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Application of aziridines for the synthesis of isoquinoline derivatives

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Aziridines are attractive and versatile building blocks in organic synthesis and medicinal chemistry because they allow convenient access to useful nitrogen-containing biologically active compounds. Many aziridine-containing compounds demonstrate very useful pharmacological activity including anticancer, antibacterial, antimicrobial activity, etc. strongly indicating that the presence of the aziridine ring in natural as well as synthetic compounds is essential for such activities. Chiral aziridines have found widespread use in organic synthesis. This manuscript shows variety of methods for the synthesis and ring0opening of three-membered aziridines and their application for the synthesis of six-membered isoquinolines.

***Keywords**: aziridines, synthesis, biological activity, isoquinolines*

BIOLOGICAL IMPORTANCE OF AZIRIDINES RING-SYSTEM

Small heterocyclic ring systems are of central importance in theoretical, synthetic organic, bioorganic, and medicinal chemistry, and in particular aziridines are very useful and interesting systems as they occur in a number of natural and biologically active substances [1-7]. Aziridines are highly valuable heterocyclic compounds and are widely used during the synthesis of numerous drugs and biologically active natural products (and their derivatives) [8–13]. Over 100 biologically active aziridine-containing compounds demonstrate confirmed pharmacological activity including antitumor, antimicrobial, and antibacterial effects [14].

While the aziridine group is known as a useful reaction intermediate [15, 16], it is also an interesting structural fragment in bioactive compounds. The aziridine's proton accepting properties, its rigidity and its potential reactivity can all contribute to specific molecular interactions with proteins, and indeed several important natural products such as mitomycin C [17], porfiromycin [18], and carzinophilin A [19] contain the aziridine functionality. A number of saccharide derivatives containing the aziridine group have been made, mostly as intermediates [20], but also as glycosidase inhibitors [21].

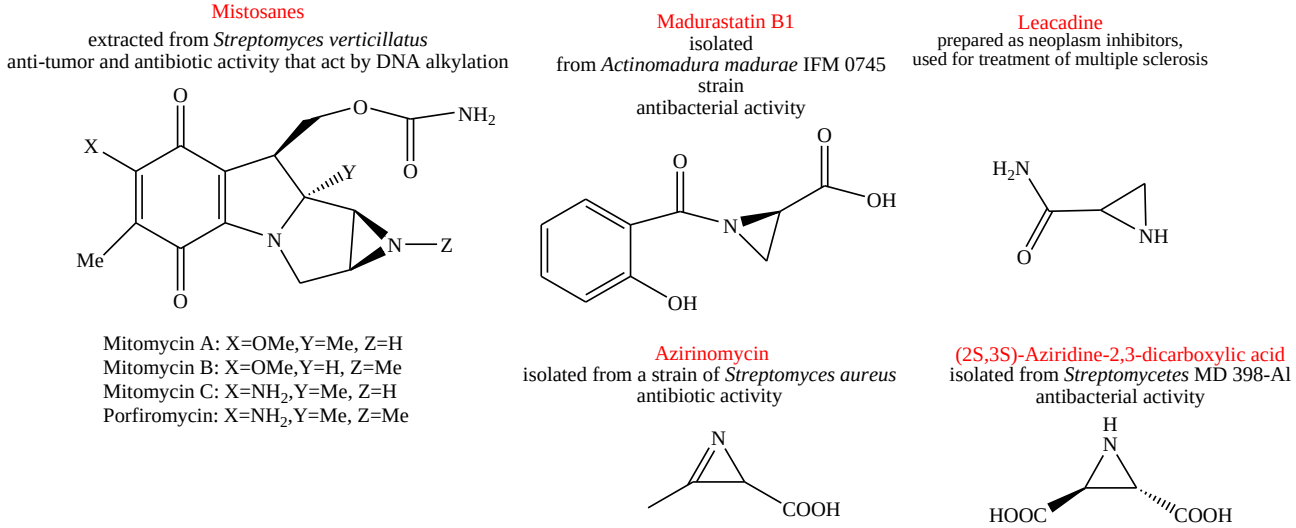

Fig. 1. Natural products containing an aziridine ring fragment.

