Review

Non-Aziridination Approaches to 3-Arylaziridine-2-carboxylic Acid Derivatives and 3-Aryl-(aziridin-2-yl)ketones

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Abstract: Highly functionalized aziridines, including compounds with aromatic moieties, are attractive substrates both in synthetic and medical areas of chemistry. There is a broad and interesting set of synthetic methods for reaching these compounds. Aziridination represents the most explored tool, but there are several other more specific, less well-known, but highly promising approaches. Therefore, the current review focuses on recently described or updated ways to obtain 3-arylated aziridines via different non-aziridination-based synthetic methods, reported mainly since 2000. The presented methods belong to two main directions of synthesis, namely, cyclization of open-chain substrates and rearrangement of other heterocycles. Cyclization of open-chain substrates includes the classic Gabriel-Cromwell type cyclization of halogenated substrates with amines, base-promoted cyclization of activated aminoalcohols (or its analogues), and the oxidative cyclization of β-dicarbonyls. Rearrangements of other heterocycles are presented as the Baldwin rearrangement of 4-isoxazolines, the cycloaddition of 1,3-dipoles or dienes to 2H-azirines, and the oxidative cyclization of β-dicarboxyls.

Keywords: aziridines; 4-isoxazolines; azirines; cyclization; cycloaddition; Baldwin rearrangement

1. Introduction

Finding new potential antiviral, antibacterial, and anti-cancer drugs, as well as the development of efficient methods to synthesize building blocks for them, is one of the most important problems in synthetic and medical chemistry. Due to the high reactivity of the strained aziridine ring, derivatives of aziridine-2-carboxylic acid react with various nucleophilic agents. Therefore they remain interesting synthetic substrates for constructing different amino acids including unnatural amino acids and different heterocyclic compounds [1]. Some derivatives of aziridine-2-carboxylic acid, e.g., imexon, azimexon [2], and leakadine [3], have been explored as anti-cancer immunomodulators.

Highly functionalized, especially with aromatic moieties, aziridine-2-carboxylic acid derivatives are now in the focus of interest because their close analogues—aromatic α,β-unsaturated carboxylic acids, such as caffeic acid [4] and its esters [5]—have demonstrated cytotoxic effects and enhancement of apoptosis in lung carcinoma cells. Their analogue, p-coumaric acid, features an anti-angiogenic effect [6]. Angiogenesis is necessary for tumor development. Therefore antiangiogenetic properties also may be a background of antitumor drug design.

In this light, the combination of (1) potential properties of specific apoptotic and antiangiogenic effects of α,β-unsaturated β-arylated compounds and (2) cytotoxic and possible immunomodulating activity of aziridine-2-carboxylates in the same drug-candidate molecule should be a promising direction in the search for new antitumor agents. Based on these considerations, 3-arylated derivatives of aziridine-2-carboxylic acid 1a,b (Scheme 1)
are attractive as potential anticancer and antibacterial drug candidates and building blocks for the development of small-molecule-based, relatively inexpensive medications.

There is a series of general reviews summarizing the recent advances in the synthesis of aziridine-2-carbonyl compounds (Zalubovskis and Ivanova [7]) and general aziridine synthesis and chemistry (Singh [8] and Luisi [9]). The universal methods for the construction of these compounds are via aziridination, elucidated in our previous review [10]. In contrast, this review is focused on selected methods to obtain the same 3-arylated aziridines 1a–c using different, specific approaches. In general, two main directions of synthesis are presented (Scheme 1):

- **Cyclization of open-chain substrates**
- **Rearrangement of other heterocycles**

Cyclization of open-chain substrates includes the classic Gabriel-Cromwell type cyclization of halogenated substrates 2 and 3 with amines, base-promoted cyclization of activated aminoalcohols or its analogues 4–6, and oxidative cyclization of β-dicarbonyls 7 (Scheme 1).

Rearrangements of other heterocycles are presented as the Baldwin rearrangement of 4-isoxazolines 8, the cycloaddition of 1,3-dipoles or dienes to 2H-azirines 9, and the addition of C- and N-nucleophiles to the double bond of azirines 10 (Scheme 1).

In some cases, these methods allow the necessary specific 3-arylated aziridine products to be obtained from easily accessible substrates and may show appropriate chemoselectivity.

