SYNTHESIS AND PROPERTIES OF SUBSTITUTED 3-AMINO-2H-AZIRINES (REVIEW)

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Methods for the synthesis of and the results of studies of the chemical properties of 3-amino-2H-azirines – compounds that have a highly reactive three-membered nitrogen heteroring and an amidine system, which predetermines their multifaceted reactivity and wide use as convenient synthones for organic synthesis – are correlated.

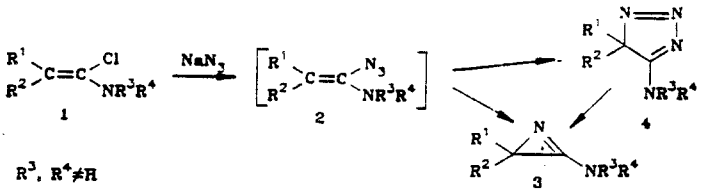
METHODS FOR THE SYNTHESIS OF 3-AMINO-2H-AZIRINES

Reaction of α-Chloro Enamines with Sodium Azide

The first information regarding representatives of a new class of cyclic amidines – 3-amino-2H-azirines – was published in 1970, when N-substituted 3-amino-2H-azirines 3 were obtained on the basis of the reaction of α-chloro enamines 1 with sodium azide, which proceeds through intermediate vinyl azides 2 [1].

A practicable method, developed by Ghosez and coworkers [2], for the synthesis of α-chloro enamines based on the reaction of N,N-substituted amides of carboxylic and thiocarboxylic acids with phosgene in the presence of a base promoted a thorough study of the reaction of α-chloro enamines with azides. On the basis of these studies it was shown that the reaction of α-chloro enamines with sodium azide is the most general preparative method for obtaining N-substituted 3-amino-2H-azirines 3, which contain alkyl, allyl, and aryl substituents in the 2 position [1, 3-5]

The formation of N-substituted 3-amino-2H-azirines in the reaction of α-chloro enamines I with sodium azide can be conceived of as being the result of decomposition of the intermediately formed vinyl azide 2 via two possible mechanisms: 1) through a step involving the formation and decomposition of triazole 4; 2) as a result of synchronous elimination of nitrogen and intramolecular cyclization to azirine 3 [6, 7]:



It should be noted that the production of 2-monosubstituted 3-amino-2H-azirines is restricted to the use of weakly basic stable α-monosubstituted α-chloro enamines in the cited reactions [7, 8].

Thermal Decomposition of Triazines

The possibility of obtaining N-substituted 3-amino-2H-azirines starting from 4H-1,2,3-triazoles 8 was first discovered in [9]. In the opinion of Neuhoeffer and Ohl [9], the 4H-1,2,3-triazole 8 formed in the reaction of cyclopropenyl azides 5 with ynamines 6, inasmuch as it is a thermally unstable compound, readily eliminates nitrogen and is converted to 3-amino-2H-azirine 9, even though the yield is low (20%) (see scheme on top of following page).

It should be noted that 3-amino-2H-azirines 9 are extremely unstable and are obtained only at reduced temperatures.

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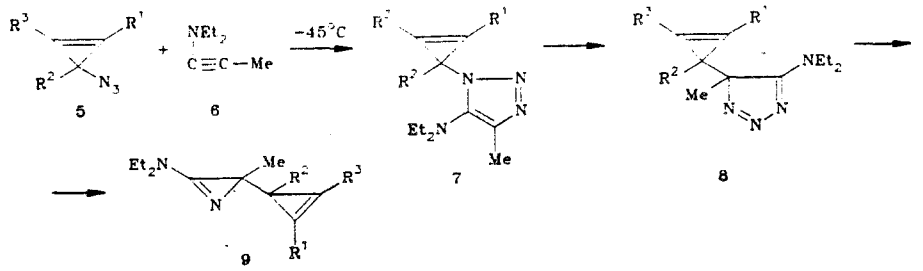
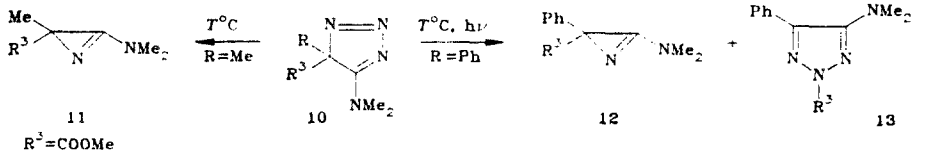


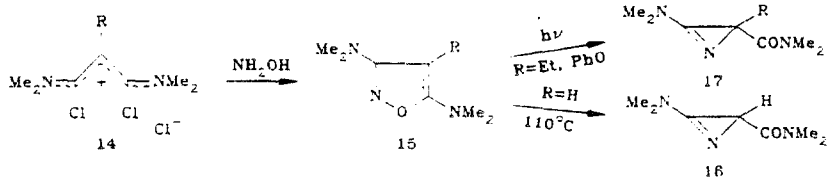
The production of 3-dimethylamino-2H-azirines 11 and 12 as a result of the thermal decomposition of 4-H-1,2,3-triazoles 10, synthesized from α-chloro enamines and sodium azide, was reported later [8]; the pyrolysis of 4H-1,2,3-triazole 10 (R = C_6H_5) leads to 3-amino-2H-azirine 12 and 2H-1,2,3-triazole 13.



As a rule, only 3-dimethylamino-2H-azirines 11 and 12 (in 93% yield) are formed in the photolysis of 4H-1,2,3-triazoles 10 [8].

Photolysis and Pyrolysis of Isoxazoles

One method for the synthesis of 2H-azirines is the photolysis and thermolysis of isoxazoles [10-20]. In 1976 a convenient method was proposed for obtaining 3,5-bis(dimethylamino)isoxazoles 15 from 1,3-dichlorotrimethylcyanine 14 and hydroxylamine; isoxazoles 15 were used for the synthesis of functionally substituted 3-amino-2H-azirines 16 and 17 [21].

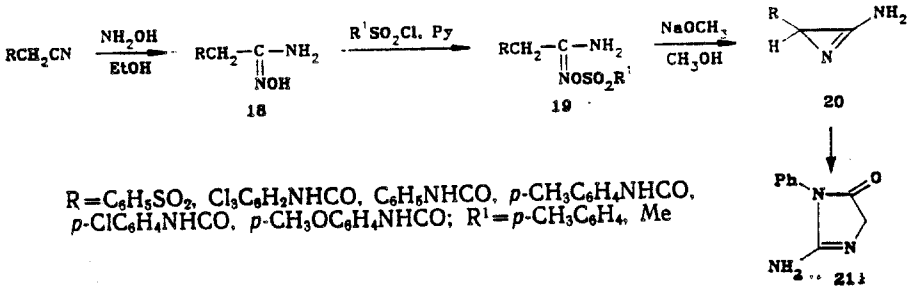


The thermal method for obtaining 3-amino-2H-azirines 16 and 17 from isoxazoles 15 has substantial limitations (R = H) because of the decomposition of 3-amino-2H-azirines at elevated temperatures. However, azirines 17 can be obtained in high yields in the photolytic conversion of the corresponding aminoisoxazoles.

Modified Neber Reaction

In 1932, Neber and coworkers proposed 2H-azirines as intermediates in the rearrangement of oxime p-toluenesulfonates to amino ketones in the presence of bases [22], and the formation of azirines was subsequently confirmed in [23, 24]. However, 3-amino-2H-azirines containing a primary amino group in the 3 position could be obtained for the first time under the conditions of a modified Neber reaction only in 1982. Acetamide oxime O-tosylates and O-mesylates 19, which are converted to the corresponding stable aminoazirines 20 (in 70-90% yields), were used as the starting compounds [25, 26] (see scheme on top of following page).

It should be noted that the direction of the reaction is determined by the conditions under which it is carried out. In particular, in the case of excess sodium methoxide in the reaction medium the principal product of the reaction of phenylcarbamoylacetamide oxime O-tosylate (or O-mesylate) 19 with sodium methoxide is 2-amino-1-phenylimidazol-5-one (21) [25, 26].



R=$C_6H_5SO_2$, $Cl_3C_6H_2NHCO$, C_6H_5NHCO, p-$CH_3C_6H_4NHCO$, p-ClC_6H_4NHCO, p-$CH_3OC_6H_4NHCO$; R^1=p-$CH_3C_6H_4$, Me

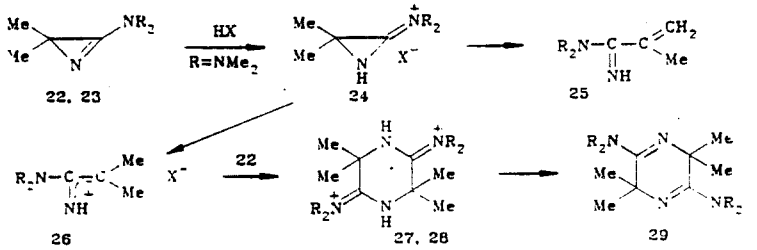
CHEMICAL PROPERTIES OF 3-AMINO-2H-AZIRINES

The peculiarities of the structure of 3-amino-2H-azirines, which are cyclic amidines with an endocyclic C=N bond, are responsible for their reactivities and chemical properties which, in turn, have great practical value in the synthesis of acyclic and heterocyclic nitrogen-containing compounds, including peptide and depsipeptide systems.

The strain of the azirine ring predetermines its chemical transformations; in particular, almost all reactions proceed with opening of the three-membered ring at the C–N, C–C, or C=N bonds.

