

DSM Science & Technology Awards 2007

Name	Matthias D'hooghe
University	Ghent University (B)
Department	Faculty of Bioscience Engineering, Department of Organic Chemistry
PhD Supervisor	Prof. Dr. Ir. N. De Kimpe

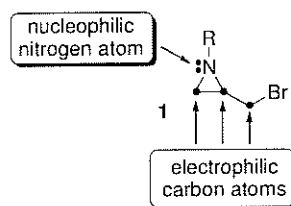
2-(Bromomethyl)aziridines as versatile building blocks in organic chemistry

Matthias D'hooghe

*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University,
Coupure Links 653, B-9000 Ghent, Belgium
matthias.dhooghe@UGent.be*

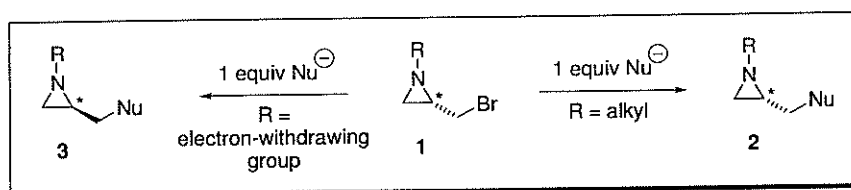
Abstract: The chemistry of the unexplored class of 2-(bromomethyl)aziridines has been evaluated thoroughly, resulting in a set of new and useful synthetic tools for the preparation of different types of nitrogen-containing compounds. The versatility of 2-(bromomethyl)aziridines has been demonstrated by the synthesis of a large variety of different target compounds with potential biological activity due to their structural resemblance to other compounds with known activity. In this way, it was shown that the use of 2-(bromomethyl)aziridines offers promising perspectives for potential industrial applications in the field of medicine and crop protection.

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. This inherent reactivity can result in a plethora of organic transformations towards different classes of target compounds. 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 suitable and functional substrates in organic chemistry.

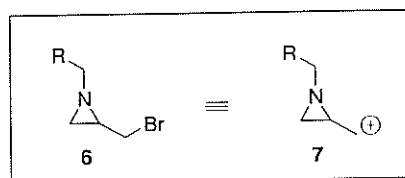
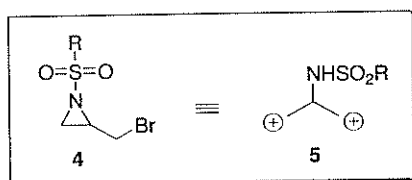


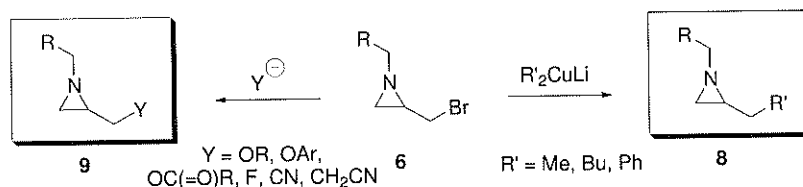
However, the study of 2-(halomethyl)aziridines is still an underdeveloped area in organic chemistry. Especially for the non-activated 1-alkyl-2-(halomethyl)aziridines, little or no information can be found in the literature regarding their reactivity profile and their utility as building blocks. Consequently, an in-depth investigation of the reactivity and synthetic potential of both activated and non-activated 2-(halomethyl)aziridines is of significant importance in order to provide a general view on their scope and limitations in organic synthesis.

The first part of this work comprised an extensive evaluation of the reactivity of activated 1-sulfonyl- and non-activated 1-alkyl-2-(bromomethyl)aziridines. A comparative study between the behavior of activated versus non-activated 2-(bromomethyl)aziridines upon treatment with *one equivalent of a nucleophile* revealed a totally different yet complementary reactivity profile. This study showed that non-activated 1-alkyl-2-(bromomethyl)aziridines **1** (R = alkyl) undergo direct S_N2 substitution at the halogenated carbon atom with retention of configuration towards aziridines **2**, whereas activated 1-sulfonyl-2-(bromomethyl)aziridines **1** (R = EWG) suffer from ring opening – ring closure with inversion of configuration towards aziridines **3**.¹ These observations are of significant importance whenever asymmetric synthesis towards chiral targets compounds is contemplated, e.g. starting from chiral substrates **1**, as the availability of straightforward asymmetric approaches towards single enantiomers has become indispensable in for example the preparation of new drugs.