**Scheme 1.** Non-aziridination approaches for aziridines 1a–c.
2. Cyclization of Open-Chain Substrates

2.1. Classic Gabriel-Cromwell Type Cyclization of Halogenated Substrates

The most popular and well-explored synthetic method for obtaining aziridines in general, especially 3-aryl substituted aziridines including (2-aziridinyl) ketones $1a$, aziridine-2-carboxylates $1b$ and carboxamides $1c$ is the cyclization of dihalogen derivatives $2$ and halogenated olefins $3$ with amines. The first 3-aryl-(2-aziridinyl) ketones $1a$ were reported by Cromwell and co-workers in 1943 [11] (Scheme 2).

\[
\begin{align*}
2a & \quad \text{A: 2 eq R-NH}_2, \\
& \quad 0 \degree C, 1 \text{ d} \\
& \quad R = \text{Bn, cyclohexyl} \\
3a & \quad \text{B: 2 eq ChNH}_2, \\
& \quad 0 \degree C, 1 \text{d} \\
& \quad R = \text{cyclohexyl} \\
1a & \quad 52-54\%
\end{align*}
\]

Scheme 2. Cromwell cyclization of substrates $2a$ and $3a$.

Aziridine ketones $1a$ were obtained from $\alpha,\beta$-dibromo-benzyl-acetophenone $2a$ (Scheme 2; path A) or $\alpha$-bromobenzalacetone $3a$ (Scheme 2; path B) in moderate yields by reacting with corresponding amines, in the given example—cyclohexylamine and benzylamine. This is a classical approach, used repeatedly in many studies during XX and XXI centuries. Pathway B is partly like the aziridination reactions in which the double bond in the substrate reacts with an active nitrogen source—nitrene. In the cases discussed therein, the process is different and proceeds through a $\beta$-haloamine intermediate. Below in this review, we will focus on the further development and recent more advanced similar methodologies.

A simple in situ iodination/amination protocol using chalcone type substrates for obtaining type $1a$ aziridines was reported in 2001 [12]. The antibacterial activity of these compounds has been discussed. Aziridine ketones $1a$ were obtained in 55–57% isolated yields using benzene as a solvent; reactions were performed at room temperature for 1 h. No chromatography was required, as the products were purified by simple recrystallization. Application of similar amination for $\alpha$-bromo cinnamates $3b$ was reported later [13] (Scheme 3).

\[
\begin{align*}
3b & \quad \text{R-NH}_2, \text{Cs}_2\text{CO}_3, \\
& \quad \text{xylene}, 95 \degree C, 1 \text{ h} \\
& \quad 90-93\% \\
& \quad R = \text{Bn, allyl} \\
1b & \quad \text{trans-1b} \quad \text{cis-1b}
\end{align*}
\]

Scheme 3. Cromwell cyclization of cinnamates $3b$.

In this case, the yields were excellent, exceeding 90%; aziridines $1b$ were obtained as a mixture of diastereomeres trans-$1b$ and cis-$1b$, and the authors noted that it was the first report on the synthesis of cinnamate-derived aziridine esters of type $1b$. These cinnamate-derived aziridines ($1a$, $1b$) obtained by the given methods were used as templates for the stereospecific synthesis of 2-azetidinones [14] and in the construction of a series of
diverse alkaloid molecules [15]. The study [16] demonstrated that the cinnamate, chalcone bromination, or iodination/amine cyclization procedure tolerated another triple bond and allene system into the molecule allowing specific O-propargyl (1a2, 1b2) and buta 2,3-dien-1-yloxy (1a3, 1b3) derived aziridines to be obtained (Scheme 4).

![Diagram](image1)

**Scheme 4.** Functionalized aziridine ketones 1a2, 1a3 and esters 1b2, 1b3.

The simple Cromwell-type aziridine synthesis was successfully used to create aziridine libraries to screen for potential antiplasmodial protease inhibitors [17] and anti-yeast *Candida albicans* agents [18,19].

Like halogen, triflate can be used as the leaving group in this type of cyclization. Thus vinyl triflates 3c [20] (Scheme 5) form aziridines 1b4 in reactions with amines. The best solvents for this process are MeCN and DMF, and the yields of aziridines 1b4 are slightly better in MeCN. The reaction time strongly depends on the nature of vinyl triflate substrate 3c. Thus, 3-nitrophenyl substituted substrate 3c requires only 10 min at 0 °C and demonstrates 2.5:1 *trans* selectivity, but in the case of other triflates, the reaction ends only after 24–36 h.

