Chapter 1
Three-Membered Azaheterocycles

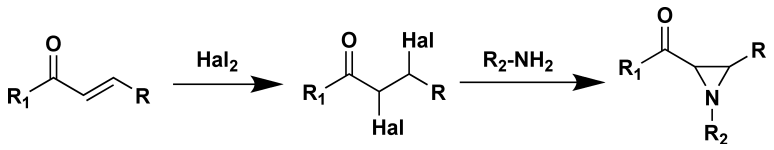
One of the features of α,β-unsaturated ketones is the presence of two electrophilic centers. Because of this feature, reactions with binucleophiles can proceed as a 1,2-addition or as a 1,4-addition. Regarding three-membered nitrogen-containing heterocycles formed from α,β-unsaturated ketones and their derivatives, the unsaturated ketone acts either as a 1,2-bielectrophile (substituted ethylene), which leads to the formation of ethyleneimines, or as a 1,4-bielectrophile, giving rise to either bi- or tricyclic aziridines. Hence, the present chapter is divided into two parts, one which is entirely dedicated to aziridinyl ketones and the other to bi- and tricyclic aziridines.

Fused aziridines are interesting compounds owing to the fact that the strained three-membered ring can easily open and cause dipolar cycloaddition reactions as well as their photochromic properties. Therefore, most of this chapter covers the chemical and photochemical properties of bi- and tricyclic aziridines. Some properties of aziridinyl ketones are also reviewed, in particular, reactions leading to aziridinyl anils.

1.1 Synthesis of Aziridinyl Ketones and Their Chemical Properties

Methods of obtaining aziridine derivatives from α,β-unsaturated ketones can be divided into two basic groups: one-pot synthesis directly from an unsaturated ketone or stepwise synthesis involving the initial modification of a double bond.

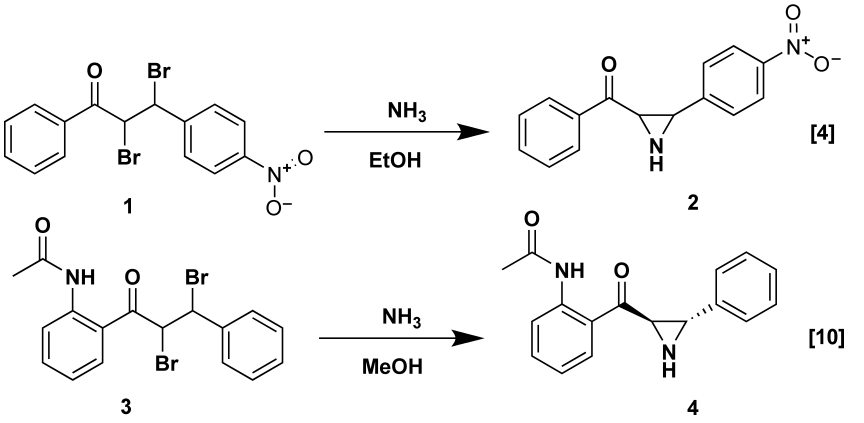
In practice the most common method is the one based upon obtaining α,β-dihalogen derivatives of unsaturated ketones with their subsequent interaction with ammonia or primary amines, known as the Gabriel reaction (Scheme 1.1).



Scheme 1.1

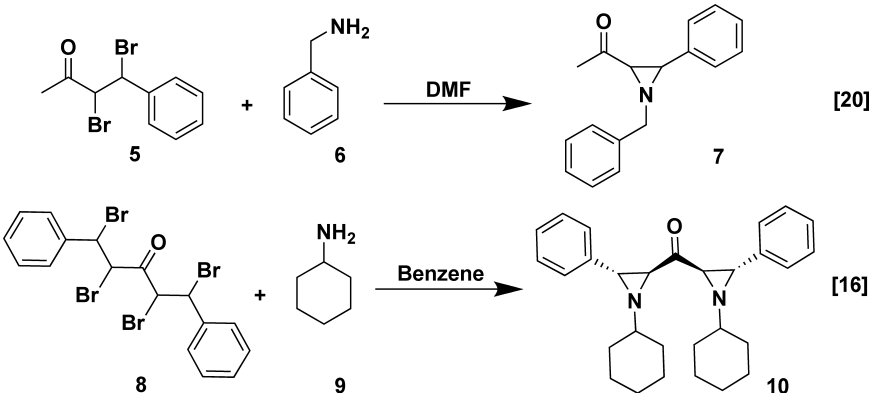
V.A. Chebanov et al., *Azaheterocycles Based on α,β-Unsaturated Carbonyls*,

