pyrrolidine (full line).

an ion pair which is further solvated in acetonitrile. In our previous communication on the ring opening of 1-alkyl-2-(aryloxymethyl)aziridinium salts by bromide,[16c] preliminary indications were found that the explicit account of solvent molecules together with further embedding in a continuous dielectricum was crucial for the prediction of the correct reactivity pattern. The importance of explicit solute−solvent interactions and the bulk electrostatic effects is properly investigated on the intermediate aziridinium salts. A first point of interest concerns the degree of coordination of the ion pair under consideration. The coordination number is estimated by coordinating the intermediate 2-(cyanomethyl)aziridinium salts **7** by an increasing number of explicit acetonitrile molecules and calculating the coordination solvation energy (CSE). These values are shown in Figure 1.

The coordination of the intermediate aziridinium salt **7** (Scheme 2) is highly exothermic, giving 95, 176, and 192 kJ/mol for two, four, and five acetonitrile molecules. These results are not too surprising, as it concerns a bromide anion that is coordinated with the aziridinium ion but that is further largely stabilized by surrounding solvent molecules. From these numbers it can already be expected that the correct reaction preference for attack at the less or more hindered carbon atom will be sensitive to the number of acetonitrile molecules that is explicitly taken into account. For the intermediate aziridinium salt **7** which is additionally surrounded by a pyrrolidine molecule (Scheme 4), the degree of coordination was also determined. The coordination of the first two acetonitrile molecules is still very exothermic, but the CSE value is smaller in absolute value, as a large amount of the stabilization of the bromide anion is already captured by the surrounding pyrrolidine ring (i.e., −444 kJ/mol). The Gibbs free energy change is expected to converge more rapidly than the CSE because of the entropic effect of the solvation.

Geometries of the Intermediates 7. Before studying the transition-state structures, it is interesting to study some geometrical properties of the intermediate aziridinium salts. The approach of the aziridinium ion **7** with bromide (Scheme 2) leads to a stable intermediate on the potential energy surface. The bromide ion prefers a position located above the aziridinium moiety at a distance of about 3.6 and 3.7 Å from the unhindered and hindered carbon atom, respectively. The C−N bond lengths of the intermediate are different, the one involving the substituted carbon atom (C_2) being longer. The optimized structure with four acetonitrile molecules is shown in Figure 2. In the aziridinium intermediate **7**, additionally surrounded by a pyrrolidine molecule (Scheme 4), the bromide has a similar position with respect to the aziridinium moiety, but it makes an additional contact with the hydrogen of pyrrolidine ($Br-H_{pyrrolidine} = 2.573$ Å).

Some important geometrical parameters of **7** in terms of a varying coordination number are given in Table 2. As for the CSE values discussed previously, also the distances of the bromide with respect to the aziridinium moiety are only converged when taking four explicit acetonitrile molecules into account. However, the C−N distances seem to be less sensitive to the coordination number.

Atomic Charges of the Intermediates 7. The nature of the intermediates can be further understood by studying the atomic charges on the optimized geometries. The Mulliken atomic charges with the hydrogens summed into the heavy atoms at the MPW1B96/6-31+g(d) level of theory are listed in Table 3 for varying coordination numbers. In the gas-phase calculation without explicit account of acetonitrile molecules, both the hindered and unhindered carbon atom of the aziridine moiety carries a partial positive charge. The latter charges are sensitive to the number of coordinating solvent molecules. With two, four, or five acetonitrile molecules the hindered carbon atom carries a partial positive charge, whereas the unhindered position is partially negatively charged. These observations give a good indication that the hindered position is preferred for the further reaction with the bromide anion. The partial charges give further evidence that the correct reaction preference will be sensitive to the account of the first solvation shell of the bromide anion. For the intermediate **7**, the largest partial positive charge is also located at the hindered carbon atom, indicating reaction preference at this site.

Transition State Structures. The transition state structures for ring opening at the more or less hindered carbon atom starting from intermediate **7** (Scheme 2) are shown in Figure 3. A specific geometrical feature of the transition states in aziridinium salt **7** surrounded by an additional pyrrolidine molecule (Scheme 4) is the length of the breaking carbon−nitrogen bond, which amounts to 1.77 and 1.82 Å for attack at C_3 and C_2, respectively. In the latter case, the bond is already far elongated in the transition state, and this is an indication for a "late transition state" which is in most cases an indication of a lower reaction barrier compared to "early transition states".[27] For the transition states following from the intermediate **7** (Scheme 2), the differences in geometrical characteristics between the two possible ring openings is less pronounced, and this is a preliminary indication that the correct prediction of the reaction preference is subjected to a lot of factors, such as a proper account of the solvent environment. Moreover, the geometrical characteristics of forming and breaking bonds in the transition state vary largely on the number of explicit solvent molecules that is accounted. The underlying reason for this different behavior of the two intermediates is probably the coordination of the bromide anion with pyrrolidine in intermediates **7** as shown in Scheme 4. Therefore, an already large part of

(27) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340.