Addition of Acids to 3-Amino-2H-azirines

The reaction of 3-dimethylamino-2,2-dimethyl-2H-azirine (22) with inorganic acids (hydrochloric, perchloric), as well as with toluene- or methanesulfonic acid, leads to the formation of methacrylamidine 25 and piperazine salt 27 [1, 27, 28].

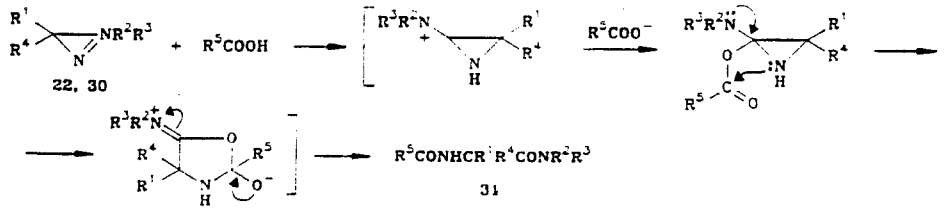


22, 24—27 NR_2=NMe_2; 23, 28, 29 NR_2=piperidino; X=Cl, ClO_4, n-CH_3SO_3, n-$CH_3C_6H_4SO_3$

It is assumed that the resulting aziridinium cation 24 undergoes 1,3 cleavage of the ring and is converted to 1-azaallyl cation 26, the reaction of which with a second molecule of azirine 22 gives a pyrazine salt. Deprotonation of cation 23 leads to methacrylamidine 24 [1, 27, 28].

The reaction of 3-amino-2H-azirine 23 with hydrochloric acid to give salt 28, the alkaline hydrolysis of which leads to dihydropiperazine 29, proceeds similarly [1].

The reactions of azirines 22 and 30 with mono- and dicarboxylic acids proceed with opening of the azirine ring and lead to the formation of 2-acylaminoisobutyramides 31, which are excellent synthones for obtaining peptides and depsipeptides [26, 29, 30].

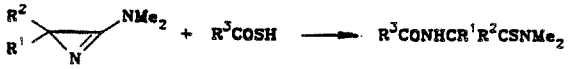


30 R^1=R^2=R^3=H, R^4=C_6H_5NHCO, R^5=COOH, C_6H_5, $C_6H_5CH_2$, C_6H_5C=C, HOOCCH=CH, Me, CH_2=CH

Aminoazirine 22 reacts similarly with benzene- and p-toluenesulfinic acids [28].

The mechanism proposed by Vittorelli and coworkers [29] for these reactions is similar to the transformation of other functionally substituted 2H-azirines with carboxylic acids [31-33].

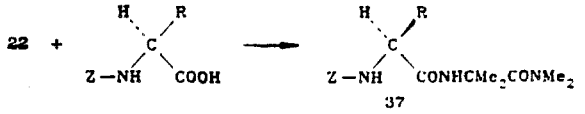
The reaction of thiocarboxylic acids with aminoazirines 22, 30, and 32-35 is a convenient method for the synthesis of thioamides 36 (in 70-94% yields) [26, 34, 35]:



22, 30, 32–35 — 36

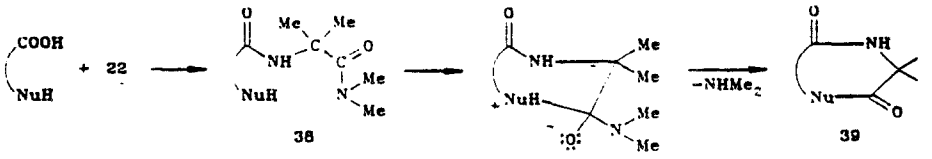
R^3 = Ph, Me; 22 $R^1 = R^2 = Me$; 32 $R^1 = R^2 = Ph$; 33 $R^1 = Me$; $R^2 = CHMe_2$; 34 $R^1 = Me$, $R^2 = CH_2{=}CH$; 35 $R^1 = CH_2{=}CH{-}CH_2$, $R^2 = Me$

The reaction of dimethylaminoazirine 22 with N-substituted amino acids and peptides, which leads to the formation of 2-aminoisobutyramides 37 which, in turn, are convenient starting compounds in the synthesis of optically active peptides, was recently reported [36, 37].



37

It should be noted that the reactions of azirine 22 with hydroxy, mercapto, and amino carboxylic acids have great synthetic value, since diamides 38 formed during the reactions additionally have a nucleophilic center, which promotes their facile cyclization to numerous heterocyclic systems 39 with 5 to 15 links [30, 38-40].

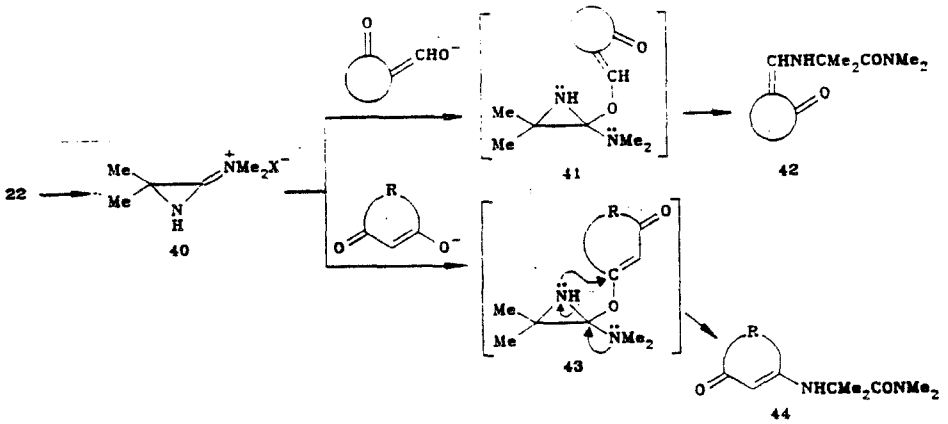


38 — 39

Similarly, diaminoazirine 22 reacts with a disubstituted malonic acid monoamide to give a triamide, which is readily converted to a 1,4-diazocine-2,5,7-trione [41, 42].

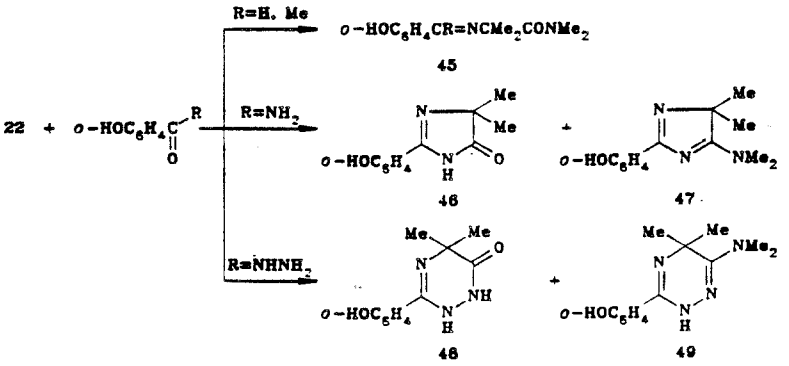
Reactions of 1,3-Dicarbonyl Compounds, Phenols, and Aryl Halides with 3-Amino-2H-azirines

1,3-Dicarbonyl compounds – 2-formylcycloalkanones and enol forms of cyclic 1,3-diketones, which can be represented as vinylogs of carboxylic acids with $pK_a \leq 8$ – react with azirine 22 in the same way as carboxylic acids to give N-substituted derivatives of 2-amino-N,N-dimethylisobutyramides [28, 29].

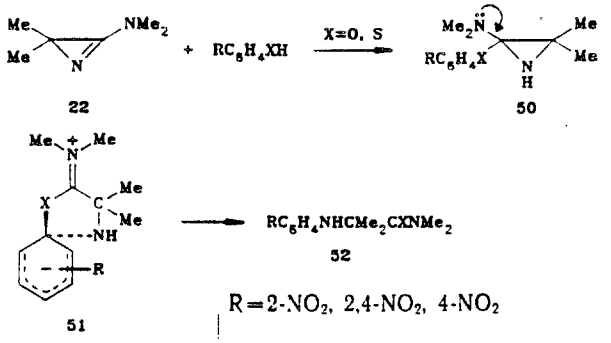


40 — 41 — 42 — 43 — 44

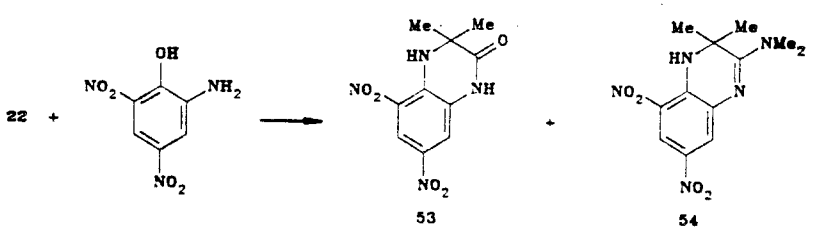
2-Acylphenols also react with aminoazirine 22 via a similar mechanism; however, the natures of the final products of these reactions are extremely diverse. Thus, if salicylaldehyde and 2-hydroxyacetophenone (R = H, CH_3) react with aminoazirine 22 to give N-substituted derivatives 45 of isobutyramide 45, a similar reaction with salicylic acid hydrazide and amide (R = $NHNH_2$, NH_2) leads to imidazolone 46, imidazole 47, and 1,2,4-triazine 48 and 49 derivatives [27, 42].