The synthesis of 1,3-diaryl-2,3-dibromopropan-1-one and its interaction with ethanolic [1, 2, 3, 4, 5, 6, 7, 8, 9] or methanolic [10] ammonia solutions is often described in the literature. Examples of two aziridinyl ketones **2** and **4** synthesized from the corresponding dibromides **1** and **3** are shown in Scheme 1.2.



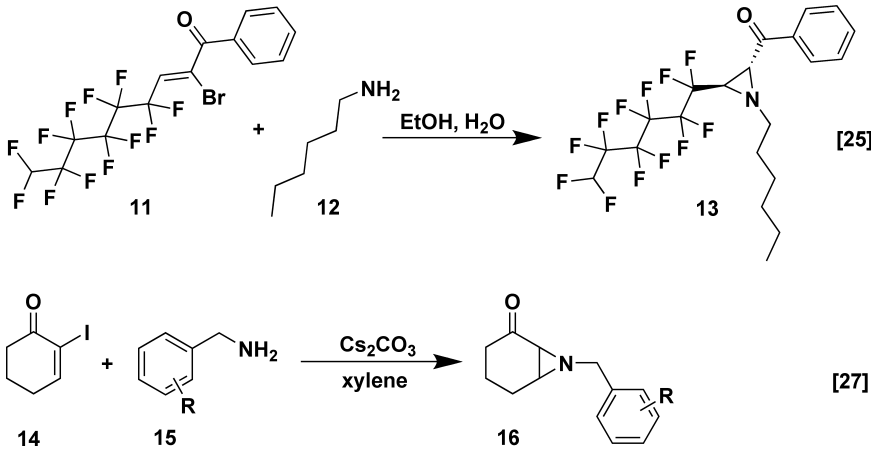
Scheme 1.2

For synthesis of N-substituted aziridinyl ketones, primary amines such as methylamine [11, 12, 13], cyclohexylamine [8, 11, 14, 15, 16, 17] and benzylamines [17, 18, 19, 20] are introduced in the reaction instead of ammonia. These reactions can be carried out in different solvents, such as alcohols, benzene, toluene, dimethylformamide, etc. On the basis of this chemistry, aziridinyl ketones containing either one or more three-membered cycles can be synthesized (e.g., compounds **7** and **10**; Scheme 1.3).



Scheme 1.3

It is known that the first stage of the reaction of α,β-dibromoketones with amines is their dehydrobromination leading to α-bromo derivatives [9, 21]. α-Bromochalcones are mentioned in the literature and also can be used for the synthesis of aziridinyl ketones [8, 11, 22, 23, 24, 25]. For example, Khomutov et al. [25] carried out the synthesis of the dodecafluoro derivative **13** by the interaction of the corresponding α-bromoketone **11** with hexylamine **12** (Scheme 1.4).

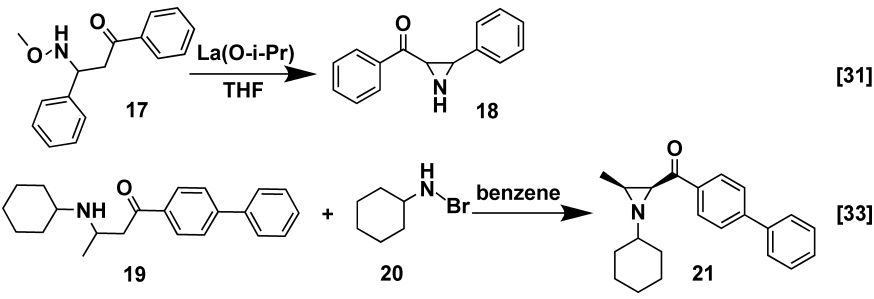


Scheme 1.4

Besides α,β-dibromopropan-1-ones, there are references related to using α,β-dichloro [26], α-chloro [19] and α-iodo derivatives [27] in the Gabriel reaction. Bicyclic aziridines **16** were obtained by the treatment of α-iodocyclohexene **14** with benzylamines **15** in the presence of cesium carbonate in xylene [27] (Scheme 1.4).