![Diagram](image2)

**Scheme 5.** Amine cyclization of vinyl triflates 3c.

In reactions of phenyl substituted triflate 3c with ethanolamine or ethylenediamine, interesting bicyclic structures—fused bicyclic lactone 1d1 and lactam 1d2 were obtained in mixtures with the corresponding *cis*-aziridine-2-carboxylates 1b5 and 1b6 [20] (Scheme 6).

![Diagram](image3)

**Scheme 6.** Reaction of vinyl triflate 3c with ethanolamine and ethylenediamine.
2.2. Base-Promoted Cyclization of β-Substituted Amino Substrates

α-Amino-β-halo-esters 4a derived from corresponding precursors, e.g., cinnamates, undergo cyclization into aziridines 1b7 (without racemization), using TsNCl2 mediated aminohalogenation under mild basic conditions in the presence of potassium carbonate [21] (Scheme 7).

\[
\begin{array}{c}
\text{Ar}_1 \text{SO}_2 \text{Ar}_2 \\
\text{Cl} \quad \text{COOMe} \\
\text{4a} \\
\end{array} \quad \begin{array}{c}
\text{K}_2\text{CO}_3, \text{MeCN}, \\
\text{rt}, 3\ \text{h} \\
75-97\% \\
\end{array} \quad \begin{array}{c}
\text{Ar}_1 \text{N} \\
\text{OMe} \\
\text{1b7} \\
\end{array}
\]

Ar₁ = Ph, 4-MeC₆H₄, 2-MeC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-NO₂C₆H₄, 2-Napht,
Ar₂ = 4-MeC₆H₄, 2-NO₂C₆H₄

Scheme 7. Base cyclization of esters 4a.

The isolation procedure is also simple and does not require flash chromatography. The efficacy of the protocol has been demonstrated in 11 examples and with seven different β-aryl substituents [21].

The base-promoted cyclization into trans-3-aryl aziridine-2-carboxylates trans-1b7 and carboxamides trans-1c1 is similar in the α-chloro-β-amino substrates 5a,b [22] (Scheme 8), despite having an opposite structure. Six examples and three different aryl substituents have been reported.

\[
\begin{array}{c}
\text{Ar}_1 \text{Cl} \\
\text{NHSO}_2 \text{Ar}_2 \\
\text{COR} \\
\text{5ab} \\
\end{array} \quad \begin{array}{c}
\text{K}_2\text{CO}_3, \text{MeCN}, \\
\text{rt}, 3\ \text{h} \\
76-98\% \\
\end{array} \quad \begin{array}{c}
\text{Ar}_1 \text{SO}_2 \text{Ar}_2 \\
\text{N} \\
\text{O} \\
\text{R} \\
\text{trans-1b7}, \\
\text{trans-1c1} \\
\end{array}
\]

Ar₁ = Ph, 4-MeOC₆H₄, furan-2-yl,
Ar₂ = 4-MeC₆H₄, Ph
R = OMe (5a), NH₂ (5b)

Scheme 8. Base cyclization of esters 5a and amides 5b.

The optimization of this type of aziridine synthesis using a TsNCl2-mediated aminohalogenation-cyclization sequence was reported in 2004 for chalcone- and cinnamate-type substrates as “indirect aziridination” [23]. This is a stereoselective one-pot process leading to aziridines 1b (10 examples); the isolation of aminohalogenation intermediate products 5 was considered unnecessary.

β-Halo-α-aminoesters 4b derived from corresponding halohydrins were used as the source in the synthesis of specific N-alkoxy-3-arylated aziridine-2-carboxylate 1b8 series [24] (Scheme 9).
The products 1b8 were demonstrated in 12 examples with good yields. Thus, it appeared to be a reliable and promising method for synthesizing limited access 3-aryl-N-hydroxy and N-methoxy aziridines.

3-Arylaziridine Weinreb amides 1c2 can be synthesized in a similar way from the corresponding chlorinated Weinreb amides 5c. The reaction benefits from the retention of configuration [25] (Scheme 10).

Significant development has been reported simplifying the synthesis of aziridine ketones 1a4 and esters 1b7 from 1.2-vicinal haloamines 4c [26] (Scheme 11). Base/additive (urea)-promoted cyclization proceeds in solvent-free conditions by grinding components together at room temperature during different time intervals (ranging from 1 min to 1 h), resulting in quantitative chemical yield.

The said procedure was approved in 18 examples. In 13 of them, products were 3-aryl (2-azirindinyl) ketones 1a4 and 5-3-arylanziridine-2-carboxylates 1b7.