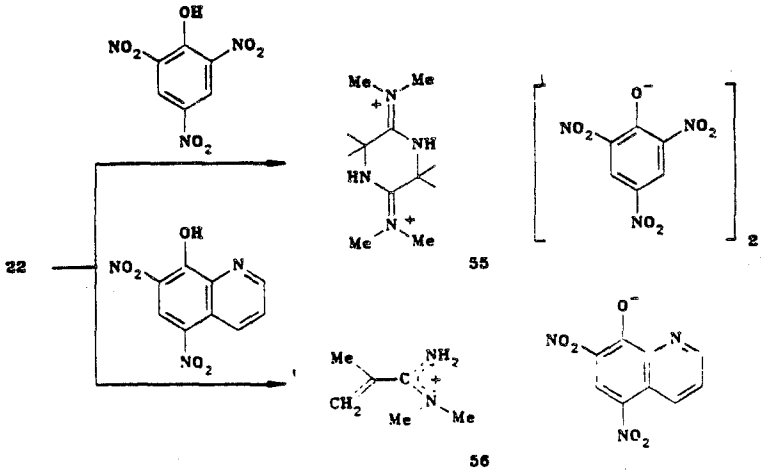
The reaction of 2H-azirine 22 with activated phenols [27, 38, 43] which, in the opinion of Heimgartner and coworkers, proceeds with the formation of intermediate addition product 50 and Meisenheimer spiro complex 51, leads to isobutyramide anilino derivatives 52.



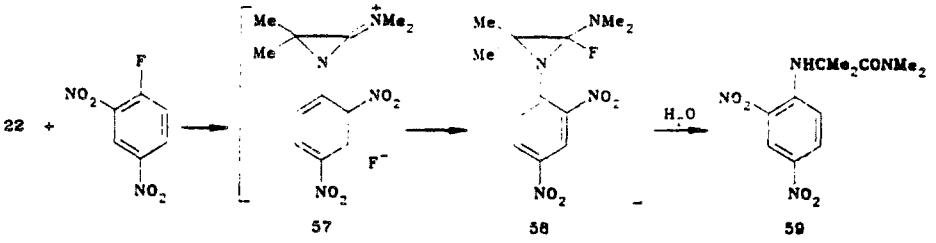
In addition, picramic acid reacts with 2H-azirine 22 through a step involving intramolecular cyclization of the addition product to give quinazoline derivatives 53 and 54 [44].



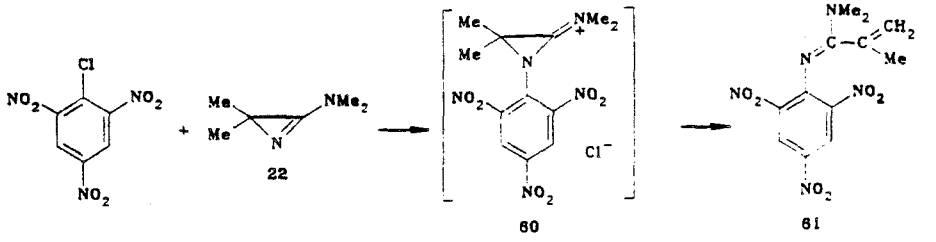
It is interesting that the reaction of azirine 22 with a more acidic phenol, viz., picric acid, as well as with 8-hydroxy-5,7-dihydroquinoline, proceeds in the same way as the reaction of 3-aminoazirine 22 with strong acids (HCl, $HClO_4$, RSO_3H) and terminates with the formation of dipicrate 55 or methacrylamidinium salt 56 [1, 27, 28].



Heating azirine 22 with aryl halides (2,4-dinitrochlorophenol or 2,4-dinitrofluorobenzene) in benzene or acetonitrile with subsequent hydrolysis leads to substituted N,N-dimethylisobutyramide 59 [27].



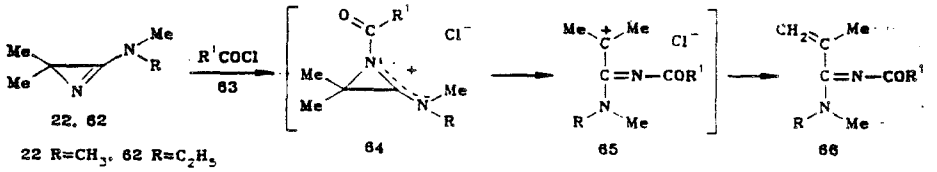
In addition, the same reaction with 2,4,6-trinitrochlorobenzene, as a result of nucleophilic aromatic substitution and subsequent 1,2 cleavage of the ring, terminates with the formation of acrylamide 61 [27]:



Similarly, 8-chloro-5,7-dinitroquinoline also reacts with azirine 22 to give an acrylamide derivative [27].

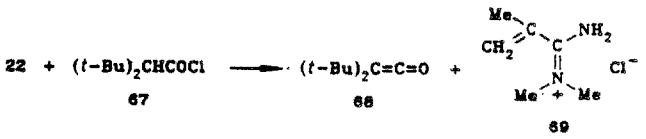
Electrophilic Addition of Acid Chlorides, Anhydrides, and Amides to 3-Amino-2H-azirines

In reactions with carboxylic acid chlorides 63 3-dialkylaminoazirines 22 and 62 undergo 1,2 cleavage of the ring to give 1-azaallyl cation 65, the subsequent deprotonation of which leads to N-acylamidines 66 [45-47].

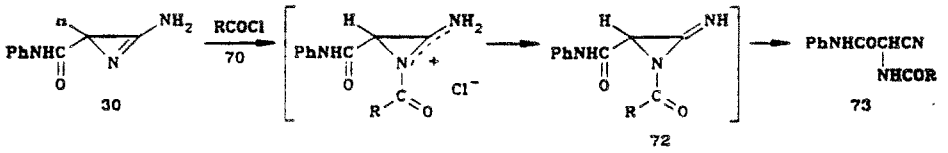


Similarly, dimethylaminoazirine 22 reacts with p-toluenesulfonyl chloride to give a tosylamidine derivative.

In the case of the reaction of azirine 22 with 2-tert-butyl-3,3-dimethylbutyryl chloride – acid chloride 67, which has a bulky substituent – ketene 68 and N-isobutyryl-N^2,N^2-dimethylmethacrylamidinium salt 69 were isolated instead of the expected N-acylamide [45].

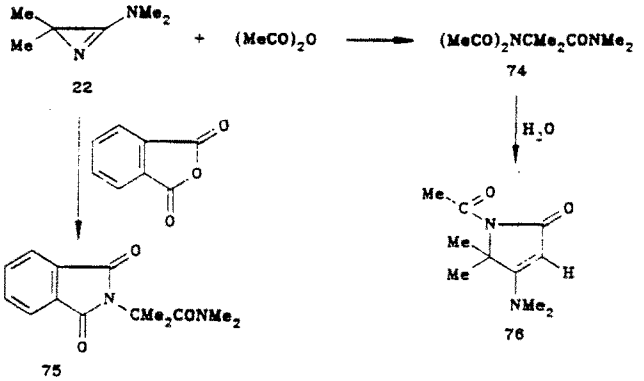


In addition to this, 3-amino-2-phenylcarbamoyl-2H-azirine (30), which contains a primary amino group in the 3 position, reacts with carboxylic acid halides to give aminomalonic acid nitriles – products of electrophilic attack by the acylating reagents at the endocyclic nitrogen atom with subsequent heterolysis of the three-membered ring at the 1,3 bond [48, 49].

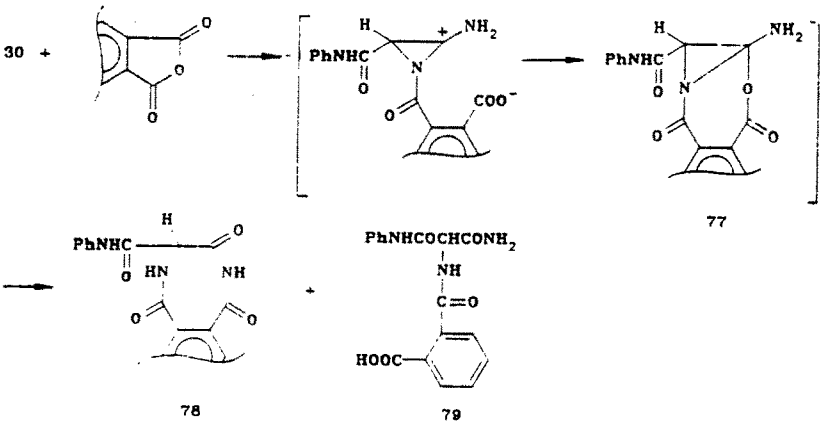


Similar products were obtained in the reaction of azirine 30 with chlorocarbonic acid esters and sulfonic acid chlorides [48, 49].

Whereas the reactions of dialkylaminoazirines with acid chlorides proceed primarily with cleavage of the C–N single bond of the ring, which is a consequence of the presence of a strong nucleophile in the reaction, the analogous reactions with acid anhydrides (acetic and phthalic) are realized through cleavage of the C=N double bond with the formation of N,N-dimethylisobutyramide diacylamino derivatives 74 and 75; the resulting amide 74 undergoes partial hydrolysis to 3-pyrrolin-2-one 76 [45].

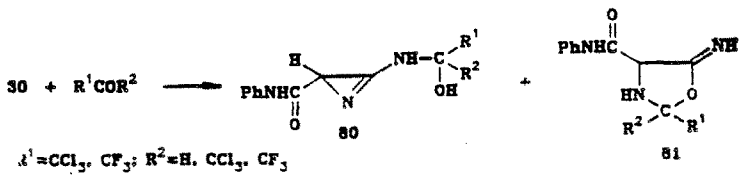


In contrast to azirine 22, 3-phenylcarbamoylazirine 30 reacts with phthalic and naphthalic anhydrides to give representatives of an extremely difficult-to-obtain class of polycyclic nitrogen-containing compounds, viz., diazocine-1,4,6-triones, which are evidently obtained through a step involving intermediate bicyclic aziridine 77 [50].