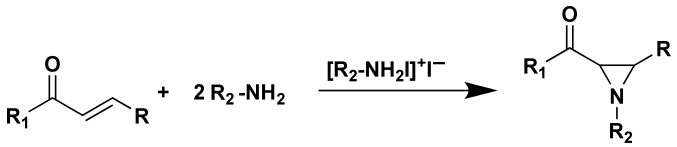
Another synthetic method for the preparation of aziridinyl ketones involves the initial modification of unsaturated ketones, with formation of β-methoxyamino derivatives, followed by treatment with either metal alcoholates [11, 28, 29, 30, 31], or hydroxylamine hydrochloride and then potassium hydroxide [32]. An obvious drawback of this approach is the possibility of obtaining an exclusively unsubstituted nitrogen atom for the aziridinyl ketones. Among the advantages are high yields for these reactions. For example, Jin et al. [31] recorded yields of aziridine **18** of 99%. In other publications the yields of target compounds were reported to be around 90%.

Additionally, Cromwell et al. [33] described obtaining the *N*-cyclohexyl derivative of aziridinyl ketone **21** by reacting β-amino adduct **19** with *N*-bromocyclohexylamine **20** (Scheme 1.5).



Scheme 1.5

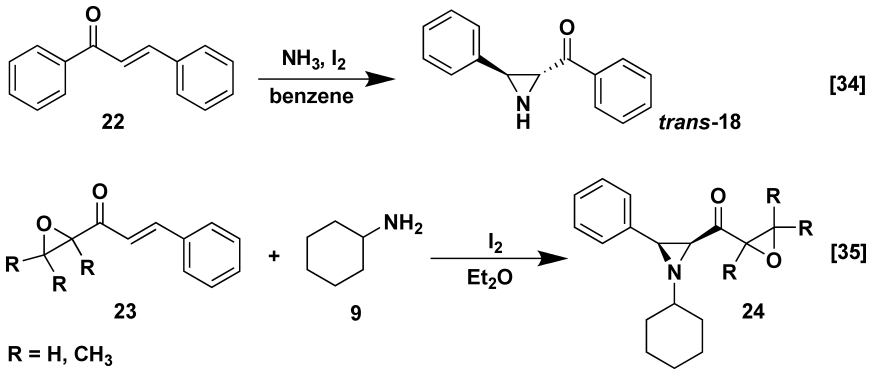
As already mentioned, besides multistage reactions there are also synthetic methods for obtaining aziridinyl ketones from α,β-unsaturated carbonyl compounds without the need for initial modification. Among such methods, the Southwick reaction consisting of the interaction of unsaturated ketones



Scheme 1.6

with amines and an iodine–amine complex should be mentioned (Scheme 1.6).

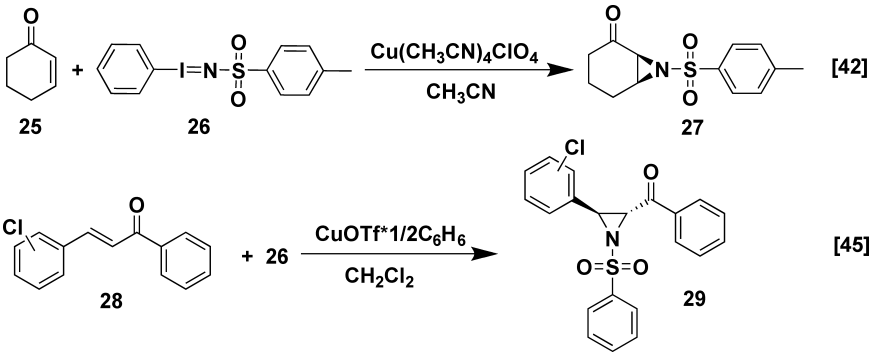
For example, Southwick and Christman [34] described obtaining *trans*-aziridine **18** from chalcone **22** (Scheme 1.7). Reactions of **22** with cyclohexylamines and benzylamines forming the corresponding N-substituted derivatives are mentioned in the same publication. Zvonok et al. [35] studied the interaction of cyclohexylamine **9** with 6-phenyl-2,3-epoxyhex-5-en-4-ones **23**, leading to compounds **24** (Scheme 1.7).