Aside from halogens, other activators/leaving groups for this type of β-amino compound cyclizations into aziridines were investigated. The methanesulfonyl O-activation of the OH group in aminoalcohol type substrates 5d allowed a series of N-alkylated trans-3-phenylaziridine-2 carboxylates 1b4 [27] to be obtained (Scheme 12).
The configuration of the aziridine product was dependent on the cyclization approach.}

The one-pot procedure was illustrated with 12 examples bearing various alkyl type N-substituents. In addition, Boc-protected 3-arylaziridine-2-carboxylates type 1b were obtained from corresponding amino acids using the same protocol with Ms and Ts O-activation [28].

The opposite substrate, namely, β-hydroxy-α-aminoester 4d has been activated with fluoroalkanosulphonyl fluoride for cyclization into 3-aryl aziridine-2-carboxylate 1b9 [29] (Scheme 13).

In a specific case, the SePh group in amino selanyl esters cis-5e and trans-5e appears to be a good activator for selective diastereomeric aziridine-2-carboxylates cis-1b10 and trans-1b10 synthesis [30] (Scheme 14).

Two different cyclization approaches were examined, using trimethyloxonium tetrafluoroborate (Scheme 14; Method A) and N-bromosuccinimide (Scheme 14; Method B). The configuration of the aziridine product was dependent on the cyclization approach.
2.3. Oxidative Cyclization

Aminoalkylation adducts of the activated methylene compound 7 undergo [1,3]-oxidative cyclization into N-benzoyl aziridines 1b11 [31] (Scheme 15) in the presence of iodosobenzene and a catalytic amount of tetrabutylammonium iodide. Another possible pathway is represented by the [1,5]-oxidative cyclization leading to oxazolines 11. The catalytic role of tetrabutylammonium iodide is to depolymerize and thus activate the polymeric iodosobenzene. If malonates are applied as the active methylene compound 7, the reaction proceeds towards aziridines 1b11 (17 examples). In contrast, if substrate 7 is represented by ketoesters and/or diketones, oxazolines 11 are obtained as the main products. At the same time, the corresponding aziridines 1b11 are observed as minor products in the reaction mixture (eight examples).

![Scheme 15. Oxidative cyclization of substrates 7.](image)

\[ \begin{align*}
\text{R} &= \text{Me, Ph, CF}_3 \\
\text{Ar} &= \text{Ph, o-Br-Ph, o-Cl-Ph, 2,4-ClCl-Ph, p-F-Ph, m-NO}_2\text{-Ph, p-NO}_2\text{-Ph, p-Me-Ph, o-BnO-Ph, p-BnO-Ph, m-BnO-Ph, p-MeO-Ph, 1-Napht} \\
\end{align*} \]

In the reported conditions, the mutual conversion of aziridines 1b11 and oxazolines 11 does not occur. Otherwise, as discussed below, 4-isoxazolines may work as aziridine precursors in the Baldwin rearrangement.

Summarizing this overview on classical and well-explored cyclization methods, some general features are evident, also setting the directions for future development of these approaches to increase the sustainability and simplicity of synthetic procedures:

- Excluding chromatography in the isolation step [13,21];
- Solvent-free reaction conditions [26];
- One-pot activation-cyclization sequences [28];
- Room temperature for reaction in most of examples.

3. Aziridines from Other Heterocycles

3.1. Aziridines from Isoxazolines. Baldwin Rearrangement

An interesting method for obtaining target aziridines 1 is the transformation of 5-membered ring substrates, especially 4-isoxazolines 8. The essence of this method is the cleavage of the N-O bond in these substrates, followed by a subsequent valence rearrangement. At first, this approach to 2-acylaziridine synthesis was demonstrated by the Baldwin team in 1968 [32]. One of the earliest attempts to convert this rearrangement into a practical method was demonstrated in 2002 by Ishikawa group [33]. Otherwise-stable isoxazolines 8a in the presence of dicobalt octacarbonyl turn into highly functionalized (including aryl substituents) aziridines 1a5 in moderate to high yields (47–64%) (Scheme 16). Ten examples have been described.
Scheme 16. Dicobalt octacarbonyl-promoted Baldwin rearrangement of 4-isoxazolines 8a.