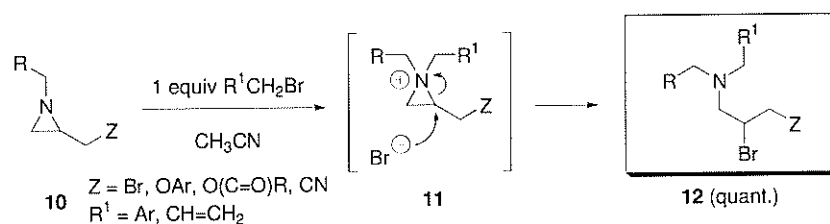
Treatment of 1-sulfonyl- and 1-alkyl-2-(bromomethyl)aziridines with *two or more equivalents* of different types of carbon-centered and heteroatom-centered nucleophiles has resulted in a different applicability, pointing to the conclusion that 2-(bromomethyl)-1-sulfonylaziridines **4** can be used successfully as synthetic equivalents for the 2-aminopropane dication synthon **5**^{2,3} towards α -branched *N*-tosylamides, whereas 1-alkyl-2-(bromomethyl)aziridines **6** can be considered as synthetic equivalents for the aziridinylmethyl cation synthon **7**⁴ towards the preparation of a large variety of 2-substituted aziridines. The latter equivalency has been exploited for the coupling between 1-alkyl-2-(bromomethyl)aziridines and organocuprates as a novel protocol towards the synthesis of 1,2-dialkylaziridines **8**,⁴ as well as the substitution by a variety of (heteroatom centered) nucleophiles towards the corresponding 2-substituted aziridines **9**. For example, this has led to the synthesis of novel 2-(fluoromethyl)aziridines and 2-(2-cyanoethyl)aziridines as versatile substrates for further elaboration, which is currently under investigation.





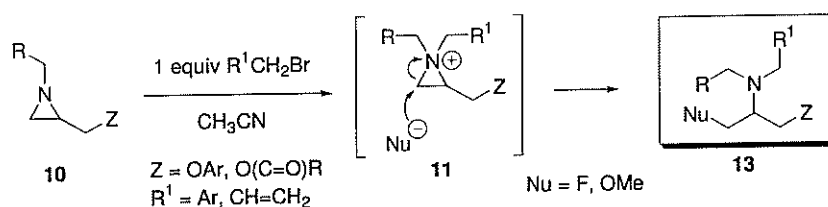
It is clear that the central element in the comparison between activated and non-activated 2-(bromomethyl)aziridines comprises the stability of the aziridine ring as compared to the reactivity of the halogenated carbon atom. The most reactive centre in 1-alkyl-2-(bromomethyl)aziridines **6** is the brominated carbon atom, whereas in 1-sulfonyl-2-(bromomethyl)aziridines **4** the aziridine moiety is the most electrophilic part.

Since 1-alkylaziridines have to be 'activated' prior to ring opening, *N*-alkylation towards aziridinium salts constitutes a powerful method for the transformation of 1-alkylaziridines into acyclic target compounds. However, very little systematic studies on this topic are available in the literature. A central theme in this research work involved the study of 2-substituted aziridinium salts as reactive intermediates in organic synthesis. Special attention was devoted to the regio- and stereoselectivity of the ring opening of 2-substituted aziridinium salts **11**, derived from the corresponding 1-alkylaziridines **10**, by bromide in acetonitrile. The applicability of this transformation has been demonstrated by the synthesis of a large variety of β -bromo amines **12** in a regiospecific way via ring opening of the intermediate aziridinium salts **11** at the more hindered aziridine carbon atom.^{5,6,7} These β -bromo amines **12** served as substrates for the preparation of biologically relevant target compounds (*vide infra*). The use of enantiomerically pure aziridines acknowledged the stereospecificity of this transformation, in accordance with an S_N2 type reaction mechanism.⁸ The regio- and stereospecificity of this transformation was rationalized on the basis of high level *ab initio* calculations (Gaussian 03).