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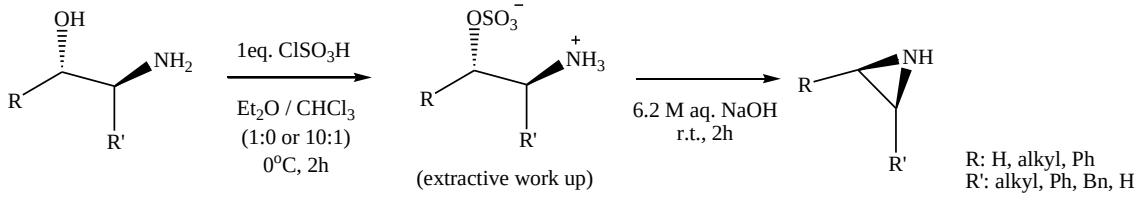
The toxicity of aziridine derivatives will depend on its own structure and activity whilst sharing the general characteristics of the aziridine group. As powerful alkylating agents, aziridines have an inherent in vivo potency [22, 23]. Mitomycins and porfiromycin, generally nonreactive in the natural oxidized state, behave as bifunctional 'alkylating' agents upon chemical or enzymatic reduction [24]. As an electrophile, substituted aziridines are subject to attack and ring-opening by endogenous nucleophiles such as nitrogenous bases in DNA base pairs, resulting in potential mutagenicity [22, 23]. Aziridine alkaloids also belong to a rare and somewhat neglected group of natural products which are known to play a seminal role in the secondary metabolism of some micro-organisms, plants and various marine organisms [25]. The aziridine-containing compounds have been of interest as both immuno-modulatory and anticancer agents since the late 1950s [26]. Polymerization products of ethylenimine, their polymerizable homologs, as well as substitution products were considered useful for disinfecting [27–29]. Aziridines are inherently strained making them attractive for study because they allow for convenient access to amines, amino alcohols, diamines, and other useful nitrogen-containing molecules. Chiral aziridines have found widespread use in organic synthesis. [30−33] The development of efficient and stereoselective methods for synthesis of aziridines is an inviting challenge in organic synthesis. General approaches to the asymmetric synthesis of aziridines through cyclization methods can be divided into two main categories: (A) nitrogen nucleophilic cyclization on the adjacent position bearing a leaving group and (B) ring closure to three-membered ring via attack of a stabilized carbanion on the electrophilic nitrogen bearing a leaving group [34].

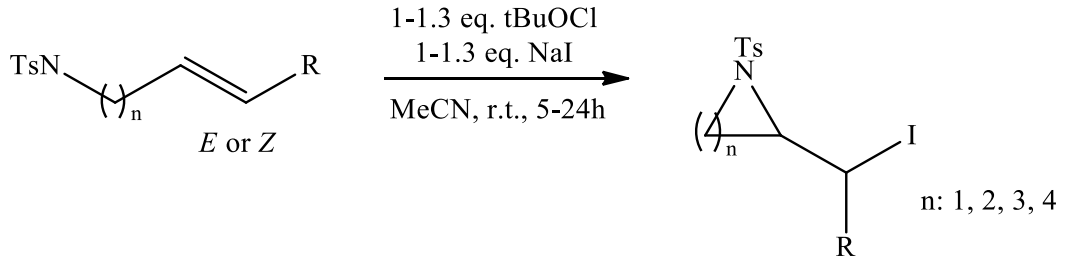
METHODS FOR AZIRIDINE SYNTHESIS

The synthesis of an aziridine derivative is most frequently accomplished in a two-step synthesis from a suitably substituted β-amino alcohol. Instead of classical and well-known Gabriel and Wenker reactions, a lot of reactions have been recently discovered. The De Kimpe Azirdine Synthesis allows the generation of various aziridines by the reaction of α-chloroimines with nucleophiles such as hydride, cyanide, or Grignard reagents. Denolf *et al.* [35] reported the Asymmetric Synthesis of Aziridines by Reduction of N-tert-Butanesulfinyl α-Chloro Imines. Amino alcohols were converted into their hydrogen sulfates with chlorosulfonic acid. Li *et al.* used improved, mild variation of the typical Wenker synthesis for the synthesis of aziridines [36] (.Scheme 1.)