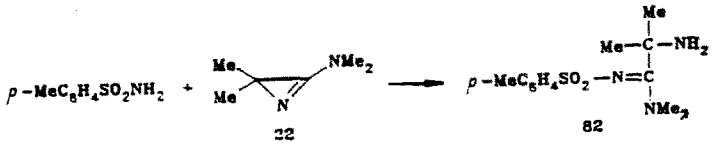


It should be noted that, in addition to diazocine-1,4,6-trione, amide 79 is formed in up to 30% yield in the reaction of azirine 30 with phthalic anhydride [50].

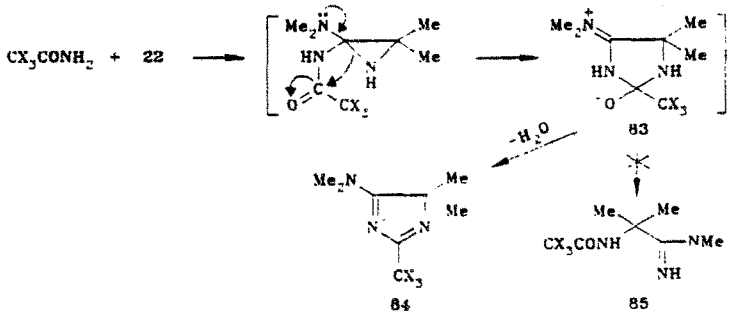
The reaction of 3-aminoazirine 30 with chloral and hexachloro- and hexafluoroacetone is the only example of reactions of azirines that proceed with retention of the three-membered ring and opens up a pathway to N-(1-azirin-2-yl)amino alcohols 80 – the first representatives of α-amino carbinols of the azirine series. In addition to an α-amino carbinol, a very small amount of 5-iminooxazolidine 81 was detected when the reaction of aminoazirine 30 with hexachloroacetone was carried out [51].



Heating 3-dimethylamino-2,2-dimethyl-2H-azirine with p-toluenesulfonamide in 2-propanol leads to sulfonylamidine 82 in 60% yield as a result of cleavage of the ring 1,2 bond [44].



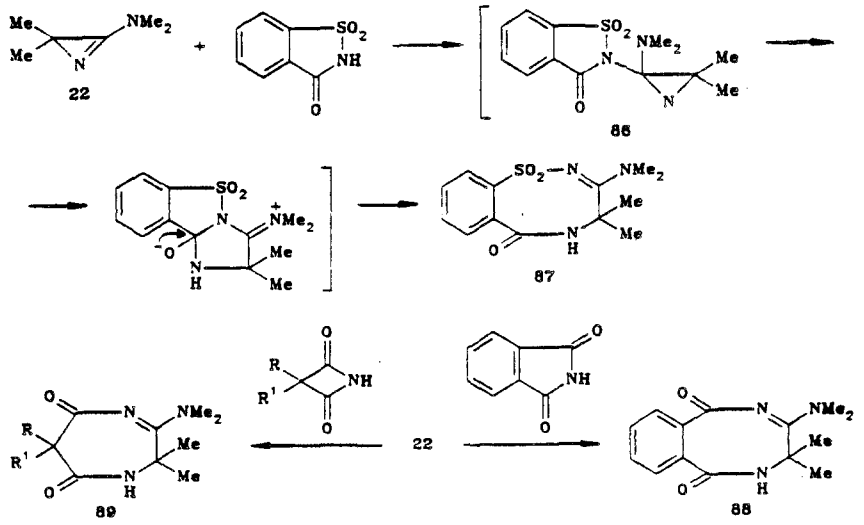
Trifluoro(chloro)acetamides react unusually with azirine 22; instead of the hypothetical 85, these amides form 4H-imidazole 84 in 80% yield as a result of the elimination of water from intermediate zwitterion 83 [44].



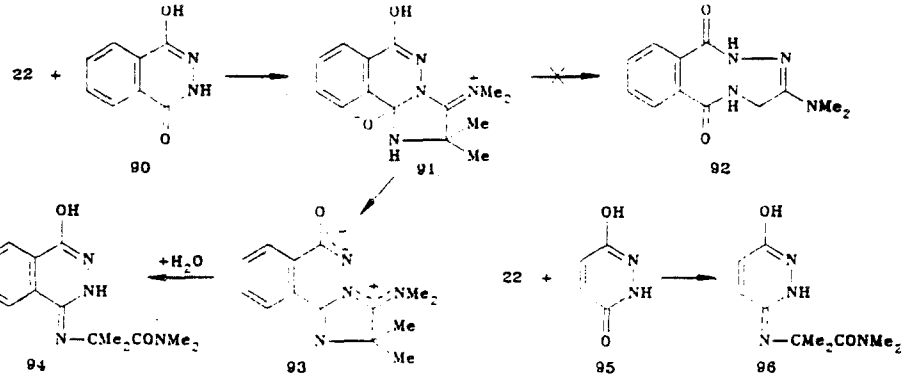
Addition of NH Acids to 3-Amino-Substituted 2H-Azirines

The reaction of 3-dimethylamino-2,2-dimethyl-2H-azirine with NH acids such as saccharine, phthalimide, and disubstituted malonimides proceeds with ring expansion and the formation of seven- and eight-membered heterocyclic systems [52, 53]. It is assumed that the latter arise as a result of intramolecular rearrangement of addition product 86 with subsequent ring cleavage to substituted benzothiodiazocines 87 and 88 and diazocine 89 [52, 53] (see scheme on top of following page).

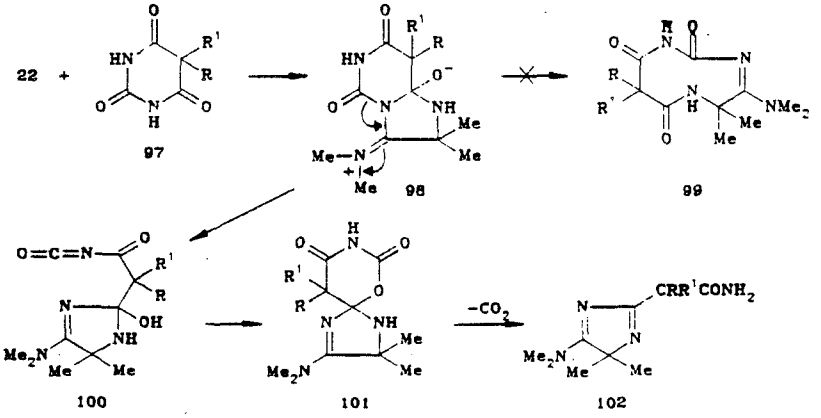
It is surprising that 2H-azirine 22 reacts differently with NH-acidic six-membered heterocycles, viz., 2,3-dihydrophthalazine-1,4-dione (90) and 1,2-dihydropyridazine-3,6-dione (95) [54]. The resulting intermediate 91, instead of the expected stabilization to nine-membered heterocycle 92, is converted, as a result of proton transfer and the elimination of water, to zwit-



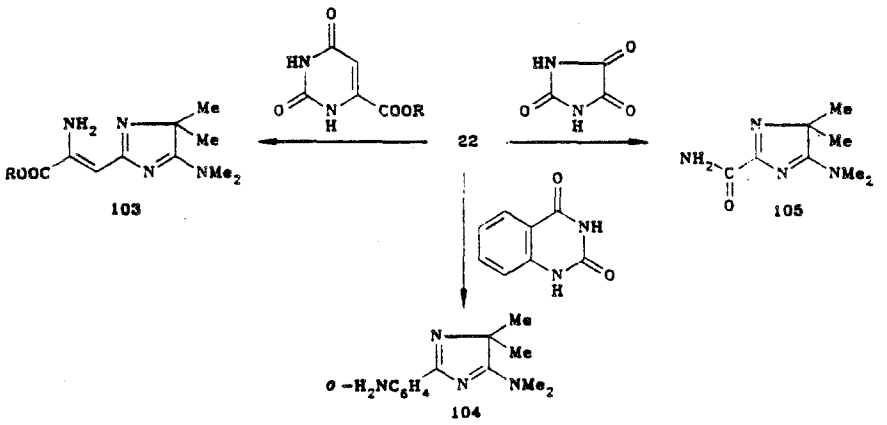
terion 93, the hydrolysis of which leads to 1,2-dihydrophthalazine derivative 94. Hydrazide 95 reacts with azirine 22 to give 2,3-dihydropyrazine derivative 96.



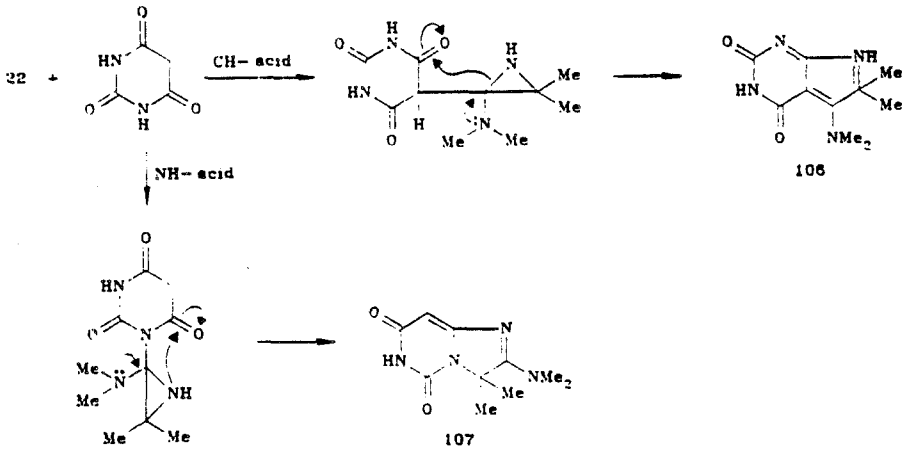
Similarly, the formation of nine-membered heterocyclic systems 99 is not observed in the reaction of 3-amino-2H-azirine 22 with 5,5-disubstituted barbituric acids 97 [55]. It is assumed that the resulting zwitterion 98 is stabilized by a different energically more favorable pathway through isocyanate 100, the subsequent intramolecular cyclization of which leads to spiro compound 101, which undergoes rearrangement with splitting out of CO_2 to give 4H-imidazole derivatives 102 [55].