Using optically pure substrate 8a with α-phenylethyl N-protection instead of benzyl-protects for obtaining a single isomer of aziridine 1a5. Therefore, a possibility of a general strategy of chiral 3-arylated aziridine 1a5 synthesis from 4-isoxazolidinones 8a has been demonstrated.

Using electron acceptor N-substituent (N-benzenesulfonylamide) on 4-isoxazoline substrate 8b (Scheme 17) in combination with microwave treatment without catalyst was reported as a useful method for the synthesis of 3-arylated aziridines cis-1a6 [34]. Remarkably high cis-selectivity (~97%) was shown.

\[
\begin{align*}
\text{Ar} &= p\text{-tol, } o\text{-tol, } m\text{-tol, Ph, } p\text{-F-Ph, } p\text{-Ph-Ph, } 2\text{-Napht, } p\text{-BrPh, } p\text{-MeOPh} \\
R &= n\text{-Bu, } c\text{-Pr, } i\text{-Pr, } t\text{-Bu, Ph}
\end{align*}
\]

Scheme 17. Microwave-mediated Baldwin rearrangement of 4-isoxazolines 8b.

The evaluation of different solvents, temperature regimens, and reaction times showed that the best cis-selectivity in products cis-1a6, together with appropriate yields, was reached using acetonitrile as a solvent at 110–130 °C during an approx. 30 min reaction time. Reaction tolerated a wide range of substrates with different aryl substituents (13 examples).

4-Isoxazolines 8c as intermediates in cyclization-Baldwin rearrangement cascade reaction allows the synthesis of cis-2-acylaziridines cis-1a7 from N-(propargylic) hydroxylamines 12 [35] (Scheme 18) in a one-pot procedure at room temperature.

\[
\begin{align*}
\text{R} &= n\text{-Hex, } t\text{-Bu, Ph}
\end{align*}
\]

Scheme 18. Cascade cyclization-Baldwin rearrangement reaction of hydroxylamines 12.

The cyclization of hydroxylamine 12 into isoxazole intermediate 8c was catalyzed by AgBF₄ and Baldwin rearrangement by copper salt. Screening copper salt additives showed that the best additive is CuCl. Moderate to high yields and cis-selectivity in β-phenyl aziridines 1a7 has been reported in four examples.
Finally, an effective and highly stereoselective synthesis of β-arylated aziridines cis-1a8 and cis-1b12 has been developed, constructing the necessary N-substituted 4-isoxazolines 8d from nitrones 13 and alkynes 14 through 1,3-dipolar cycloaddition in ionic liquid with subsequent microwave treatment of obtained isoxazolines 8d in acetonitrile leading to Baldwin rearrangement into aziridines cis-1a8 or cis-1b12 [36] (Scheme 19). The initial nitrones 13 were obtained in the reaction of corresponding aldehydes with hydroxylamines.

Scheme 19. Synthesis and Baldwin rearrangement of 4-isoxazolines 8d.

Aziridines cis-1a8 and cis-1b12 were obtained in high cis-selectivity, as almost single isomers in nine examples. A remarkable feature of this synthesis is the absence of promoting additives and catalysts. Antibacterial properties of obtained aziridines cis-1a8 and cis-1b12 have been discussed. Highly functionalized bis (aziridine) products 15 (eight examples, >70% yields) have been synthesized using the same protocol [37] (Scheme 20).

Scheme 20. Bis-Aziridines 15.

In summary, in the case of available isoxazolines Baldwin rearrangement appears as a fast, clean, and easy pathway to reach highly functionalized β-arylated aziridines 1a–c in appropriate chemical yields and high diastereoselectivity.

3.2. Aziridines from Azirines

2H-Azirines are considered reactive species and have been employed as substrates in various transformations, including formation of aziridines. Therefore, reactions of azirines seem to be an interesting and useful set of synthetic methods, as discussed below.

3.2.1. 2H-Azirine as 1,3-Dipolarophile

2H-Azirine 9a was reported as an efficient substrate for constructing complex aziridine-containing structures 1b13 in reaction with β-lactam adduct 16 [38] (Scheme 21)—a useful precursor for 1-azacepham type structures. Azirine 9a has been employed as 1,3-dipolarophile towards structure 16 based azometine ylides. Isomers of the obtained adduct 1b13, namely, the aziridine esters 1b13a and 1b13b, are separable by preparative chromatography and can be used in further transformations separately.
3.2.2. Azirines as Dienophiles