Scheme 1.7

It should be noted that the stereochemistry of the Gabriel and Southwick reactions depends essentially on both the structure of the starting compounds and the reaction conditions. It was established [36, 37, 38, 39, 40, 41] that increasing the *trans* to *cis* isomer ratio is promoted by the volume extension of the substituent in the β-position of the starting enone, whereas volume extension of the N-substituent leads to the opposite effect. The preferred formation of *cis*-aziridinyl ketones in the Gabriel reaction is also promoted by the use of methanol as a solvent instead of benzene at the stage where the 2,3-dibromopropan-1-one interacts with amines. In the Southwick reaction the opposite effect of the solvent is observed. A more detailed analysis of the mechanism and stereochemistry of the reactions mentioned is given in [36, 37, 38, 39, 40, 41]; however, as Tarburton et al. [41] themselves note, the models proposed do not explain all the features of the interaction.

One more method used in the last decade is the interaction of unsaturated ketones with *N*-tosyliminoaryliodinanes in the presence of monovalent copper complexes [42, 43, 44, 45]. A serious disadvantage of this method is low yields. For example, in the reaction of cyclohexenone **25** with compound **26** in the presence of $Cu(CH_3CN)_4ClO_4$, the target bicyclo[4.1.0]heptanone **27** was obtained with 21% yield [42] (Scheme 1.8).

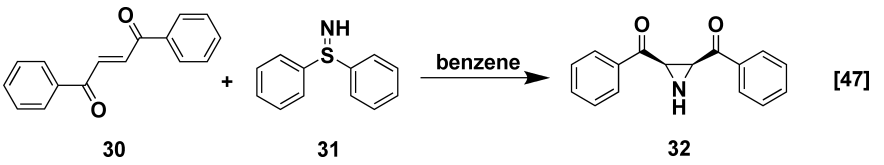


Scheme 1.8

In the case of 2-chlorochalcone, 3-chlorochalcone and 4-chlorochalcone **28**, compounds **29** could not be separated completely from the by-products [45] (Scheme 1.8). The same problem was observed in [44].

Bis(acetoxyphenyliodane) can also take part in such reactions [46]. In this case, the yields and purity of aziridinyl ketones are much higher than in the case of the *N*-tosyliminoaryliodinanes.

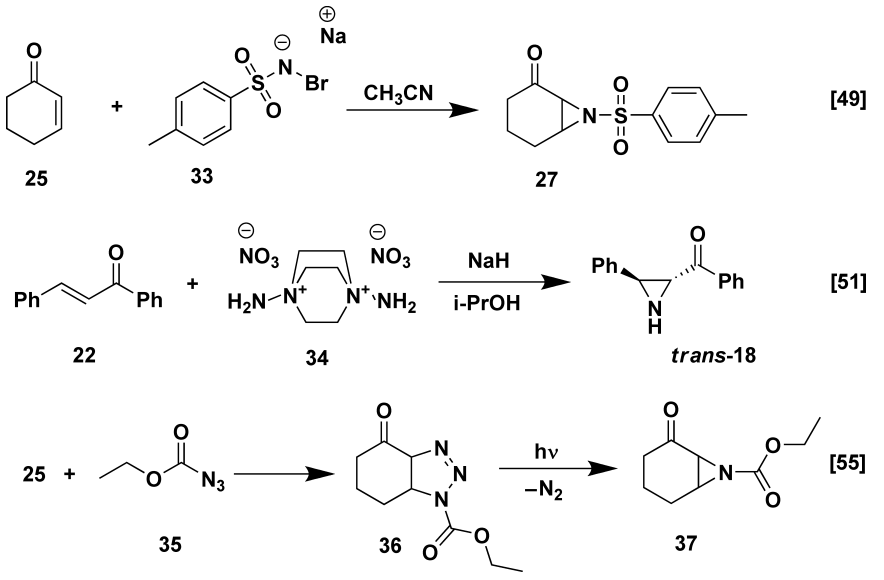
Among other important practical methods, the reaction of unsaturated ketones, in particular, dibenzoyl ethylene **30**, with *S*,*S*-diphenylsulfimide **31** [47, 48] should be mentioned. The yields of the target aziridines **32** in this case are high and sometimes close to quantitative (Scheme 1.9).