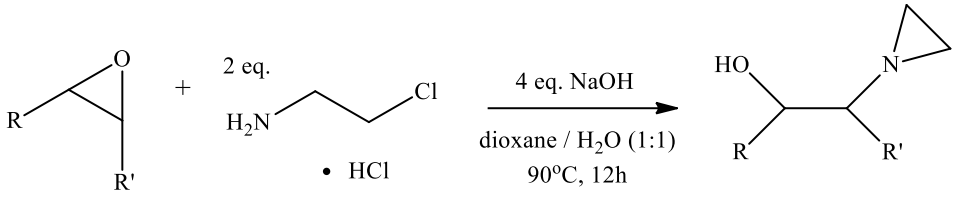
Bieber presented two alternative and complementary one-pot procedures for the direct transformation of 2-amino alcohols to *N*-tosyl aziridines [37]. The authors found that less hindered aziridines can be obtained in high yields by tosylation and in situ cyclization affected by potassium hydroxide in water/dichloromethane. Minakata *et al.* [38] used *tert*-butyl hypoiodite as a mild and powerful reagent for the cyclization of *N*-alkenylamides leading to various *N*-heterocycles. *N*-alkenylsulfonamides gave three- to six-membered saturated *N*-heterocycles in good yields, whereas alkenylbenzamide derivatives afforded *N*-, O- or *N*-, *S*-heterocycles (.Scheme 2.).