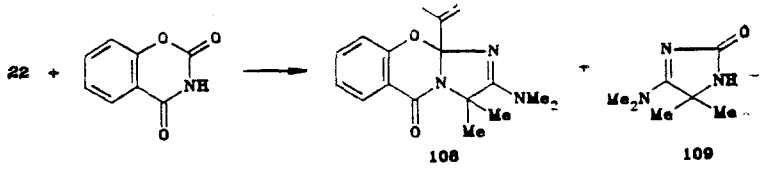
Such structures of the imidazole type are formed in the reaction of azirine 22 with other heterocyclic compounds that contain an NHCONHCO fragment, viz., uracil-4-carboxylic acid isopropyl ester, quinazoline-2,4(1H, 3H)-dione, and imidazolidinetrione; this constitutes evidence for the general character of the mechanism of these reactions, which open up a new approach to structural analogs of 4H-imidazole [55, 56].



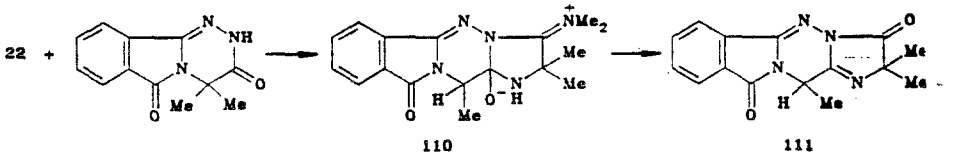
In its reaction with 3-amino-2H-azirine 22 unsubstituted barbituric acid displays bifunctional properties and, as a result, 2H-pyrrolo[2,3-d]pyrimidine-2,4-dione 106 (40%) and 3H-imidazo[1,2-c]pyrimidine-5,7-dione 107 (10%) derivatives are formed [58].



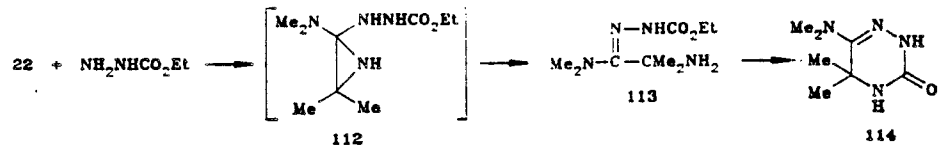
Heating benzoxazine-2,4-dione with azirine 22 in 2-propanol leads to the formation of imidazo[2,1-b]-1,3-benzoxazin-5-one 108 and 3-imidazolin-2-one 109 derivatives [58].



Azirine 22 reacts with 1,2,4-triazolo[3,4-*a*]isoindole-3,6-dione to give unstable zwitterion 110, which is readily converted to tetracyclic system 111 under the conditions of the hydrolysis [59].

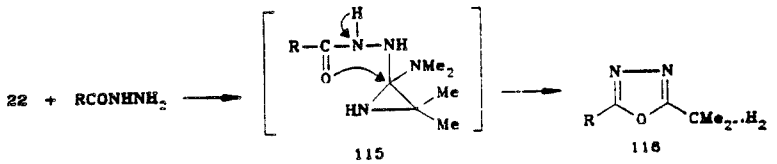


The reaction of dimethylaminoazirine 22 with ethyl carbazate in 2-propanol at 70°C leads to the formation of an amino ester, which is readily cyclized to 4,5-dihydro-1,2,4-triazine-3-one 114 [60].



Oxalic acid hydrazides react similarly with azirine 22 to give hydro-1,2,4-triazine derivatives [60].

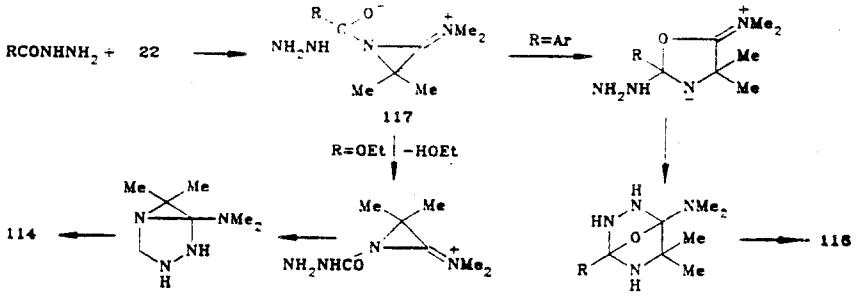
However, hydrazides of aromatic carboxylic acids react with azirine 35 to give substituted 1,3,4-oxadiazoles [60].



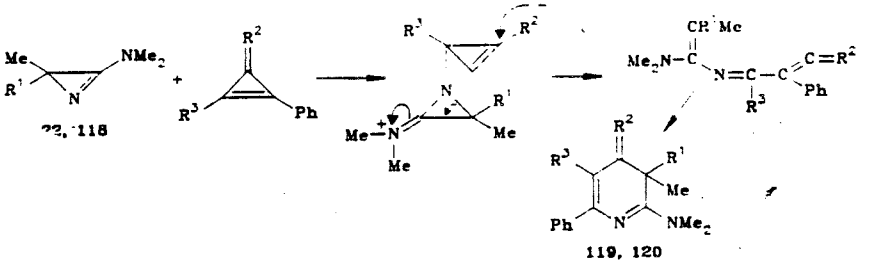
R=Ph, *p*-NO_2—C_6H_4, 4-pyridyl.

It is assumed that the first step in the reaction of azirine 22 with carboxylic acid hydrazides is protonation of azirine 22 and the formation of aminoaziridines 112, 115, which undergo 1,3 cleavage of the ring with the subsequent elimination of ethanol or dimethylamine and the formation of heterocyclic nitrogen- and oxygen-containing systems 114 and 116.

However, considering the low basicities of carboxylic acid hydrazides, one cannot exclude the possibility that these reactions proceed through the nucleophilic addition of azirine 22 to the carbonyl group of the hydrazide with the formation of zwitterion 117, the subsequent transformation of which leads to products 114 and 116 [44, 60].



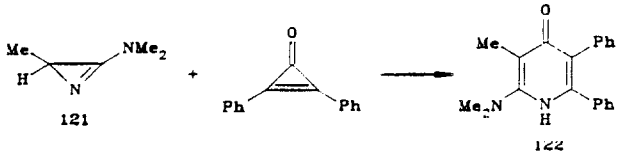
The formation of 4(3H)-pyridinethiones 120 or 4(3H)-pyridones 119 is observed in the reactions of azirines with cyclopropenones as a result of nucleophilic attack by azirine 22 or 118 at the C=C bond [61-64].



22 R^1=Me; 118 R^1=Ph; 119 R^1=Me, Ph, R^2=O, R^3=Ph, $CHMe_2$; 120 R^1=Me, Ph, R^2=S, R^3=Ph

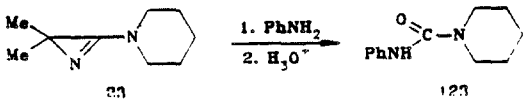
3-Phenyl-2H-azirines also react similarly with cyclopropenones [65, 66].

However, 3-dimethylamino-2-methyl-2H-azirine (121), which is monosubstituted in the 2 position, reacts with diphenylcyclopropenone to give (1H)-pyridone 122 [61].

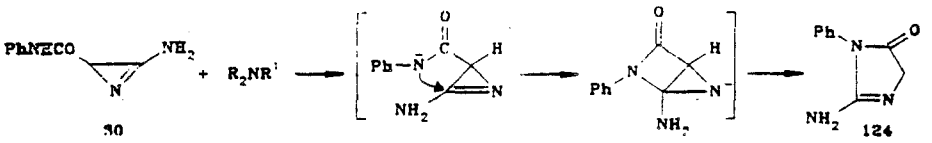


Reactions of Aminoazirines with Nitrogen Bases

The reaction of azirine 23 with aniline and subsequent acidic hydrolysis lead to the formation of ureide 123 [1].