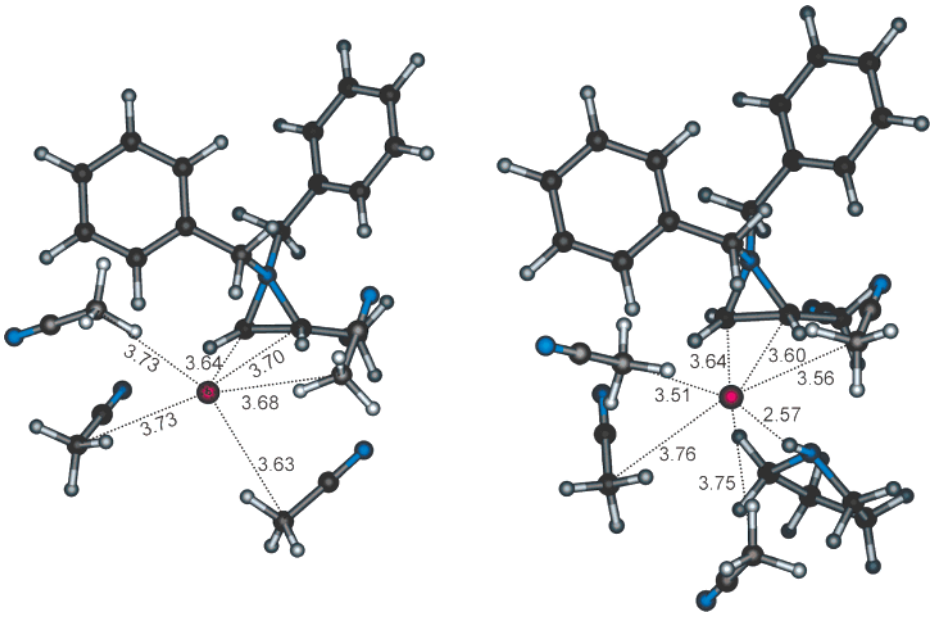

FIGURE 2. Geometries of intermediates **7** which are further coordinated by four acetonitrile molecules.

TABLE 2. Most Important Geometrical Characteristics of the Intermediates 7 at the MPW1B96/6-31+g(d) Level of Theory (Å). C_2 and C_3 Are the Hindered and Unhindered Carbon Atoms of the Aziridinium Salts

	gas phase	two acetonitrile molecules	four acetonitrile molecules
	Intermediate **7** (Scheme 2)		
C_3-N	1.483	1.485	1.486
C_2-N	1.498	1.493	1.496
C_3-Br	3.407	3.447	3.641
C_2-Br	3.313	3.394	3.703
$Br-C_{aceto1}$		3.728	3.729
$Br-C_{aceto2}$		3.619	3.629
$Br-C_{ateto3}$			3.726
$Br-C_{acteo4}$			3.676
	Intermediate **7** + Pyrrolidine (Scheme 4)		
C_3-N	1.483	1.486	1.486
C_2-N	1.500	1.501	1.498
C_3-Br	3.452	3.557	3.645
C_2-Br	3.374	3.449	3.601
$BrvH_{pyrrolidine}$	2.525	2.584	2.573
$Br-C_{aceto1}$		3.719	3.764
$Br-C_{aceto2}$		3.687	3.752
$Br-C_{ateto3}$			3.556
$Br-C_{acteo4}$			3.511

TABLE 3. Mulliken Atomic Charges at the MPW1B96/6-31+g(d) Level of Theory and with Hydrogens Summed into Heavy Atoms for the Intermediates 7

	gas phase	two acetonitrile molecules	four acetonitrile molecules
	Intermediate **7** (Scheme 2)		
N	−0.61	−0.60	−0.54
C_3	+0.30	−0.22	−0.44
C_2	+1.11	+0.96	+0.69
Br	−0.55	−0.70	−0.86
	Intermediate **7** + pyrrolidine (Scheme 4)		
N	−0.53	−0.45	−0.30
C_3	+0.76	+0.19	+0.29
C_2	+0.53	+0.86	+0.46
Br	−0.61	−0.71	−1.21
$H_{pyrrolidine}$	+0.39	+0.44	

solvation is captured by the presence of pyrrolidine, which coordinates strongly with Br^- (cfr. CSE indicated in Figure 1). In case of the intermediate **7** without the presence of pyrrolidine (Scheme 2), the bromide anion behaves as an unscreened ion which must fully be solvated by solvent acetonitrile molecules, and proper embedding will be essential.