Scheme 1.9

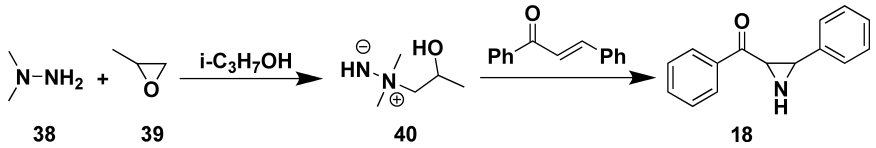
Aziridinyl ketones can be synthesized from unsaturated carbonyls using a series of other methods. For example, azabicyclo[4.1.0]heptanone **27** was obtained from cyclohexenone **25** in its reaction with *N*-bromotoluenesulfonamide sodium salt **33** [49] (Scheme 1.10). The reaction of chalcone with *N*-chlorotoluenesulfonamide in the presence of silver nitrite is described in [50]. *Trans*-Aziridinyl ketone **18** was synthesized by reacting chalcone **22** with *N*,*N*-diamino-1,4-diazoniabicyclo[2.2.2.]octane dinitrate **34** and sodium hydride in 2-propanol [30, 51]. Aziridinyl ketones can be obtained in the reaction of α,β-unsaturated ketones with *N*,*N*-dichlorosulfonamines [52] and with amines in the presence of lead tetraacetate and trifluoroacetic acid [53] or in the presence of triethylammonium acetate under electrochemical reaction conditions [54].

One-pot synthesis of aziridinyl ketones including the initial dipolar addition of azides to the ethylene bond with subsequent elimination of the nitrogen by photolysis is also possible [55, 56]. For example, in the case of azidocarboxylic acid ethyl ester **35,** 2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylic acid ethyl ester **37** was synthesized via the formation of the cycloadduct **36** [55] (Scheme 1.10).



Scheme 1.10

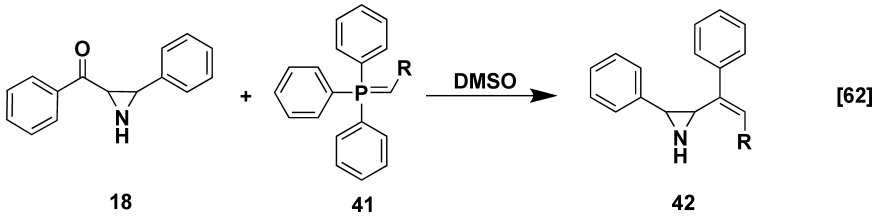
One more method which we would like to mention is the direct aziridination of unsaturated ketones using aminoimides **40** obtained in the reaction of *N*,*N*-dimethylhydrazine **38** with methyl oxirane **39** [57] (Scheme 1.11):



Scheme 1.11

Aziridination of (*E*)-chalcones can be carried out with other aminoimines which are formed by deprotonation of *N*-amino-*N*-methylmorpholinium salts [58].

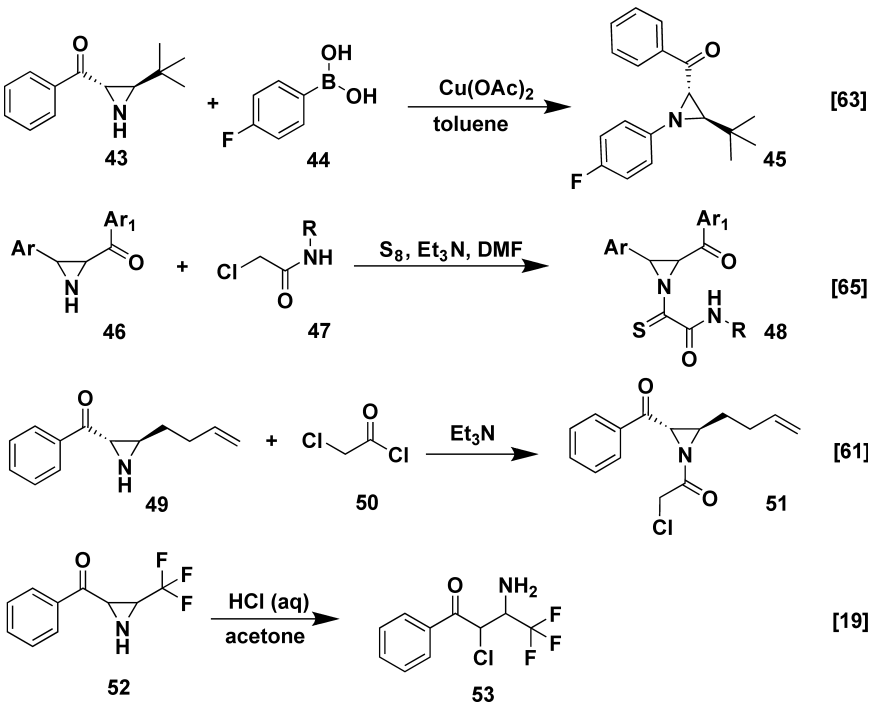
Owing to the presence of two highly reactive fragments (the aziridine cycle and the carbonyl group), aziridinyl ketones are characterized by the diversity of their chemical transformations. They can react as secondary amines, undergo nucleophilic or electrophilic cycle opening, or react as carbonyl derivatives. In particular, reactions involving only the carbonyl group include reduction to alcohols [59, 60, 61] or formation of styrylaziridines **42** by the action of diverse ylidenetriphenylphosphanes **41** [30, 62] (Scheme 1.12).