The study of the reactions of aminoazirine 30 with amines, hydrazines, and semicarbazide led to the formation of a new type of rearrangement in the 2H-azirine series, which is accompanied by the formation of 2-amino-5-imidazolone 124 in all cases:

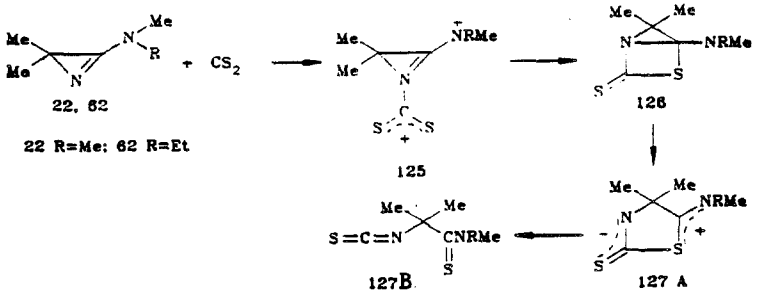


R=H, R¹=Me, *t*-C_4H_9, CH_3NH, NH_2NHCO, NH_2, $(CH_3)_2N$; R=Et, R¹=H, Et

Reactions of 3-Amino-2H-azirines with Heterocumulenes

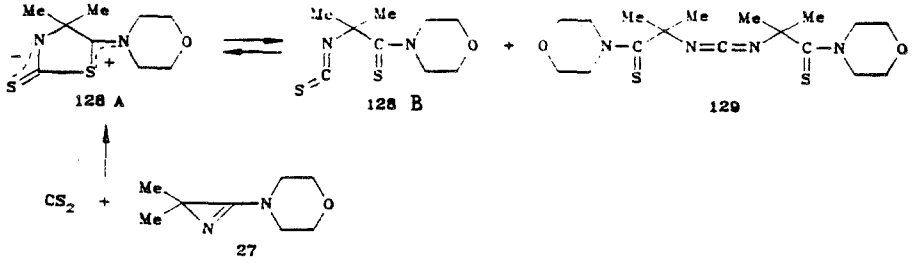
The reactions of N-substituted 3-amino-2H-azirines with heterocumulenes – carbon disulfide, isocyanates, ketenes, and imides – proceed in the same way as reactions involving the addition of amidines to heterocumulenes [68-76].

3-Dialkylamino-2H-azirines 22 and 62 react with carbon disulfide at room temperature to give adduct 127, which in the crystalline state exists in the form of stable zwitterion A, whereas in solution it exists in the form of a tautomeric mixture of cyclic (A) and linear (B) forms [77-81].



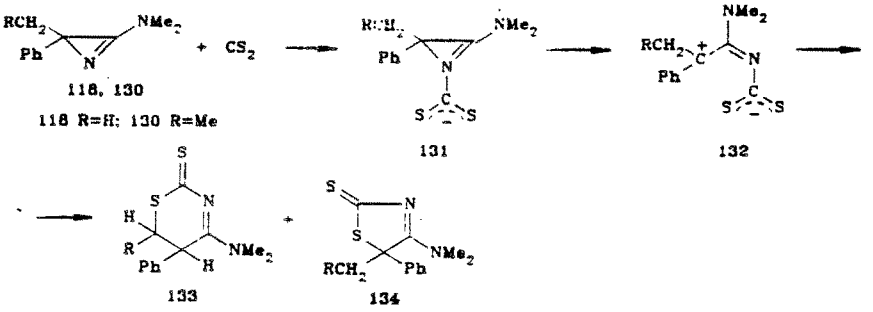
According to the data in [77-81], the initially formed iminoaziridinium zwitterion 125, as a result of intramolecular cyclization, is converted to azabicyclic compound 126, which undergoes cleavage of the 1,3 bond of the aziridine ring with the formation of stable zwitterion 127A.

In addition to the formation of adduct 128, carbodiimide 129 – the product of the subsequent reaction of 128 with azirine 27 – was obtained in 42% yield in the reaction of 3-morpholino-2H-azirine 27 with carbon disulfide [77].

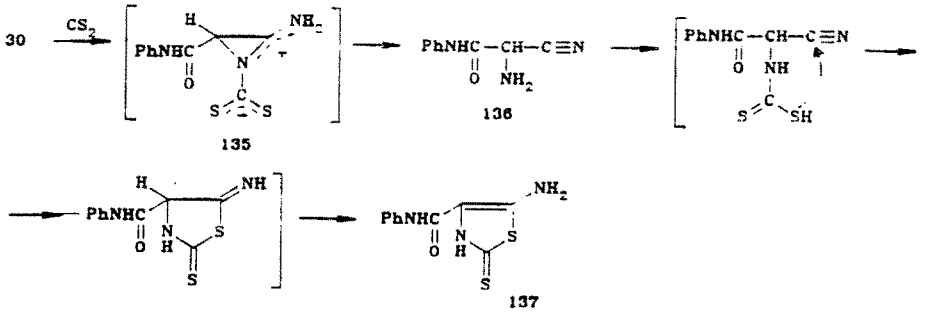


It should be noted that both tautomeric forms A and B of 127 and 128, inasmuch as they have high reactivities, can participate in subsequent reactions. Thus zwitterion structure A participates in the alkylation, hydrolysis, and reduction of 127, while linear form 127B undergoes reaction with amines and a second molecule of the aminoazirine [77, 78, 80].

In the reaction of carbon disulfide with azirines 118 and 130, which contain a phenyl substituent in the 2 position, the initially formed zwitterion 131 undergoes 1,2 cleavage of the ring to form 1,5-dipole 132 which, in turn, as a result of intramolecular cyclization, is converted to 1,3-thiazine-2-thione 133 and 5-dimethylaminothiazoline-2-thione 134 derivatives [79].

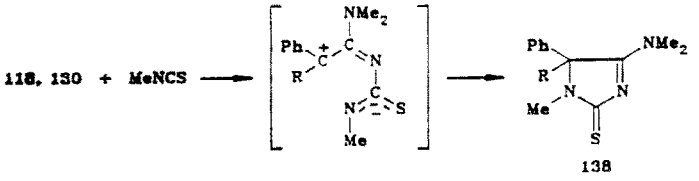


In addition, stepwise occurrence of the reaction through an intermediate α-cyanoglycine anilide, the subsequent reaction of which with carbon disulfide leads to the formation of thiazoline-2-thione 137, was established in a study of the reaction of 3-amino-2-phenylcarbamoyl-2H-azirine (30) with carbon disulfide [82].

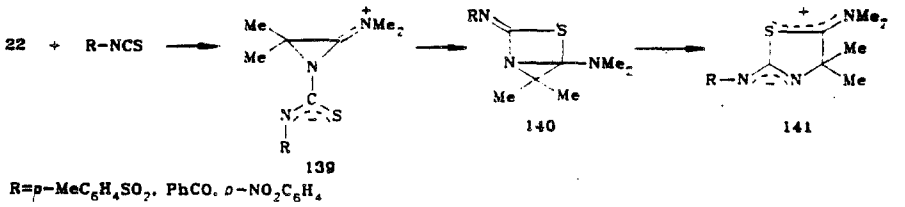


It is assumed that the initially formed zwitterion 135 is converted to α-amino nitrile 136. The subsequent electrophilic addition of carbon disulfide to amino nitrile 136, which leads to the formation of 5-amino-4-phenylcarbamoyl-4-thiazoline-2-thione (137), is realized via the scheme that is characteristic for the reaction of carbon disulfide with functionally substituted α-amino nitriles [83].

The reaction of 3-dialkylamino-2H-azirines 118 and 130 with methyl isocyanate, which leads to 3-imidazoline-2-thiones 138 [84, 85], is realized in the same way as the scheme of the reactions of these azirines with carbon disulfide.

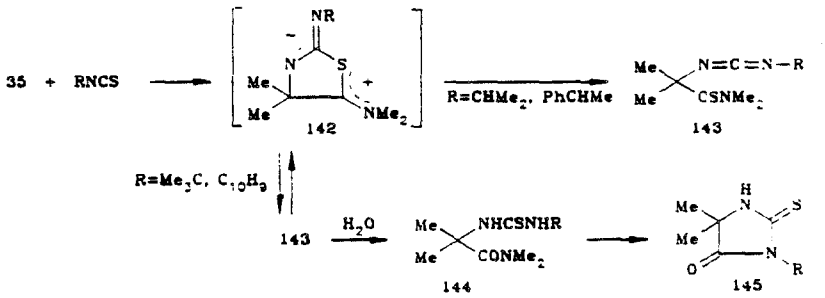


The reaction of azirine 22 with isothiocyanates that have strong electron-acceptor substituents provides evidence that the resulting aziridinium zwitterion 139 is stabilized by means of intramolecular cyclization to azabicyclic system 140 and with the subsequent formation of stable thiazolinium zwitterion 141 [86-88].

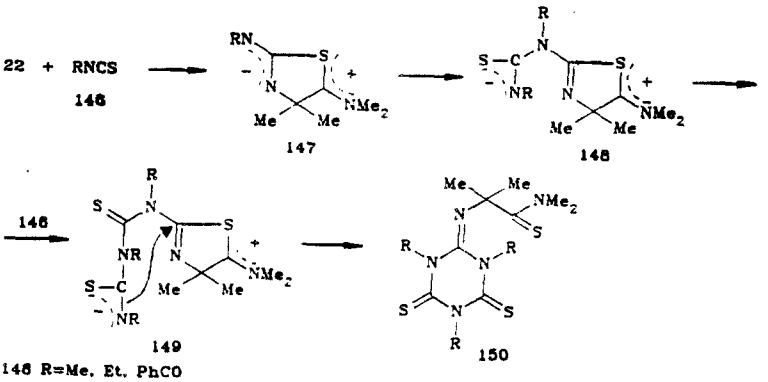


3-Amino-2H-azirines 118 and 130 react similarly with aryl isothiocyanates (R = C_6H_5, $C_6H_4CH_3$-p, $C_6H_4OCH_3$-m) [84].

However, the reaction of azirine 22 with isothiocyanates that have bulky alkyl substituents gives unstable zwitterions 142, which are converted completely to carbodiimides 143; in the case of tert-butyl and 1-adamantyl isothiocyanates carbodiimides 143 are hydrolyzed in situ to thiourea derivatives 144. The latter on heating readily undergo cyclization to 2-thiohydantoins 145 [86].