A series of studies by the Alves group established that 2H-azirines 9, especially aryl substituted azirine 9a, served as potent dienophiles in Diels-Alder reactions, forming highly functionalized tri- and tetracyclic aziridines bearing β-aryl substituents. Thus, 2H azirine 9a reacts with furan ring-based dienes: furan 17a [39], 2.5-dimethylfuran 17b and 1.3-diphenylbenzofuran 17c [40] to form highly functionalized 3-arylated aziridine-2-carboxylates 1b14–1b18 (Schemes 22–24). Reaction with furan d4 leads to aziridine adduct ester 1b14 [39,40] (Scheme 22). Nucleophilic ring opening of aziridine 1b14 with alcohols forms dihydrofurane-substituted aziridine isomers 1b15a and 1b15b (three examples). Consequently, the oxazoline ring in adduct 1b14 is more reactive toward O-nucleophiles than the aziridine ring, and it is a promising pathway to obtain specific 2,2-disubstituted 3-arylated aziridines of type 1b15.

\[
\text{Scheme 21. 1,3-Dipolar cycloaddition of azirine 9a to β-lactam 16.}
\]

C(2) unsubstituted azirines—analogue of 9a also are suitable for this reaction and can be generated in situ from the corresponding azides.

\[
\text{Scheme 22. Diels-Alder cycloaddition of azirine 9a to furan 17a.}
\]
In the reaction of azirine 9a with 2.5-dimethylfuran 17b, only a hydrolysis product—dihydrofuran-substituted aziridine 1b16—was isolated in moderate yield after chromatography as a mixture of isomers (Scheme 23).

In contrast, 1.3-diphenylbenzofuran 17c in reaction with azirine substrate 9a forms two separable tetracyclic aziridine adducts endo-1b17 and exo-1b17 [40] (Scheme 24). Observations show that endo-5c1 is the kinetic product, as it is the first to precipitate from the reaction mixture by crystallization (no chromatography is required for the isolation of this product). Further crystallization yielded a mixture of endo-1b17 and exo-1b17. Endo product can be transformed into thermodynamic exo product 1b17 by heating in THF for 3 h.

Hydrolysis of adduct exo-1b17 yielded a pure sample of 3-aryl 2.2-disubstituted aziridine 1b18.

2-Azadienes 18 react with azirine 9a in a similar manner, forming bicyclic adducts 1b19 [41] (Scheme 25). Reactions are selective: only endo- products were observed. The products were isolated after desilylation as bicycles 1b20. The isolation procedure was very simple—via filtration, no chromatography was required. In some cases (three examples), a mixture of isomers 1b20a and 1b20b were obtained, but if R1 = Et, R2 = R3 = Me, a single isomer 1b20a was obtained as a precipitate. Chemical yields were moderate. As in the previous case, mixtures can be transformed into a single isomer-thermodynamic product 1b20a by treatment with silica in dichloromethane (a single example).
In the subsequent study [42], the same authors discussed the synthesis of the precursor azadienes 18, stereochemistry of the aziridine products 1b20, possible isomerization pathways between compounds 1b20a and 1b20b, and their structures in higher detail. The acidic hydrolysis of the aziridines 1b20 forming 3-aryl-NH-aziridines 1b21 (Scheme 26) was reported in five examples.

\[
\text{aq HCl, THF, rt, 1 h} \rightarrow \text{68-87%} \rightarrow \text{O} \quad \text{NH} \quad \text{Ar} \quad \text{R}_2 \quad \text{COOMe} \\
\text{Ar} = 2.6\text{-diClPh} \quad \text{R}_2 = \text{Me, Ph} \quad \text{R}_3 = \text{H, Me, Ph} \\
1b21
\]

Scheme 26. Hydrolysis of aziridines 1b20.

Hydrolysis was carried out in acidic media in mild conditions and resulted in aziridines 1b21 with high yields. Both diastereomers 1b20a and 1b20b formed the same products 1b21. Diastereoselective approaches of these transformations using chiral auxiliaries in aziridine ester moiety were reported in the further study [43].

Exploration of azirine Diels-Alder cycloaddition to dienes was continued with oxazilidin-2-one moiety containing diene substrates 19 [44] (Scheme 27).
In a reaction with stable 2H-azirines 9a and 9b, the cycloadducts 1b22 and 1b23 were obtained. Remarkably, the direction of cycloaddition depends on the aryl substituent. Thus, in case of the 2.6-dichlorophenyl group in the azirine substrate 9a, a 7-arylated aziridine cycloadduct 1b22 was formed. However, in the case of 2-pyridil substituent (substrate azirine 9b), a 6-arylated cycloadduct 1b23 was obtained. This shows the possibility of driving cycloaddition via selection of aryl substituents.

