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[A0033]

Highly regioselective synthesis of functionalized aminonitriles starting from 2-(ω-cyanoalkyl)aziridines

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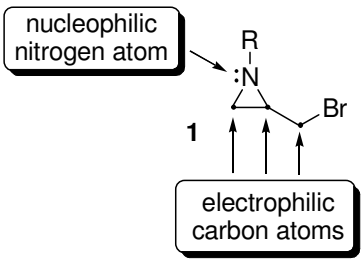
Abstract

1-arylmethyl-2-(bromomethyl)aziridines were transformed into the corresponding 2-(cyanomethyl)aziridines and 2-(2-cyanoethyl)aziridines upon treatment with potassium cyanide in DMSO and α-lithiated trimethylsilylacetonitrile in THF, respectively. Further elaboration of 1-arylmethyl-2-(cyanomethyl)aziridines afforded 4-amino-2-butenenitriles, 3,4-diaminobutanenitriles and 2-aminocyclopropanecarbonitriles. Additionally, 1-arylmethyl-2-(2-cyanoethyl)aziridines were efficiently converted into biologically relevant 2-(aminomethyl)-cyclopropanecarbonitriles.

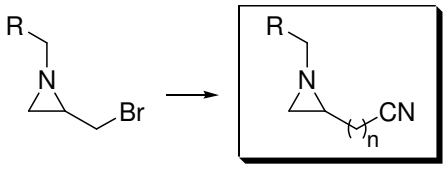
Introduction

2-(Bromomethyl)aziridines **1** comprise a peculiar and scarcely evaluated class of constrained β-halo amines with high synthetic potential due to the presence of three different electrophilic carbon atoms and the nucleophilicity of the nitrogen atom. Furthermore, these synthons can be prepared in high yield and high purity using simple and straightforward methodologies, and their relative stability allows a long shelf life.



Based on these features, 2-(bromomethyl)aziridines **1** can be considered as functional substrates in organic synthesis suitable for a plethora of organic transformations towards different classes of target compounds. However, little or no information could be found in the literature regarding their reactivity profile and their utility as building blocks, especially concerning non-activated 1-alkyl-2-(halomethyl)aziridines. These observations formed the onset of an in-depth investigation of the reactivity and applicability of 2-(bromomethyl)aziridines, which has revealed the enormous synthetic potential of these substrates in organic chemistry.[1]

One of these new methods comprised the introduction of cyanide into the aziridine side-chain, affording 2-(ω-cyanoalkyl)aziridines **3** (n = 1 or 2) as new and versatile substrates for further elaboration. This novel approach, i.e. the combination of an aziridine moiety and a nitrile group in the same framework, provides an easy and convenient entry into the emerging field of aminonitrile chemistry. Although the search for novel types of functionalized aminonitriles has gained much interest from both a biological and synthetic point of view, the systematic use of 2-(cyanoalkyl)aziridines as synthons in aminonitrile chemistry has not been evaluated so far. Besides the interesting medicinal applications of aminonitriles (e.g. pyrrolidine-2-carbonitriles as dipeptidyl peptidase IV inhibitors), aminonitriles are frequently used as substrates for the synthesis of the corresponding biologically relevant amino acids (peptidomimetics and foldamers) and amino amides (e.g. the antidepressant Milnacipran®). Consequently, there is an increasing demand for easy and straightforward synthetic approaches towards novel functionalized aminonitriles suitable for further elaboration.

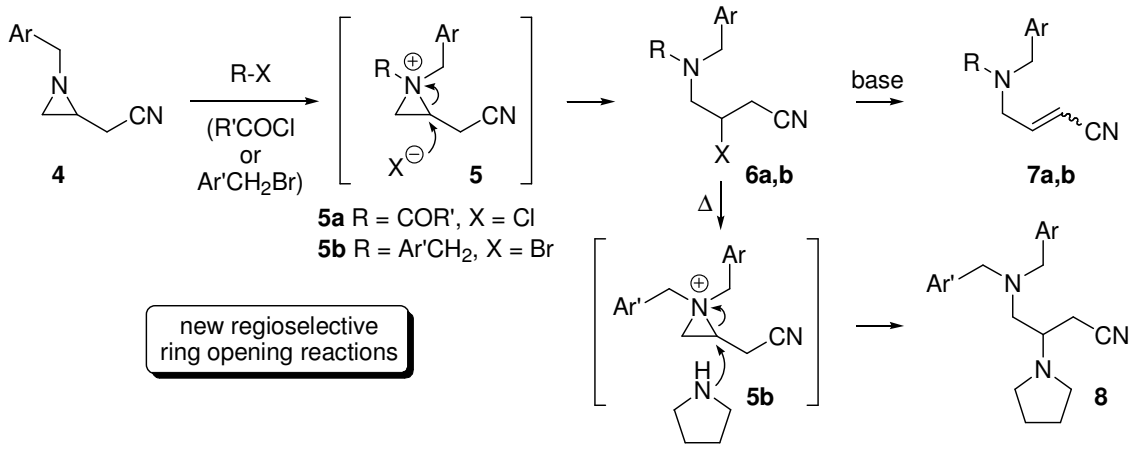


2 **3**
n = 1, 2

Results and discussion

In the present work, 2-(ω-cyanoalkyl)aziridines are evaluated as synthons for the preparation of a large variety of aminonitrile derivatives. The desired 2-(cyanomethyl)- and 2-(2-cyanoethyl)aziridines can be easily prepared from the corresponding 1-arylmethyl-2-(bromomethyl)aziridines in high yield and purity upon treatment with potassium cyanide in DMSO or α-lithiated trimethylsilylacetonitrile in THF, respectively.[1]