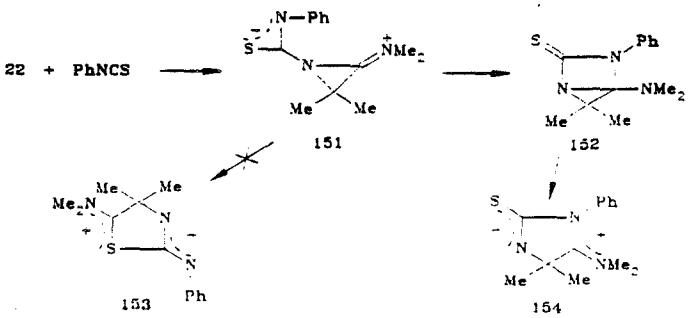


It has been shown [86, 87] that the reaction of azirine 22 with methyl, ethyl, or benzoyl isothiocyanate (146) leads, depending on the reaction temperature, to the formation of adducts (1:2 or 1:3) 148 and 150. Thus 1:2 adducts, viz., 3-thiazoline-2-thioureide zwitterions, are formed when this reaction is carried out at 20-30°C, while an increase in the temperature to 50-60°C leads to 1:3 adducts, viz., iminotriazinedithiones 150.

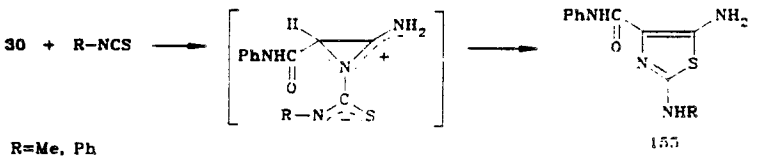


The formation of triazines 150 is due to intramolecular rearrangement of addition product 149 which, in turn, is formed as a result of the reaction of zwitterion 147 with two molecules of the isothiocyanate.

A special case is the reaction of phenyl isothiocyanate with 3-aminoazirine 22, in which, instead of the expected thiazolinium zwitterion 153, an adduct identified as imidazolinium zwitterion 154 was isolated [68].



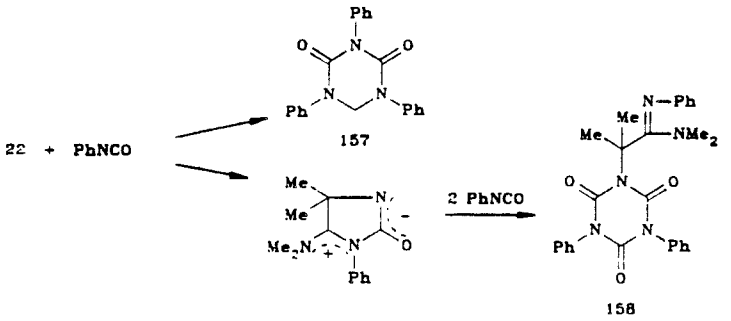
In the case of the reaction of isothiocyanates with aminoazirine 30, which has a primary amino group, 2,5-diaminothiazoles 155, which are products of electrophilic addition of the isothiocyanates to the endocyclic nitrogen atom of azirine 30, were obtained [89].



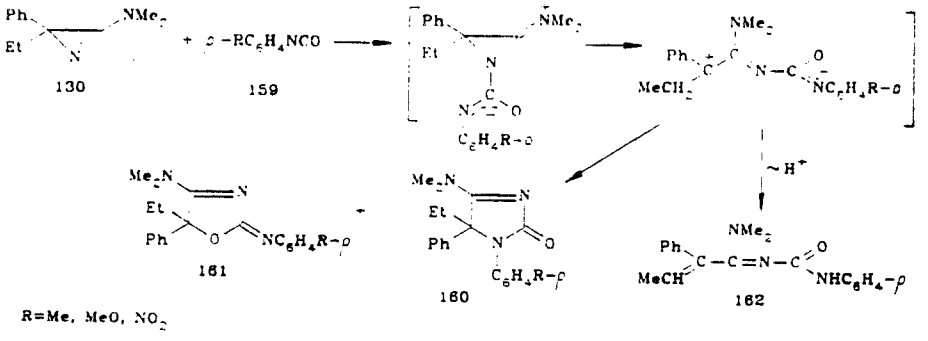
R=Me, Ph

The reaction of phenyl isocyanate with 3-dimethylaminoazirine 22 leads to the formation of 1,3,5-triazabicyclo[4.1.0]-heptane-2,4-dione 156, which undergoes decomposition to the starting components on heating [80].

On the other hand, it has been reported [90] that a 1:3 adduct, viz., perhydro-1,3,5-triazine-2,4,6-trione derivative 158 (in 36% yield), and triphenylisocyanuric acid 157, viz., the product of trimerization of phenyl isocyanate (in 18% yield), are formed in the reaction of azirine 22 with phenyl isocyanate under similar conditions.



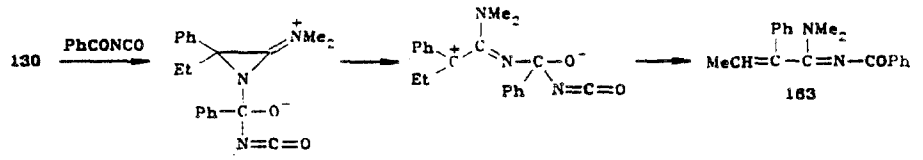
In a study of the reaction of azirine 130 with aryl isocyanates 159 it was established that the products are mixtures of 3-imidazolin-2-one 160 and 2-imino-3-oxazoline 161, as well as 2-phenylcrotonic acid derivative 162; imidazoline 160 predominates in the reaction with p-methyl- and p-methoxyphenyl isocyanates, while oxazoline 161 predominates in the reaction with p-nitrophenyl and phenyl isocyanates [84].



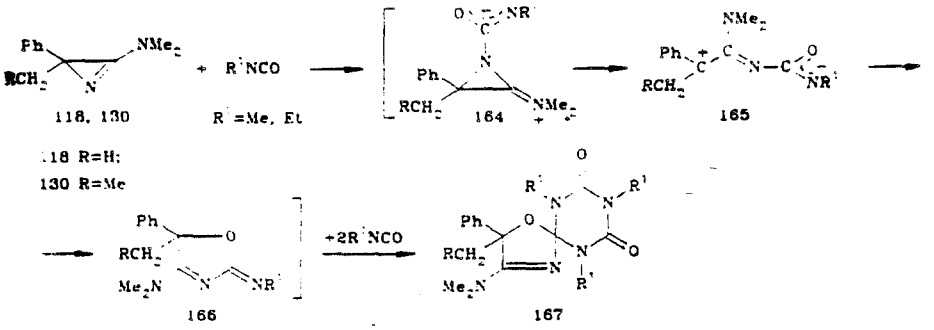
R=Me, MeO, NO_2

It should be noted that the yields of cycloadducts 160 and 161 decrease with a decrease in the electrophilicity of aryl isocyanates 159.

In contrast to aryl isocyanates 159, N^2-benzoyl-N',N'-dimethyl-2-phenylcrotonamidine (163), rather than cyclic products, is formed in the reaction of aminoazirine 130 with benzoyl isocyanate [84].



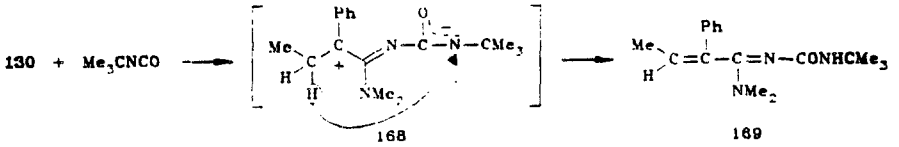
The formation of trialkylisocyanuric acids from azirine 22 and alkyl isocyanates constitutes evidence that the aminoazirine does not undergo an addition reaction with alkyl isocyanates [88].



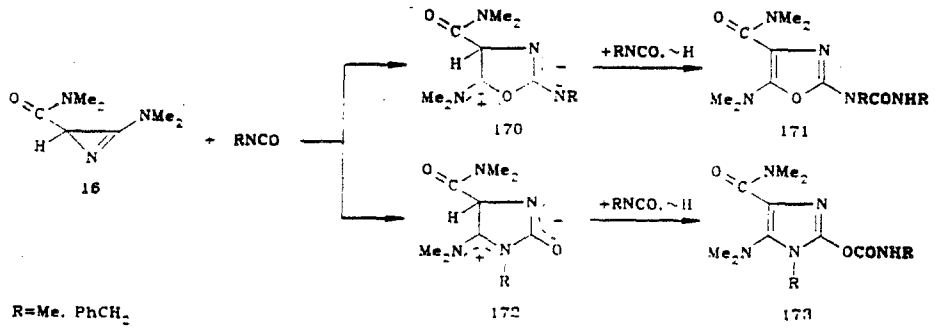
In contrast to azirine 22, azirines 118 and 130 react with alkyl isocyanates to give 1:3 adducts, viz., 1,3,5-trialkyl-4,6-dioxohexahydro-1,3,5-triazine-2-spiro-2'-(4-dimethylamino-5-alkyl-5-phenyl-3-oxazolines) 167 [91].

It is assumed that the resulting zwitterion 164 undergoes 1,2 cleavage of the ring with subsequent intramolecular cyclization of 1,5-dipole 165 to oxazoline 166, the subsequent addition of two molecules of alkyl isocyanate to the exocyclic C=N bond of which leads to spiro compound 167.

However, in the reaction of azirine 130 with tert-butyl isocyanate the resulting 1,5-dipole 168, in contrast to 1,5-dipole 165, undergoes intramolecular proton transfer with the formation of N^2-(tert-butylcarbamoyl)-N',N'-dimethyl-2-phenylcrotonamidine (169) in 64% yield [91].