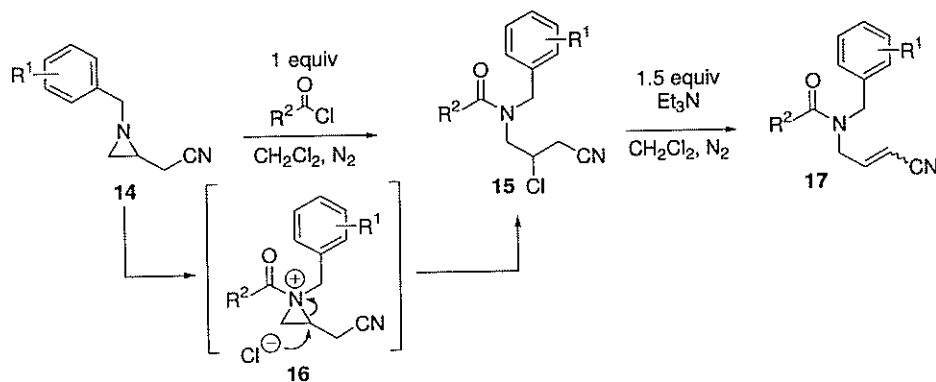


Recently, the regiospecific ring opening of aziridinium salts **11** (with Z = CN) by pyrrolidine at the more hindered aziridine carbon atom has been observed to afford 4-(*N,N*-di(arylmethyl)amino)-3-(pyrrolidin-1-yl)butanenitriles in excellent yields. In the literature, there are no reports on the regioselective ring opening of 2-substituted aziridinium salts, different from 2-acyl- and 2-arylaziridines, by amines at the more hindered aziridine carbon atom.⁹

In contrast with the ring opening by bromide and pyrrolidine, an opposite regioselectivity was observed in the ring opening of the same aziridinium salts **11** by methoxide⁶ and fluoride,⁷ resulting in the formation of 2-aminopropane derivatives **13** as the main reaction products via ring opening of the intermediate aziridinium salts **11** at the less hindered aziridine carbon atom. Functionalized amines **13** are of particular importance in pharmaceutical sciences (*vide infra*).



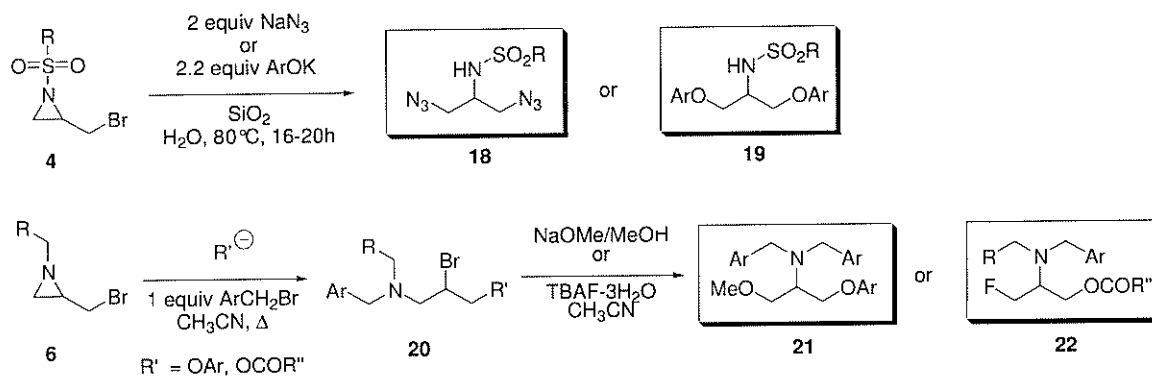
Furthermore, the ring opening of 2-(cyanomethyl)aziridines **14** by means of acid chlorides has been studied, affording new *N*-(2-chloro-3-cyanopropyl)amides **15** through ring opening of intermediate aziridinium salts **16** with preferential attack of chloride at the more hindered aziridine carbon atom. β -Chloro nitriles **15** were subsequently converted into novel *N*-(3-cyano-2-propenyl)amides **17** by means of a dehydrochlorination reaction.¹⁰ The latter compounds can have potential applications as structural unsaturated analogues of the neurotransmitter γ -aminobutyric acid (GABA).



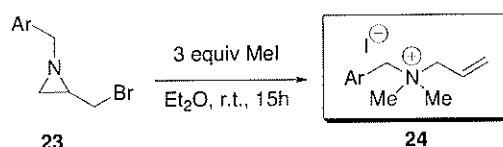
Due to the broad applicability of 1,2,3-triheteroatom substituted propane derivatives in medicinal chemistry, for example as β -blockers (propranolol, atenolol, metoprolol) and as antibiotics (chloramphenicol, thiamphenicol and florfenicol), the conversion of both 1-sulfonyl- and 1-alkyl-2-(bromomethyl)aziridines **4** and **6** into a wide variety of aminopropane derivatives has been evaluated thoroughly using the methodologies described above.