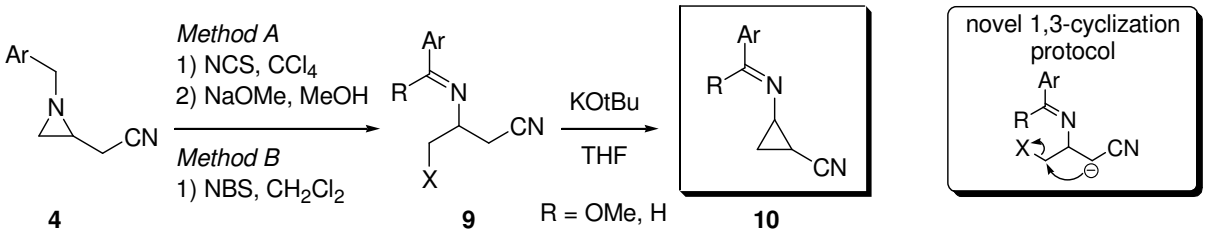
In order to provide a basis for further research, the first objective was the study of ring opening reactions of 2-(ω-cyanoalkyl)aziridines towards acyclic targets or towards intermediates for further elaboration. Whereas the ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines **4** by means of acid chlorides afforded a useful transformation into new *N*-(2-chloro-3-cyanopropyl)amides through regioselective ring opening of intermediate aziridinium salts **5** by chloride at the more hindered aziridine carbon atom,[2] the ring opening of 2-(cyanomethyl)aziridines **4** upon treatment with arylmethyl bromides provided an efficient entry into 4-amino-3-bromobutanenitriles through regiospecific ring opening of intermediate 2-(cyanomethyl)aziridinium salts by bromide, again at the more hindered aziridine carbon atom.[3] The latter approach was based on a preceding model study in which the regio- and stereoselective ring opening of chiral 2-(aryloxymethyl)aziridines was investigated.[4] In both cases, the corresponding 4-amino-2-butenenitriles **7** could be obtained easily and in high yields by dehydrohalogenation in basic medium. 4-Amino-3-bromobutanenitriles **6b** were further elaborated into 3,4-diaminobutanenitriles **8** as precursors of the biologically relevant 3,4-diaminobutanoic acids through the unprecedented regiospecific ring opening of 2-(cyanomethyl)aziridinium salts by pyrrolidine.[3]



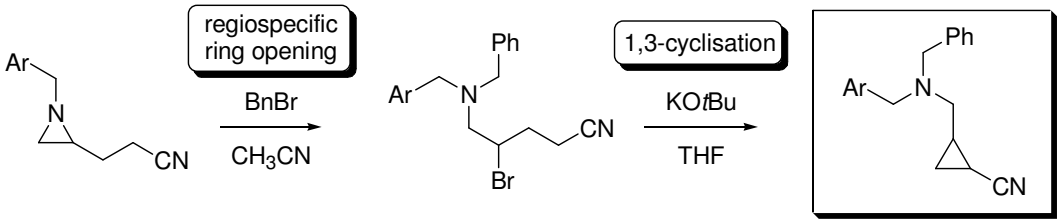
Very little information can be found in the literature with regard to the regio- and stereoselectivity of the ring opening of non-activated aziridines via intermediate aziridinium salts, and the first systematic studies in this field were performed recently.[1] The additional findings for 2-(ω-cyanoalkyl)aziridines described above, i.e. regioselective ring opening at the more hindered position by chloride, bromide and pyrrolidine, further emphasize the complementarity of non-activated aziridines with respect to their activated counterparts (dominated by ring opening at the less hindered position). These useful new insights in aziridinium chemistry were rationalized on the basis of high level *ab initio* calculations.

The second objective involved the synthesis of γ-halonitriles as suitable precursors for a novel type of 3-*exo-tet* ring closure towards cyclopropanecarbonitriles. Conformationally constrained amino acid derivatives have attracted special attention in medicinal chemistry, although synthetic approaches towards this type of compounds are rather scarce. Thus, the synthesis of conformationally constrained β- and γ-aminocyclopropanecarbonitriles as target compounds was envisaged starting from 2-(ω-cyanoalkyl)aziridines.

2-(Cyanomethyl)aziridines **4** were converted into 4-halobutyronitriles **9** either via ring opening using NCS, followed by treatment with sodium methoxide, or through ring opening with NBS. In both cases, the radical ring opening of 2-(cyanomethyl)aziridines occurred only at the unsubstituted position. The resulting γ-halonitriles **9** proved to be excellent substrates for a 3-*exo-tet* ring closure by means of potassium *tert*-butoxide in THF towards biologically relevant *N*-protected β-aminocyclopropanecarbonitriles **10**.[5] Remarkably, this type of 3-*exo-tet* ring closure had not been described previously in the literature.



The above described novel methodologies were combined successfully for the synthesis of γ-aminocyclopropanecarbonitriles **13**. 2-(2-Cyanoethyl)aziridines **11** were treated with benzyl bromide, affording 5-amino-4-bromopentanenitriles **12** through a regiospecific ring opening of intermediate aziridinium salts by bromide. Further elaboration of these γ-bromonitriles **12** resulted in the elegant synthesis of novel 2-(aminomethyl)cyclopropanecarbonitriles **13** as constrained analogues of the neurotransmitter GABA and structural derivatives of the antidepressant Milnacipran® by means of a 1,3-cyclisation protocol upon treatment with KO*t*Bu in THF.[6]



11 **12** **13**

In conclusion, the above mentioned synthetic applications of both 2-(cyanomethyl)- and 2-(2-cyanoethyl)aziridines have paved the way for further research in the field of aminonitrile chemistry. It is clear that the chemistry of 2-(ω-cyanoalkyl)aziridines is still an emerging area of research and, undoubtedly, many other interesting transformations will be described in the future.

References

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