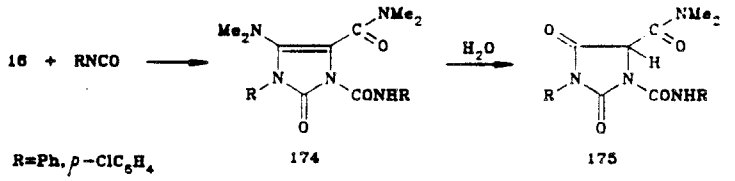


3-Dimethylamino-2-dimethylcarbamoyl-2H-azirine (16), which is monosubstituted in the 3-position, reacts with methyl and benzyl isocyanates to give 1:2 adducts with imidazole (171) and oxazole (173) structures [91].

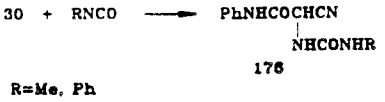


It is assumed that the reaction proceeds through 1,2 cleavage of the azirine ring to give zwitterions 170 and 172 which, as a result of intramolecular charge transfer with the simultaneous addition of a second molecule of the isocyanate, are converted to 171 and 173.

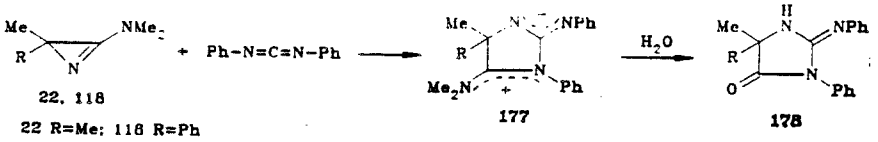
It is interesting that the reaction of azirine 16 with phenyl and p-chlorophenyl isocyanates with subsequent hydrolysis of adduct 174 leads only to imidazolidine derivative 175 [91].



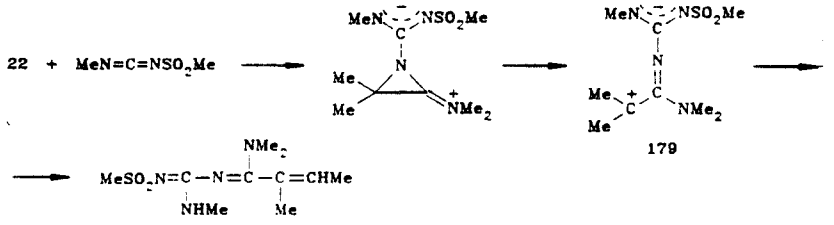
Absolutely unusual results were obtained in the reaction of 3-aminoazirine 30 with methyl and phenyl isocyanates. The principal products of these reactions are aminomalonic acid nitriles 176 [89].



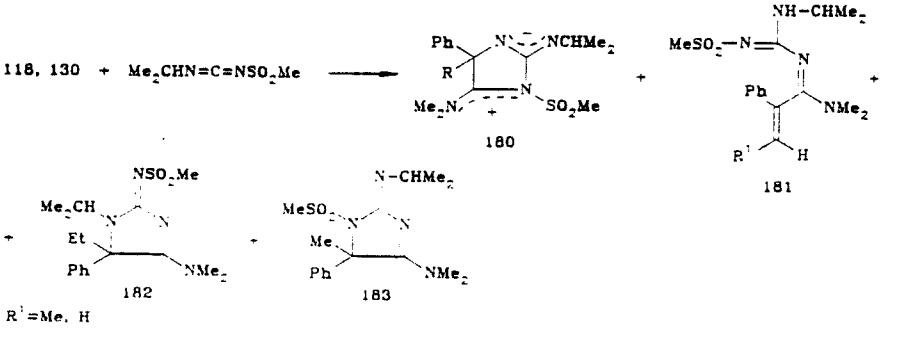
Azirines 22 and 118 react with diphenylcarbodiimide to give unstable 1:1 adducts, viz., imidazolinium zwitterions 177, which are readily hydrolyzed with the simultaneous splitting out of dimethylamine to give 4-imidazolidines 178.



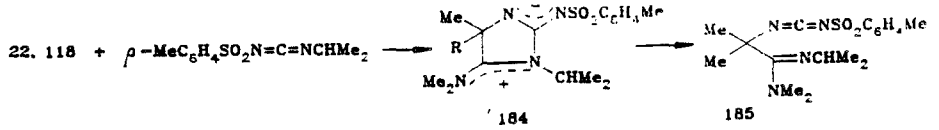
Instead of the expected zwitterionic compound, N^2-(N^2-mesyl-N′-methylamidino)-N,N′-dimethyldiglycineamidine, which is evidently formed as a result of cleavage of the 1,3 bond of the azirine through 1,5-dipole 179, was isolated in the reaction of azirine 22 with mesylmethylcarbodiimide [92].



The reaction of azirines 118 and 130 with isopropylmesylcarbodiimide, in which two competitive reactions with opening of the 1,2 or 1,3 bond of the azirine ring are observed, is interesting [83]. Stable zwitterionic imidazolinium system 180 is formed as a result of a (2 + 2)-cycloaddition reaction and subsequent 1,3 cleavage of the ring, while small amount of acrylamidine derivative 181 and imidazoline derivatives 182 and 183 are formed as a result of cleavage of the 1,2 bond [92].

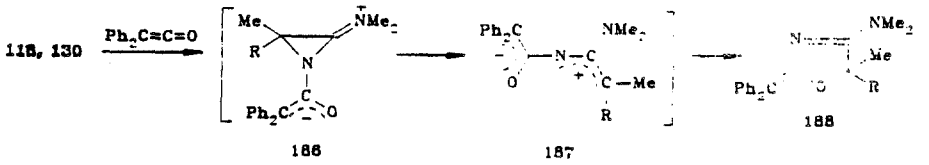


However, the reaction of azirines 22 and 118 with isopropyltosylcarbodiimide, as with diphenylcarbodiimide, leads to the formation of 1:1 adducts, viz., zwitterionic imidazolines and, in the case of azirine 22, to a carbodiimide [92].



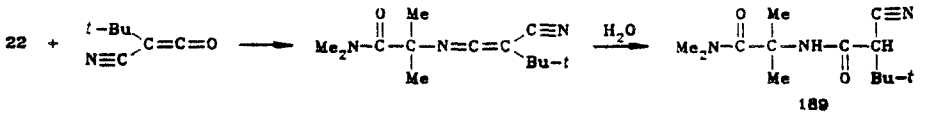
184 185

It has been established that the reaction of diphenyl ketone with amino-2H-azirines 22 and 130, in contrast to the reactions with other functionally substituted 2H-azirines [93, 94], leads to the formation of the corresponding 3-oxazoline 188 [86]:



186 187 188

The reaction of tert-butylcyanoketene with azirine 22 gives a keteneimine in 65% yield, the subsequent hydrolysis of which leads to 2-amino-N,N-dimethylisobutyramide N-acyl derivative 189 [80, 95].

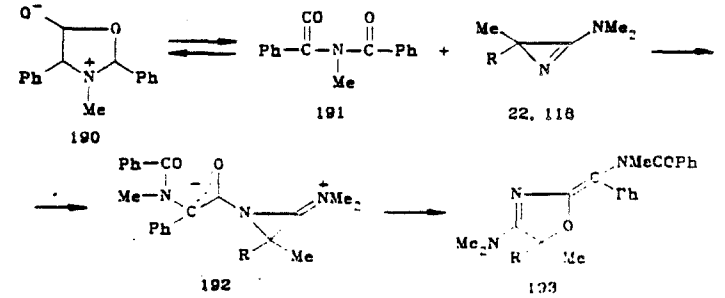


189

The reaction of 3-dimethylamino-2,2-dialkyl-2H-azirines with ketenes proceeds through a step involving 1,2 cleavage of the ring of azirinium zwitterion 186 and the formation of 1,5-dipole 187, while primarily 1,3 cleavage of the ring of the initially formed aziridinium zwitterion and the formation of the corresponding cyclic zwitterion are observed with other heterocumulenes (carbon disulfide, isocyanates, isothiocyanates, carbodiimides).

Selective 1,2 or 1,3 cleavage of the ring of 3-dimethylamino-2,2-dialkyl-2H-azirines by heterocumulenes is probably explained by the different nucleophilicities of the ring heteroatoms in the primary adduct, viz., the aziridinium zwitterion.

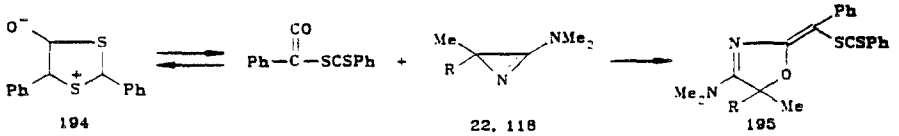
One of the most interesting reactions involving the addition of 3-dialkylamino-2H-azirines was realized by Lukas and coworkers [96, 97] in the reaction of 2,2-dimethyl-2H-azirine 22 and 2-phenyl-2H-azirine 118 with 1,3-oxazolium-5-olate 190; they obtained 1:1 adducts, viz., the corresponding oxazolines 193, in 75% yield.



190 191 22, 118 192 193

The azirine in this case is used as a reagent-trap for ketene 191 – the hypothetical tautomeric form of cyclic mesoionic compound 190 [98, 99].

The reaction of azirines 22 and 118 with 2,4-diphenyl-1,3-dithiolium-5-olate (194) leads to thio-substituted oxazolines 195 [97].



194 22, 118 195

The reaction evidently proceeds in the same way as the reaction of aminoazirines with ketenes [86].

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