As demonstrated in previous studies, products are formed in the endo-process. The obtained aziridines undergo acidic hydrolysis in aq HCl-THF media. Different products of hydrolysis were obtained. Thus, 7-arylated aziridine 1b22 yielded aziridine ester 1b24, while 6-arylated aziridine 1b23 resulted in the product 20 via elimination/nucleophilic aziridine ring cleavage.

In the next study [45], the exploration of the synthesis and reactivity of type 1b25 arylated aziridine cycloadducts was continued. Besides 2.6-dichlorophenyl (substrate 9a) and 2-pyridil (9b) substituents in azirine substrate, type 9 p-tolyl substituent (substrate 9c) has been investigated, and a new type of moiety—1-pyrazolyl in the diene 21 was used (Scheme 28).
Further reactions of 1b25 type cycloadducts have been studied. These transformations show relatively easy and direct access to individual isomers of highly functionalized polycyclic β-arylated aziridine products that are difficult to otherwise reach. Remarkably, the reaction conditions and procedures for isolation of products are simple in almost all cases, e.g., cycloaddition reactions were carried out at room temperature.

3.2.3. Nucleophilic Addition to the Azirine Double Bond

An significant but not widely explored approach which allows various β-aryl- and heteroaryl-substituted aziridines to be obtained is a protocol based on the addition of nucleophiles (including nitrogen heterocycles) to the 2H-azirine double bond. The initial research by Alves and coworkers demonstrated that 2H-azirine-3-carboxylic ester 9a formed 3-aryl-2-substituted aziridines 1b26 [46] (Scheme 29).

![Scheme 29. Addition of N- and S-nucleophiles to azirine 9a.](image)

A further study showed the synthetic potential of 2H-azirine-2-carboxylic esters 10. Previously, it was already known that optically active ester 10a reacted with Grignard reagent as a nucleophile yielding NH-aziridine 1b27 [47,48] (Scheme 30).

![Scheme 30. Addition of Grignard reagent to azirine 10a.](image)

The subsequent research by the Alves group proved that 2H-azirine-2-carboxylic ester 10b is electrophilic enough for reaction with nitrogen nucleophiles at room temperature within some hours [49] (Scheme 31). 3-Arylated chiral aziridines 1b28 were obtained using a broad spectrum of hetarylamines as nucleophiles (nine examples). This study opened the possibility of introducing different aryl substituents for the synthesis of β-arylated aziridines. The necessary chiral aziridines were produced from oximes 22 by cyclization in the presence of (+)-dihydroquinidine (Scheme 31). Chiral amine was removed from the reaction by extraction with aq. citric acid, and the obtained azirine 10b were used in reactions with nucleophiles without further purification.

Remarkably, 2H-azirines 10c may serve as components in three-component Ugi reactions with isocyanide 23 and carboxylic acid 24 [50] (Scheme 32) forming aziridine-2-carboxamides 1c3.

This protocol allows the generation of large libraries of aziridine-2-carboxamides 1c3, including 3-aryl, which are suitable for medical chemistry applications. The given study [50] contains a full and complete development of the practical synthetic method for products 1c3. Firstly, the authors performed a catalyst screening and found that zinc (2) chloride was the best catalyst. Further, the reaction conditions were optimized, finding the optimal combination: THF solvent and 55 °C temperature during 4–5 h. Finally, researchers screened the reaction components (isocyanides 23, carboxylic acids 24, and azirines 9d) in a large series of more than 40 examples. 3-Arylated aziridine products 1c3a, 1c3b were demonstrated in eight examples with moderate to good yields.
Scheme 31. Reaction of azirines 10b with hetarylamines.

Scheme 32. Ugi reaction of azirines 10c.

In general, the listed series of examples confirms 2H-azirines as promising substrates for aziridine construction via different approaches.

Summarizing the information about 3-arylated aziridine synthesis from other heterocycles, we note that these methods allow complex aziridine-containing structures to be obtained, including highly functionalized products, fused ring structures, and single isomers.