Reaction Barriers. The reaction barriers for ring opening at the hindered and unhindered carbon atom of the aziridine moiety are given in Table 4. Both the values with and without inclusion of bulk solvent effects are given. The reaction preference for the nucleophilic ring opening of the intermediate **7** by pyrrolidine (Scheme 4) is always correctly predicted at all levels of our cluster model. Even in the gas phase without explicit account of solvent molecules and without accounting for bulk solvation effects, a slight preference for ring opening at the more hindered carbon aziridine atom is found. However, the quantitative values are highly dependent on the explicit account of acetonitrile molecules. Taking into account two explicit solvent molecules which are further embedded in a continuum dielectricum gives a preference for attack at the hindered carbon atom with an energy barrier advantage of 26 kJ/mol. The results for the ring opening of the intermediate **7** by bromide (Scheme 2) are less transparent. The barriers obtained without inclusion of bulk solvent effects do not succeed in predicting the correct reaction preference, even with inclusion of two or four acetonitrile molecules. Similar observations have been reported earlier.[11a] Once bulk solvent effects are accounted for, the correct reaction preference is predicted, provided that at least two acetonitrile molecules are explicitly taken into account. From previous calculations it follows that the intermediate **7** with a naked bromide anion attacking the aziridinium moiety is challenging in order to get correct quantitative values for the barriers, and further investigation would be appropriate to design a reliable cluster model that enables prediction of correct quantitative values for the barriers. Moreover, it seems that a variety of stable minima exists on the potential energy surface that differ in orientation of the surrounding solvent molecules. The results given here are obtained by taking the energetically most stable configuration.