Scheme 1.12

The processes involving the aziridine cycle are very diverse. For instance, reactions of alkylation by alkyl halogenides [63], bromoacetic acid derivatives [29, 30] and acetoxypropene [64], are known. The use of arylboronic acids for synthesis of *N*-alkyl derivatives, e.g., compound **45**, is described in [63] (Scheme 1.13). The one-step reaction at room temperature of aziridinyl ketones **46** with chloroacetamides **47** and sulfur in the presence of Et_3N yields mono-thio-oxamidines **48** [65].

Acylation reactions can be carried out by the action of acid anhydrides [66, 67], chloroanhydrides [47, 61], isocyanates [68], isothiocyanates [68, 69] and thioamides [70]. It was shown that the reaction of aziridinyl ketone **49** with chloroacetyl chloride **50** in the presence of Et_3N [61] leads to the formation of *N*-acyl derivative **51**, whereas the alkylation product was not isolated.

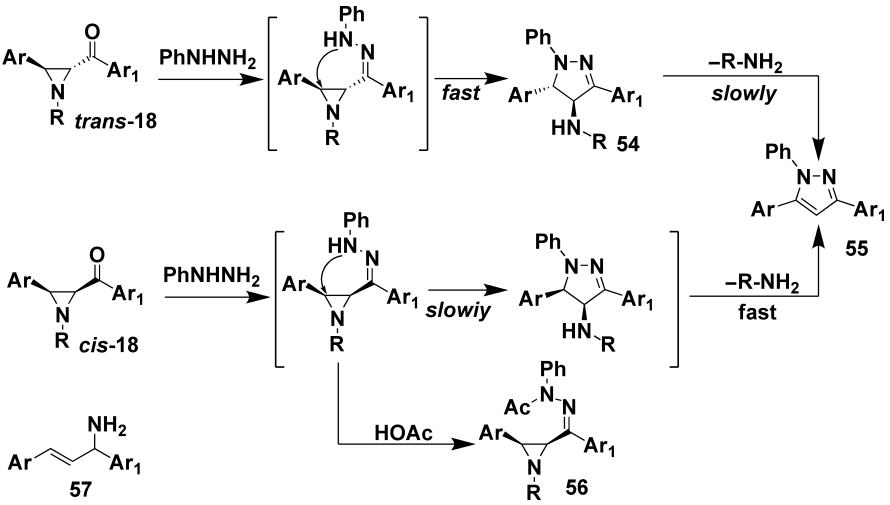


Scheme 1.13

Khomutov and Pashkevich [19] have established that the aziridine ring in compound **52** can open, giving rise to aminochlorobutanole **53**. *N*-Chloro derivatives of aziridinyl ketones can be obtained by the reaction of *tert*-butyl hypochlorite [47] or *N*-chlorosuccinimide [61]. The action of N_2O_4 on azirinochalcones in the presence of triethylamine leads to chalcones [71].

Reactions characterizing aziridinyl ketones as polyfunctional compounds are also described in the literature. An example is a widely studied [11, 15, 72, 73, 74] reaction of ketones **18** with phenylhydrazine in which the main products are pyrazole derivatives **55**.