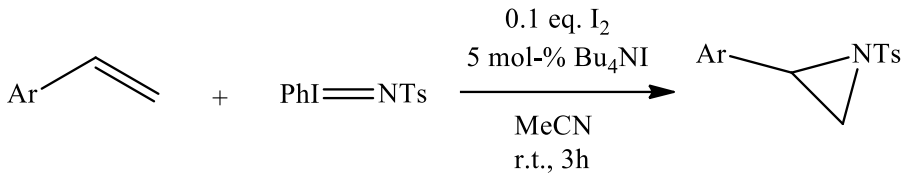
Scheme 1



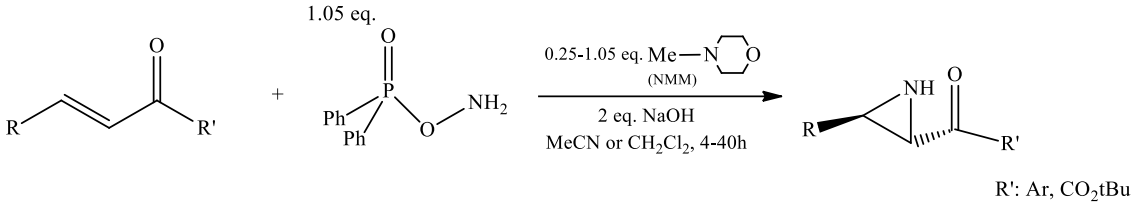
Scheme 2



Scheme 3



Scheme 4

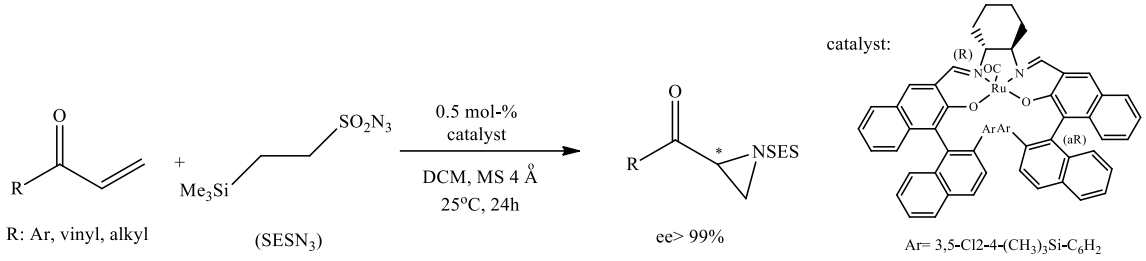


Scheme 5

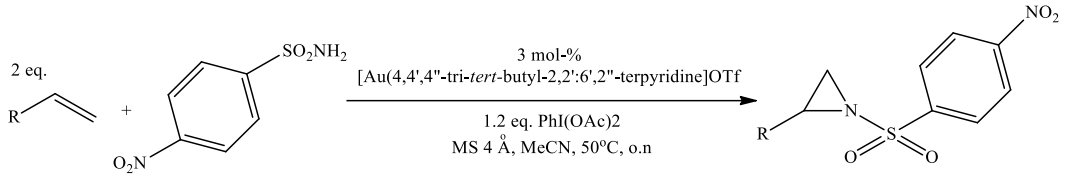
Biologically important *N*-β-hydroxyethylaziridine intermediates were conveniently prepared by regioselective ring-opening reactions of various epoxides with *in situ*-generated ethyleneimine from β-chloroethylamine under basic conditions in an aqueous environment [39] (Scheme 3).

Vinylaziridines are useful and versatile synthetic intermediates, as the relief of ring-strain provides a driving force for efficient ring-opening or ring-expansion reactions. Furthermore, the vinyl group can be derivatized into interesting functionalities. The ring-closure of vicinal amino alcohols constitutes a straightforward route to aziridines. Several methods exist for this transformation, although many cannot be applied to vinylaziridines due to their acid lability. This comparative study describes the most effective sequences for the formation of N–H vinylaziridines [40]. Hodgson *et al.* recently used reaction of *N*-(2-chloroethylidene)-*tert*-butylsulfinamide with Grignard reagents or organoceriums gives terminal *N*-tert-butylsulfinyl aziridines in good yields and with organoceriums good diastereomeric ratios [41]. The authors also found that oxidation of terminal *N*-*tert*-butylsulfinyl aziridines provides synthetically useful terminal *N*-Bus (Bus = *tert*-butylsulfonyl) aziridines. Azzena used BH_3 complexation of *N*-alkyl-2-phenylaziridines to promote a regioselective β-lithiation. The lithiated intermediates were configurationally stable, allowing an enantioselective preparation of *cis*-2,3-disubstituted aziridines. The structure and stereochemistry of the synthesized BH_3 complexes have been proved with DFT calculations and NMR experiments [42]. A mild, efficient, and selective aziridination of olefins with *p*-toluenesulfonamide catalyzed by dirhodium(II) caprolactamate is described. Aziridine formation occurs through aminobromination and subsequent base-induced ring closure [43]. A metal-free catalytic aziridination of styrene derivatives with *N*-tosyliminophenyliodinane (PhI=NTs) is promoted by a combination of I_2 and tetrabutylammonium iodide (TBAI). $TBAI_3$ as highly efficient catalyst as well as *N*,*N*-diiodotosylamide as actual aziridination reagent are generated in situ [44] (Scheme 4).

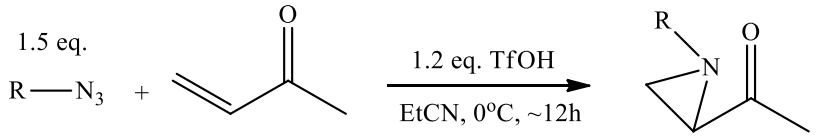
N-N ylides for the aziridination of a range of enone systems can be prepared by in situ amination of a tertiary amine. The amine may be used sub-stoichiometrically, and promising levels of enantioselectivity are observed with quinine as promoter [45] (Scheme 5).