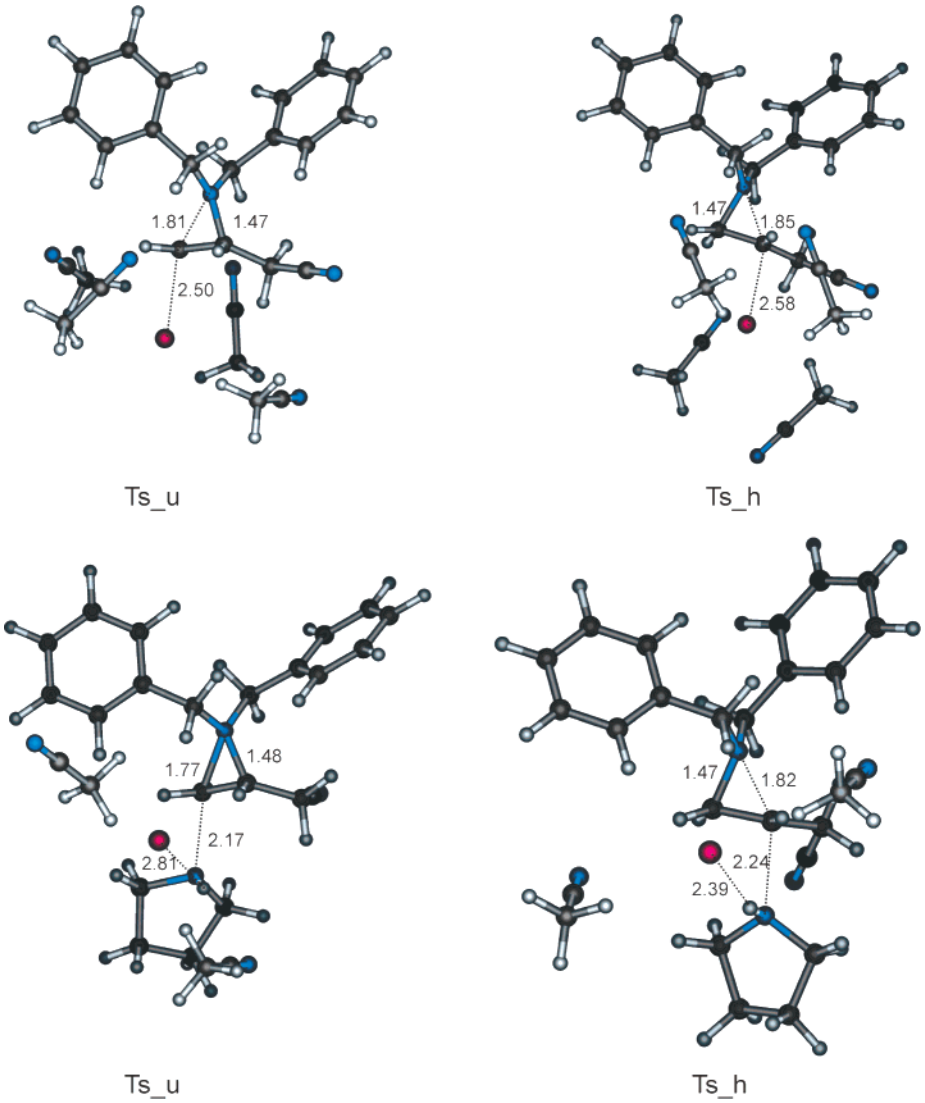

FIGURE 3. The transition state structures for ring opening at the unhindered (u) or hindered (h) carbon atom starting from intermediate **7** with or without an additional pyrrolidine.

TABLE 4. Reaction Barriers for Ring Opening at the Hindered and Unhindered Carbon Atom of the Aziridine Moiety MPW1B96/6-31+g(d) Level of Theory Starting from the Intermediates 7 (Energies Are in kJ/mol)[a]

	without inclusio n of bulk solvent effects			with inclusio n of bulk solvent effects		
	ΔE_u	ΔE_h	$\Delta(\Delta E_u - \Delta E_h)$	ΔG_u	ΔG_h	$\Delta(\Delta G_u - \Delta G_h)$
			7 (Scheme 2)			
gas phase	51.24	57.07	−5.83	41.42	45.38	−3.96
two acetonitrile molecules	37.66	70.79	−33.13	49.92	44.97	4.95
four acetonitrile molecules	51.70	56.48	−4.78	52.93	47.23	5.70
			7 + pyrrolidine (Scheme 4)			
gas phase	40.93	38.68	2.25	33.70	27.76	5.94
two acetonitrile molecules	53.95	17.34	36.61	54.71	28.61	26.1

[a] $\Delta E_u$and ΔE_h are the reaction barriers without inclusion of zero point vibrational energy for ring opening at the less hindered and more hindered aziridine carbon atom, and $\Delta(\Delta E_u - \Delta E_h)$ is the difference between the aforementioned barriers. ΔG_u and ΔG_h are the free energy reaction ring barriers for ring opening at the less hindered and more hindered aziridine carbon atom.

Conclusions

In conclusion, an efficient and straightforward synthesis of 4-(*N*,*N*-bis(arylmethyl)amino)-3-(pyrrolidin-1-yl)butanenitriles and 4-(*N*,*N*-bis(arylmethyl)amino)-2-butenenitriles is presented starting from 1-arylmethyl-2-(cyanomethyl)aziridines. The key steps comprise the novel regiospecific ring opening of intermediate 2-(cyanomethyl)aziridinium salts by bromide and pyrrolidine at the more hindered aziridine carbon atom, which was validated by means of high level ab initio calculations. For the ring opening by pyrrolidine, the correct reaction preference was always predicted irrespective of the molecular environment that was taken into account. For the reaction with bromide, the result is prone to a lot of effects such as the number of explicit acetonitrile molecules by which the intermediate is surrounded.

Beside the energetic results, several other parameters also give valuable information about the reaction preference, such as geometries, charges, etc., which all point toward a selective ring opening at the hindered carbon atom of the aziridine moiety. These experimental results comprise a useful contribution to the chemistry of 2-substituted aziridinium salts and offer perspectives for prospective research in this area.

Experimental Section

Synthesis of 4-(*N*,*N*-Di(arylmethyl)amino)-3-bromobutanenitriles 8. As a representative example, the synthesis of 4-(*N*,*N*-dibenzylamino)-3-bromobutanenitrile **8a** is described. To a stirred solution of 1-benzyl-2-(cyanomethyl)aziridine **6a** (1.72 g, 10 mmol) in acetonitrile (15 mL) was added benzyl bromide (1.71 g, 1.0 equiv), and the resulting mixture was further stirred for 10 days at room temperature. Evaporation of the solvent afforded 4-(*N*,*N*-dibenzylamino)-3-bromobutanenitrile **8a**, which was purified by means of column chromatography (hexane/ethyl acetate 9/1) on silica gel in order to obtain an analytically pure sample. 4-(*N*,*N*-Dibenzylamino)-3-bromobutanenitrile **8a**. Yellow oil. Yield 66%. R_f = 0.26 (hexane/ethyl acetate 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67 and 3.01 (2H, 2×d×d, J = 17.3, 7.4, 3.9 Hz); 2.89 and 2.96 (2H, 2×d×d, J = 13.6, 9.8, 5.2 Hz); 3.57 and 3.71 (4H, 2×d, J = 13.5 Hz); 3.71−3.81 (1H, m); 7.27−7.40 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 43.6, 59.9, 60.5, 117.1, 127.8, 128.8, 129.2, 138.4. IR (NaCl): ν_{CN} = 2252. MS (70 eV): *m*/*z* (%): 343/5 (M^+ + 1, 30); 263 (100).