The *cis* and *trans* isomers of **18** behave somewhat differently in this reaction: the *trans* isomer reacts faster at the stage of the aziridine cycle nucleophilic attack, whereas for another isomer this stage is inhibited by an adjacent *cis* substituent (Scheme 1.14). Such inhibition of the cyclization stage results in the formation of acyl hydrazone **56** as a by-product as well as the formation of pyrazole **55** from the intermediate aminopyrazoline by a rapid *trans* elimination. In the case of *trans*-aziridinyl ketone **18**, the slowest step is the *cis* elimination of RNH_2, isolating 4-alkylaminopyrazines **54** in most cases.

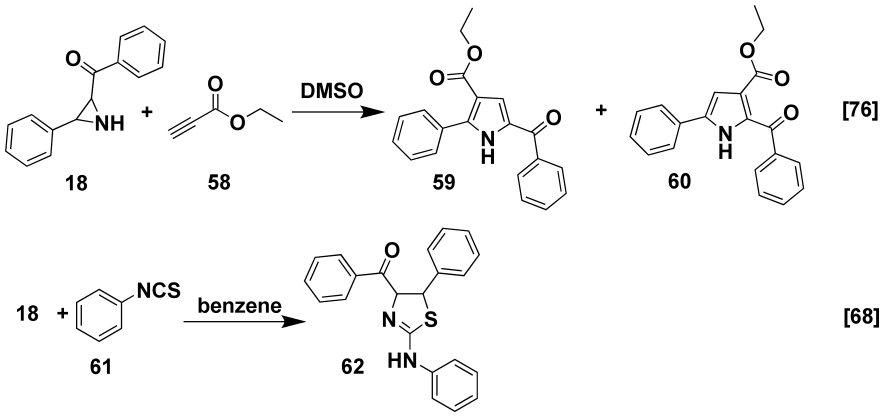


Scheme 1.14

N-Unsubstituted pyrazoles are synthesized by action of hydrazine on compounds **18**. However, the main reaction products in this case are amino chalcones **57** (up to 40%) [75].

An interesting example of heterocyclization involving both the aziridine fragment and the carbonyl group is a reaction of aziridinyl ketones with ammonia and carbonyl compounds, giving rise to 3,5a-dihydro-1*H*-azireno[1,2-*c*]imidazoles. This reaction will be considered in more detail in Sects. 1.2 and 1.3.

Treatment of aziridinyl ketone **18** with propiolic acid ethyl ester **58** leads to two regioisomeric pyrroles **59** and **60** [76] (Scheme 1.15). The reaction of ketone



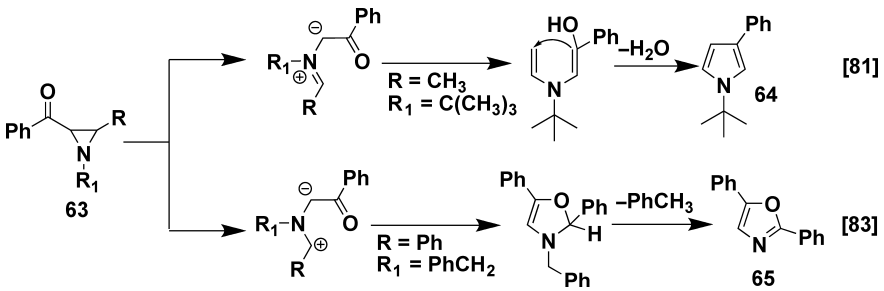
Scheme 1.15

18 with isothiocyanates, e.g., compound **61**, can lead not only to the formation of thiourea derivatives, but also to thiazolyl ketones like **62** [68].

Methylthiocyanate reacts with BF_3 complexes of 3-aroylaziridines, yielding 4-aryl-5-aroyl-2-methylthio-2-imidazoazolines. During this reaction the three-membered ring opens in a regio- and stereospecific manner at the C(2) atom with inversion of the configuration [77].