4. Perspective Photo- and Electrochemical Methods in the Synthesis of 3-Arylated Aziridines

Besides the general sustainability improvements mentioned above (no chromatography for product isolation; solvent-free and mild reaction conditions), some interesting and specific physical chemistry-based approaches in the synthesis of 3-arylated aziridine products have been reported. Thus, α-keto vinyl azides 25 react in the presence of tert-butyli hydroxy peroxide and photocatalyst tris-(2,2′-bipyridine)ruthenium (II) hexafluorophosphate with 1,2,3,4-tetrahydro-β-carbolines [51] or dimethylanilines 26 [52] under white LED
light irradiation forming corresponding bicyclic aziridine products 1a9 [52] (20 examples) or more complex fused aziridine systems 27 [51] (18 examples) in good yields (Scheme 33).

\[
\begin{align*}
\text{Ar}_1 & = 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 2.6-\text{Cl}_2\text{C}_6\text{H}_3, \\
\text{Ar}_2 & = \text{Ph}, 4-\text{ClC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4 \\
\text{Ar}_3 & = \text{Ph}, 4-\text{BrC}_6\text{H}_4, 4-\text{IC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 3.5-\text{Me}_2\text{C}_6\text{H}_3
\end{align*}
\]

Scheme 33. Photocascade reaction of azides 25.

Studies of the reaction mechanism were performed [52]. It was proved in a single example that, in the presence of visible light and ruthenium photocatalyst, \( \alpha \)-azidochalcone 25 got converted into 2H-azirine via photosensitized decomposition. Then 2H-azirine 9d underwent \([3 + 2]\) cycloaddition to azomethine ylide formed in the oxidation of amine 26. This explained the stereoselectivity of the demonstrated reaction. In the practical aspect, the authors reported the possibility of performing these reactions in a capillary flow microreactor instead of a batch. This shortened reaction time from 12 h to approx. 1 h.

Excluding external oxidants in electrochemical intramolecular oxidative dehydrogenative amination of substrates 28 has been reported [53] (Scheme 34). The resulting 3-arylated aziridines \( \text{trans-1a10} \) were obtained in good yields.

\[
\begin{align*}
\text{Ar}_1 & = \text{Ph}, 4-\text{FC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 2-\text{BrC}_6\text{H}_4, \\
\text{Ar}_2 & = \text{Ph}, 4-\text{FC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 3.4(\text{OMe})_2\text{C}_6\text{H}_3, 2-\text{F}-4-\text{OMeC}_6\text{H}_3, 2\text{-furyl}, 2\text{-thiophenyl} \\
\text{R} & = \text{Et}, \text{-t-Bu}
\end{align*}
\]

Scheme 34. Electrochemical intramolecular amination of substrates 28.

Optimization of the reaction conditions and broad substrate scope (24 examples) has been demonstrated. The reaction procedure shows high sustainability because the only byproduct is hydrogen. To turn this procedure into a practical method, gram-scale
synthesis of product trans-1a10 (Ar1 = Ar2 = Ph, R = Et) was demonstrated in a single example (2.15 g, 73%).

In summary, physical chemistry approaches allow the construction of aziridines more cleanly and economically. Therefore these procedures seem to be promising for further investigations.

5. Conclusions

The current literature analysis shows that in selected cases, specific non-aziridination-based methods for obtaining 3-arylated aziridine-2-carboxylates, carboxamides, and 2-aziridinylketones are useful and hold remarkable synthetic potential. The classical cyclization was widely used for different applications in medical chemistry, e.g., to screen for potential antibacterial and antifungal active compounds in 3-arylaziridine series. The most interesting reactions are the transformations of other heterocycles into aziridines, such as the Baldwin rearrangement of isoxazolines and the use of 2H-azirines as 1,3-dipolarophiles and dienophiles in Diels-Alder cycloadditions. These methods exhibit remarkable regio- and stereoselectivity and are very simple from the practical point of view—reactions often can be performed at room temperature and without catalysts. The high functionalization possibilities are notable, yielding fused polycyclic and highly substituted aziridine derivatives if corresponding substrates are available. Another application of the high reactivity of azirines is represented by nucleophilic addition reactions and, more recently, three-component Ugi reactions with 2H-azirines as a component. This azirine chemistry is not very widely known but highly promising. Perspective research directions include both the described chemical and promising photo- and electrochemical approaches. Comparing the analyzed set of synthetic pathways with aziridination, complementarity is evident. Thus, aziridination and classical cyclization methods are more general. However, other methods mentioned in the current review show good results in specific cases for the synthesis of complex highly substituted 3-arylaziridine moiety-containing molecules.

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