Synthesis of 4-(*N*,*N*-Di(arylmethyl)amino)-2-butenenitriles 9. As a representative example, the synthesis of 4-(*N*,*N*-dibenzylamino)-2-butenenitrile **9a** is described. To a stirred solution of 4-(*N*,*N*-dibenzylamino)-3-bromobutanenitrile **8a** (1.72 g, 5 mmol) in dichloromethane (10 mL) was added triethylamine (0.56 g, 1.1 equiv), and the resulting solution was heated under reflux for 3 h. The reaction mixture was poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 4-(*N*,*N*-dibenzylamino)-2-butenenitrile **9a** as a mixture of *E*/*Z* isomers (54/46), which was purified by means of column chromatography (hexane/dichloromethane 9/1) on silica gel in order to obtain an analytically pure sample. (*E*/*Z*)-4-(*N*,*N*-Dibenzylamino)-2-butenenitrile **9a**. Yellow oil. Yield 77%. R_f = 0.34 (hexane/CH_2Cl_2 9/1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.19 (2H, d×d, J_E = 5.3, 2.0 Hz); 3.40 (2H, d×d, J_Z = 6.0, 1.7 Hz); 3.59 (8H, s); 5.34 (1H, d×t, J_Z = 11.1, 1.7 Hz); 5.66 (1H, d×t, J_E = 16.5, 2.0 Hz); 6.55 (1H, d×t, J_Z = 11.1, 6.0 Hz); 6.73 (1H, d×t, J_E = 16.5, 5.3 Hz); 7.21−7.40 (20H, m). ^{13}C NMR (68 MHz, $CDCl_3$): δ 54.1, 54.5, 58.4, 58.7, 100.7, 100.8, 115.5, 117.3, 127.3, 127.3, 128.4, 128.4, 128.6, 128.8, 138.4, 138.6, 153.2, 153.2. IR (NaCl): ν_{CN} = 2223. MS (70 eV): *m*/*z* (%): 263 (M^+ + 1, 100); 238 (20); 210 (14); 91 (11).

Synthesis of 4-(*N*,*N*-Di(arylmethyl)amino)-3-(pyrrolidin-1-yl)-butanenitriles 10. As a representative example, the synthesis of 4-(*N*,*N*-dibenzylamino)-3-(pyrrolidin-1-yl)butanenitrile **10a** is described. To a stirred solution of 4-(*N*,*N*-dibenzylamino)-3-bromobutanenitrile **8a** (1.72 g, 5 mmol) in acetonitrile (10 mL) was added pyrrolidine (0.71 g, 2.0 equiv), and the resulting solution was heated under reflux for 3 h. The reaction mixture was poured into water (10 mL) and extracted with diethyl ether (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded 4-(*N*,*N*-dibenzylamino)-3-(pyrrolidin-1-yl)-butanenitrile **10a**, which was purified by means of column chromatography (hexane/ethyl acetate 2/1) on silica gel in order to obtain an analytically pure sample. 4-(*N*,*N*-Dibenzylamino)-3-(pyrrolidin-1-yl)butanenitrile **10a**. Yellow oil. Yield 80%. R_f = 0.23 (hexane/EtOAc 2/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68−1.78 (4H, m); 2.43−2.69 (9H, m); 3.42 and 3.75 (4H, 2×d, J = 13.3 Hz); 7.30−7.34 (10H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.6, 23.4, 51.0, 56.0, 58.8, 59.6, 119.3, 127.4, 128.5, 129.2, 138.8. IR (NaCl): ν_{CN} = 2246. MS (70 eV): *m*/*z* (%): 334 (M^+ + 1, 100).

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Supporting Information Available: Spectroscopic data of compounds **8**−**f**, **9b**−**d**,**f**, and **10b**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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