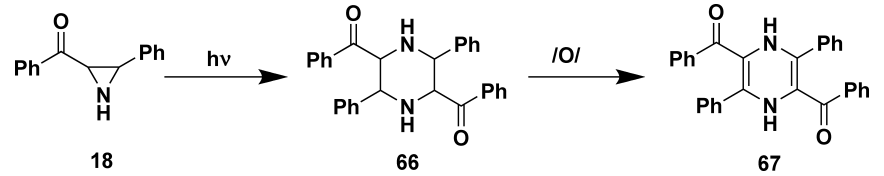
The most studied type of reaction of aziridines is the transformations via a thermo- or photoinduced bipolar ylide. Among the numerous works related to this question are the reviews by Padwa [78] and Lown [79]; the analysis of reactions of this type which do not involve the aziridine cycle are left out of this present work.

The presence of an aroyl fragment in azomethine ylides obtained from opening of three-membered rings in the case of dipolarophiles with high LUMO (lowest unoccupied molecular orbital) energy or in the absence of an "external" dipolarophile can lead to the possibility of such unusual reactions as intramolecular 1,3-dipolar cycloaddition [80]. Examples of such reactions are the thermal isomerization of aroyl aziridines **63** into a pyrrole derivative **64** [81, 82] or into 2,5-diphenyloxazole **65** (in the presence of diphenyliodonium iodide) [83] (Scheme 1.16).



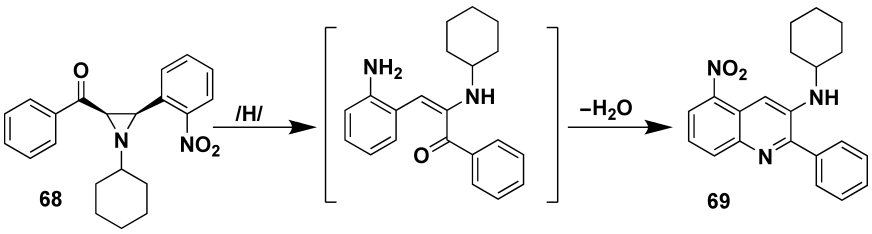
Scheme 1.16

The photoactivated intermolecular dimerization reaction of aziridinyl ketone **18** leading to heterocycle **67** after the initial oxidation of piperazine **66** has also been described [84] (Scheme 1.17).



Scheme 1.17

An example of azaheterocycle synthesis based upon aziridinyl ketones is also a reductive cyclization of 1-cyclohexyl-2-benzoyl-3-(2-nitrophenyl)aziridine **68** into quinoline **69** [14] (Scheme 1.18).

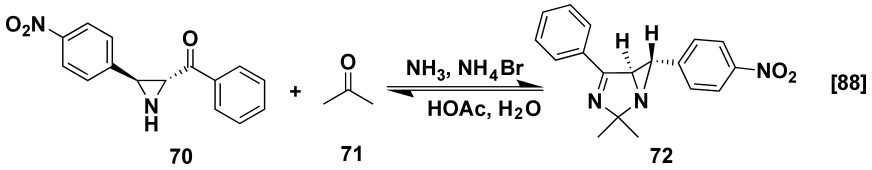


Scheme 1.18

Another process worth mentioning is the *cis–trans* isomerization of aziridinyl ketones. The transformation of *trans*-aziridines into the *cis* form was carried out in a methanol–acetone solution in the presence of triethylbenzylammonium hydrochloride [85]. However, the best yields of the *cis* isomer (up to 90%) were detected by the same authors when water was added to the reaction mixture [86]. The reverse transition from the *trans* configuration into the *cis* form is possible using methanolic solution of sodium methylate [87] or potassium hydroxide [35].

1.2 Synthesis of Bi- and Tricyclic Aziridine Derivatives

One of the initial findings about bicyclic aziridines is reported in [88]; the authors carried out the synthesis of 3,5a-dihydro-1*H*-azireno[1,2-*c*]imidazoles by reacting *trans*-2-aryl-3-aroylaziridines with carbonyl compounds in methanol saturated with ammonia in the presence of ammonium bromide. In particular, 2,2-dimethyl-6-(4-nitrophenyl)-4-phenyl-1,3-diazabicyclo[3.1.0]hex-3-ene **72** was obtained in the reaction of ketone **70** with ammonia and acetone **71** (Scheme 1.19).



Scheme 1.19

Aldehydes, symmetric and asymmetric ketones, such as formaldehyde, acetaldehyde, substituted benzaldehydes and cyclic ketones, were introduced into the reaction along with acetone. The reaction is reversible: azirenoimidazoles undergo reverse transformation forming *trans*-aziridinyl ketones in acetic acid.

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