Scheme 6



Scheme 7



Scheme 8

Recently, Fukunaga reported that aziridination of vinyl ketones using $SESN_3$ in the presence of a Ru(CO)-salen complex provides synthetically useful enantiopure aziridinyl ketones. A formal asymmetric synthesis of (+)-PD 128907 was achieved in an eight-step sequence via aziridination [46] (Scheme 6).

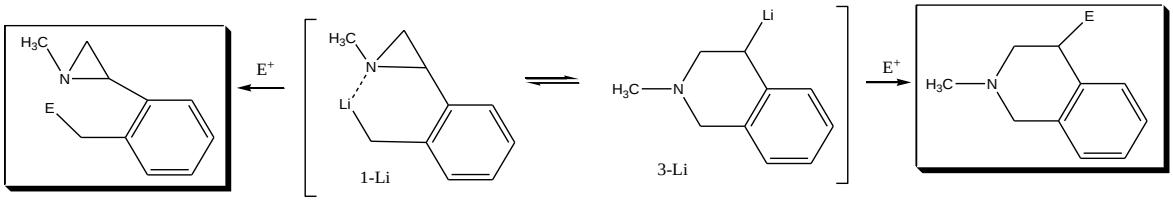
Chen reported an efficient and practical aminohalogenation and *in situ* intramolecular S_N2 substitution of α,β-unsaturated esters and ketones gave *N*-*p*-tosyl-aziridine-2-ketones and carboxylates in moderate to good yields and excellent *anti* stereoselectivity [47]. Triethylamine was found to be an effective base for the in situ cyclization for most substrates. Li *et al.* used a gold(I) compound, supported by 4,4',4"-tri-tert-butyl-2,2':6',2"-terpyridine (*t*Bu_3tpy) as the ligand for efficient catalyzis of olefin aziridination [48] (Scheme 7).

Complementary to existing routes, the Lewis acid catalyzed reactions of phenyldiazomethane with α-imino esters selectively produce *cis*-aziridine-2-carboxylates without competitive formation of enamino ester or carbene dimer byproducts [49]. An electrochemical aziridination process is described that delivers a nitrene functionality to olefins from *N*-aminophthalimide. Remarkably, both electron-rich and electron-poor olefins are converted to aziridines with high efficiency [50]. A straightforward synthesis of aziridines is reported from electron-rich azides, electron-deficient olefins, and triflic acid in cold acetonitrile [51]. Ester substrates bearing a nucleophilic carbonyl give products of an olefin aminohydroxylation (Scheme 8).

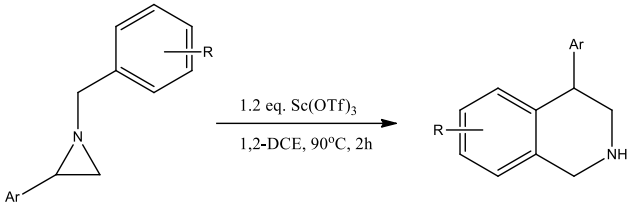
Baumann and Baxendale reported preparation of azirines from oxime precursors via mesylation and base-promoted cyclisation [52].

AZIRIDINES RING-OPENING

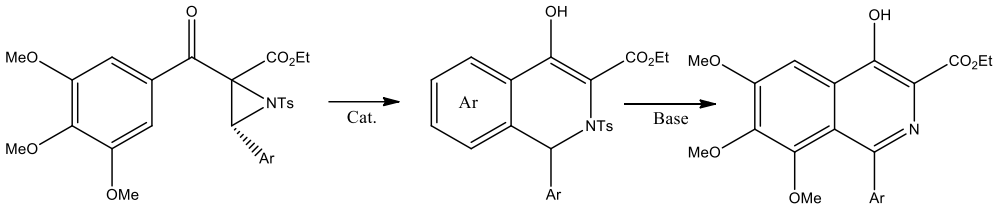
The recent studies on the chemistry of three-membered nitrogenous heterocycles [62] demonstrated the importance of this methodology to the preparation of other nitrogen- containing heterocycles. Nitrogen-containing heterocycles are ubiquitous in natural products, as well as in drugs and drug candidates.[53-55] Among nitrogenous heterocycles, the tetrahydroisoquinoline core represents a relevant structural motif frequently found in natural products and biologically active compounds.[56-59] Of the various synthetic approaches to nitrogenous heterocycles, the use of organometallic compounds has recently emerged as a particularly robust methodology [60, 61]. Recently, Giovine *et al.* reported synthesis of 1,2,3,4-Tetrahydroisoquinolines by microreactor-mediated thermal isomerization of laterally lithiated arylaziridines [63] (Scheme 9).