In this way, 1-sulfonylaziridines **4** have been converted into 2-aminopropane derivatives **18** and **19** by means of a novel environmentally benign protocol in water,³ and 1-alkyl-2-(bromomethyl)aziridines **6** have been transformed in β -bromo amines **20** and subsequently

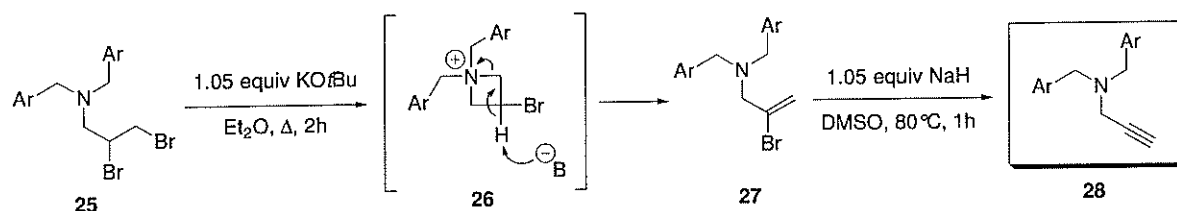
into aminopropanes **21** and **22** via intermediate aziridinium salts and substitution reactions.^{6,7} The incorporation of a β -fluoro amine moiety into a 1,2,3-triheteroatom substituted propane skeleton has led to the discovery of a new class of powerful antimicrobial agents (e.g. florfenicol), and novel approaches towards analogues such as **22** are thus of importance in medicinal chemistry.



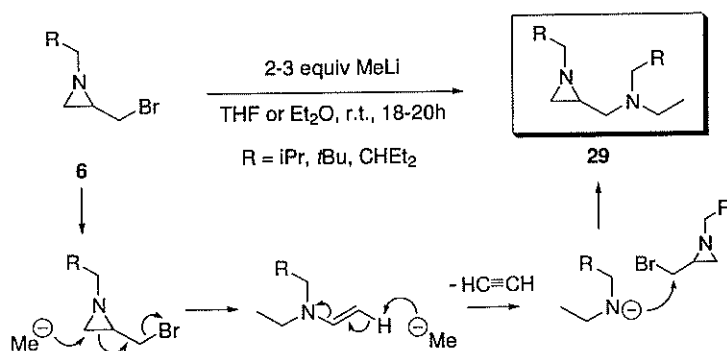
Furthermore, three remarkable transformations have been observed in the study of the reactivity of 1-alkyl-2-(bromomethyl)aziridines. The first reaction involved ring opening of 2-(bromomethyl)aziridinium salts by means of iodide via a halophilic reaction, affording a novel approach towards allylammonium salts **24**,¹¹ which have important applications in agriculture as for example plant growth regulators.



Secondly, an unexpected transformation of dibromopropylamines **25** into vinyl bromides **27** has been observed, and the intermediacy of 3-bromoazetidinium salts **26** in this novel analogue of the Hofmann elimination was irrefutably proven by means of an independent synthesis.⁵ The applicability of vinyl bromides **27** has been demonstrated by their conversion into propargyl amines **28**, the latter being known as inhibitors of the enzyme monoamine oxidase (MAO), which makes them potential drugs for treatment of neurotic, psychiatric and other disorders such as depression, Parkinson's disease and Alzheimer's disease. A Yamaguchi-Hirao alkylation, a Sonogashira coupling or a hydroarylation reaction further functionalized these propargylamines **28** towards potentially interesting compounds for medicinal and agrochemical use.⁵

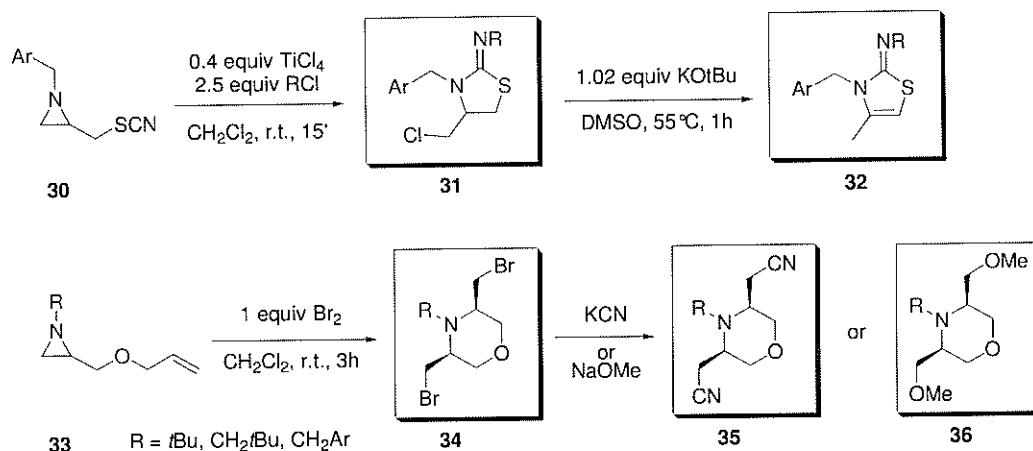


The third remarkable reaction involved treatment of 1-alkyl-2-(bromomethyl)aziridines **6** with methyl lithium, affording – totally unexpected – 2-(aminomethyl)aziridines **29**. The peculiarity in this transformation comprises the presence of an *N*-ethyl group in the end-products as well as the total number of carbon atoms, resulting from a highly unusual reaction course with a novel S_N2'-type substitution at the aziridine moiety and liberation of acetylene from an intermediate vinylamine as the key reaction steps.¹²