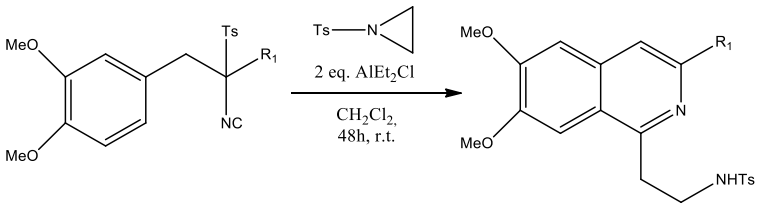
Scheme 9.



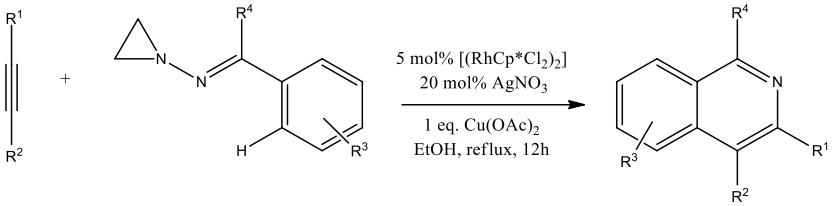
Scheme 10



Scheme 11



Scheme 12



Scheme 13

Scandium(III) triflate mediated intramolecular ring expansion of aziridineswas used also as a direct access to 4-aryltetrahydroisoquinolines [64] (Scheme 10).

Wei and Zang reported a cascade ring opening/cyclization of aziridines with catalyst $Yb(OTf)_3$ [65] (Scheme 11).

Gutierrez *et al.* successfully used the addition to the α–benzyl TosMIC derivative with N-tosylaziridine and $AlEt_2Cl$ to yielded isoquinoline in 68% yield. Similar results were obtained in the reaction of N-tosyl aziridine and the α-benzyl TosMIC derivatives [66] (Scheme 12).

Huang *et al.* used rhodium-catalyzed synthesis of isoquinolines.through selective cleavage of the N−N bond or the C=N bond followed by sequential C−H activation and cyclization with internal alkynes [67] (Scheme 13).

CONCLUSIONS

Natural and/or synthesized aziridine-containing compounds have shown to be promising candidates for the development of new drugs toward several diseases, especially neoplasms. No doubt incorporaton of an aziridine warhead will allow development of interesting new synthetic and semi-synthetic compounds with clinical utility.

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ПРИЛОЖЕНИЕ НА АЗИРИДИНИ ЗА СИНТЕЗ НА ИЗОХИНОЛИНОВИ ПРОИЗВОДНИ

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(Резюме)

Азиридините са разнообразни структурни елементи, използвани в органичния синтез и медицинската химия, тъй като позволяват удобен достъп до полезни азот-съдържащи и биологично-активни вещества. Много азиридин-съдържащи съединения проявяват фармакологична активност, в това число противоракова, антибактериална, антимикробна и др., доказващи че азиридиновият пръстен е отговорен за проявената активност. Хиралните азиридини са често употребявани в органичния синтез. Статията описва синтезът и отварянето на тричленният пръстен на азиридините и употребата им за синтез на шестчленни изохинолини.

***Ключови думи**: азиридини, синтез, биологична активност, изохинолини*