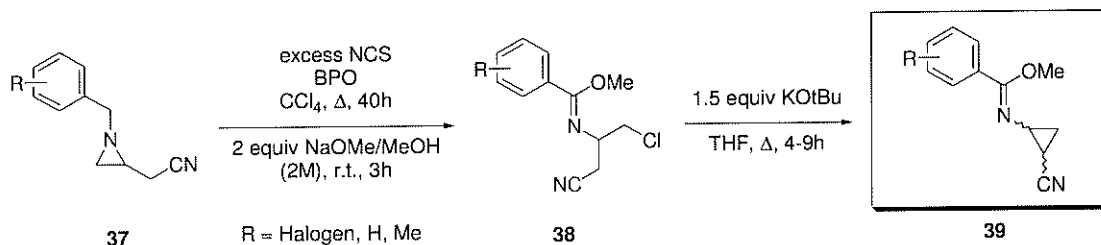


A different part of this work comprised the elaboration of 1-alkyl-2-(bromomethyl)aziridines towards other (azahetero)cyclic compounds.

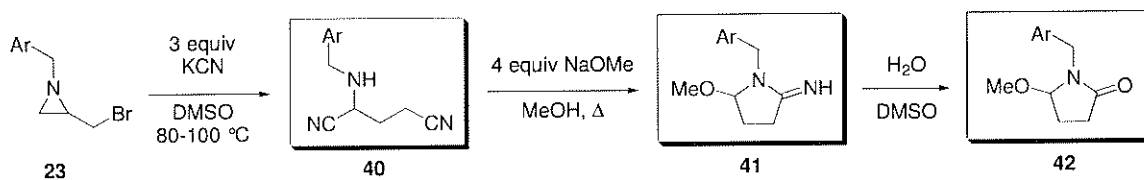
This has resulted in the development of a novel protocol for the synthesis of 2-iminothiazolidines **31** and 2-iminothiazolines **32**, compounds known for their anti-inflammatory, antimicrobial, antihistaminic, antihypertensive, anticonvulsant and anti-Alzheimer activity and their use as pesticides, by Lewis acid mediated ring expansion of 2-(thiocyanomethyl)aziridines **30**.¹³ Furthermore, 2-(allyloxymethyl)aziridines **33** have been transformed diastereoselectively into *cis*-3,5-disubstituted morpholine derivatives **34** (proven by X-ray analysis) and the corresponding substitution products **35** and **36** for the first time.¹⁴ The interest in the synthesis of carbon-substituted morpholine derivatives results from their applicability in medicine (antidepressants, appetite suppressants, antitumor agents, antioxidants, antibiotics, anti-HIV) and agriculture (fungicides).



In a totally different approach, 2-(cyanomethyl)aziridines **37** were transformed into suitable substrates **38** for a novel type of 3-*exo-tet* ring closure towards methyl N-(2-cyanocyclopropyl)benzimidates **39**,¹⁵ the latter being of interest as precursors of biologically relevant 2-aminocyclopropanecarboxylates or β -ACC derivatives with promising applications in peptide chemistry.



Finally, 1-Arylmethyl-2-(bromomethyl)aziridines **23** were transformed into 2-aminopentanedinitriles **40** via an unprecedented reaction mechanism upon treatment with an excess of potassium cyanide. The thus obtained 2-aminopentanedinitriles **40** can be considered as derivatives of the naturally occurring neurotransmitter glutamic acid, and served as substrates for the synthesis of novel 2-imino-5-methoxypyrrolidines **41** as an unexplored class of heterocycles with potential applications. The latter 2-iminopyrrolidines were further hydrolyzed towards the corresponding synthetically relevant 5-methoxypyrrolidin-2-ones **42** as precursors for cyclic *N*-acyliminium intermediates.⁹



In conclusion, a variety of different reactions and transformations of 2-(bromomethyl)aziridines has been elaborated in order to demonstrate the synthetic potential of these substrates in organic chemistry. This has resulted in the synthesis of no less than 200 novel compounds with potential applications in different fields. It is clear that the chemistry of 2-(halomethyl)aziridines is still an emerging area of research and, undoubtedly, many other interesting transformations will be described in the future.

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