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SYNTHESIS AND PROPERTIES OF FUNCTIONALLY SUBSTITUTED 1,2-AZOLIDINES

I. A. Motorina and L. A. Sviridova

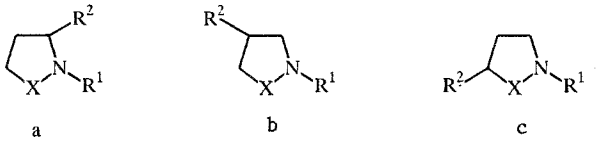
Results of investigations on the synthesis and properties of functionally substituted 1,2-azolidines are reviewed.

Compounds having azolidine fragments in their structure have a broad spectrum of biological activity. Among derivatives of substituted isoxazolidines and pyrazolidines have been found substances with fungicidal [1, 2], herbicidal [3], antiinflammatory [4, 5], and antibacterial [6, 7] activity. N-Acylisoxazolidines and benzylpyrazolidines exhibit properties of minor tranquilizers [8, 9]. Isoxazolidine derivatives that are lysergic acid antagonists [10] and pyrazolidine derivatives that are good anesthetics [11] are also known. The isoxazolidine fragment is contained in alkaloids [12, 13], terpenes [14], condensed heterocycles [15, 16], some sugar derivatives [17, 18], and antibiotics [19].

Extensive investigations in the field of the chemistry of functionally substituted azolidines began in the middle of the 1960's; in particular, there was especially rapid development of the chemistry of isoxazolidines after the appearance, in the 1960's and 1970's, of publications on the valence-molecular-orbital theory and its application (together with calculations of molecular-orbital parameters) to 1,3-dipolar cycloaddition reactions. At the same time, there is virtually no published systematization of data on the synthesis and properties of functionally substituted azolidines. (There is only a review on the chemistry of isoxazolidines [20] containing data up to May of 1974.) The present review covers the literature for mainly the last 15-20 yr. We review data on the structure, methods for synthesis, and chemical properties of isoxazolidines and pyrazolidines having heteroatomic substituents (amino, hydroxy, alkoxy, hydrazino groups, etc.) at carbon atoms.

1. STRUCTURE OF 1,2-AZOLIDINES

All possible isomers of the substituent position in the ring (3- (a), 4- (b), and 5-substituted (c) derivatives) are known for molecules of functionally substituted isoxazolidines and pyrazolidines,



and stereoisomers are known for disubstituted azolidines.

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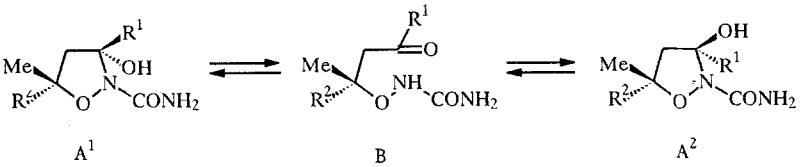
In polysubstituted *N*-alkoxyisoxazolidines, hindered inversion of the cyclic nitrogen atom may be observed together with stereoisomerism of the $C_{(3)}$ and $C_{(5)}$ atoms [21-23], and in some cases this makes it possible to obtain only one invertomer [24].

Most of the isoxazolidine derivatives have an envelope conformation in the crystalline state, with the nitrogen atom projecting from the plane of the four atoms of the ring [25-29], but for *cis*-3-methoxy-5-methyl-2-benzoylisoxazolidine the $O_{(ring)}$–envelope conformation predominates with deflection of the oxygen atom of the ring from the plane by 0.35 Å [30]. According to x-ray diffraction-analysis data, 1-acetyl-2-phenyl-3-methyl-5-hydroxypyrazolidine in the crystalline state forms a centrisymmetric dimer due to intermolecular hydrogen bonding between the hydroxyl group and the carbonyl oxygen atom [31]. The molecule consists of a flattened envelope with the $C_{(5)}$ atom extended from the ring plane and the hydroxy group in a quasi-axial position. Such a configuration reflects the optimal correlation of all the stereo-electronic factors.

The 3- and 5-hydroxy-substituted isoxazolidines and pyrazolidines have in their molecules hemiaminal or hemiacetal fragments, which leads to their high lability. It has been shown by IR spectroscopy that, in addition to the relatively high acidity of the hydroxyl group of these compounds, the exocyclic oxygen atom has rather high basicity, close to the basicity of ethers [32, 33]. In the case of 3-hydroxyisoxazolidines and 5-hydroxpyrazolidines the electrophilic center in the formation of an intermolecular hydrogen bond is the hydroxyl oxygen atom, and for 5-hydroxyisoxazolidines the electrophilic center is the ring oxygen atom.

The 3- and 5-hydroxyisoxazolidines and -pyrazolidines and 5-hydrazinopyrazolidines can exist both in a cyclic form (A) and in a linear form (B) [34-42]; in a number of cases there is tautomeric equilibrium.



[35]

The equilibrium position depends on the substituents [38, 40-42], the temperature [35] (heating leads to an increase of the fraction of form B), and the polarity of the solvent [41-43]. It has been shown that an increase of the polarity of the solvent regularly increases the content of the linear tautomer [41-43]. It should be noted that in the great majority of cases the adducts of alkenals (R_1 = H) in the solid state and in solutions of nonpolar solvents exist in the cyclic form of hydroxyazolidines A [7, 41], whereas adducts of methyl vinyl ketone exist partially or wholly in linear form B [42]. Cyclic structure A is characteristic of amino derivatives [44, 45], and mainly linear structure B is characteristic of hydrazine derivatives [46]. We should note the existence of a direct relation of the lability of functionally substituted azolidines to the presence of a linear tautomer in solution because it is precisely in this case that the decomposition of compounds with the formation of a hydrazide or hydroxamic acid and aldehyde (ketone) polymers becomes significant. Indeed, 1-acetyl-5-hydroxypyrazolidines decompose to the starting compounds only insignificantly in solutions: their instability is related mainly to the formation of pyrazoline derivatives [7, 45, 46], whereas aroylpyrazolidines and derivatives of isoxazolidines decompose rather rapidly during standing, especially in light [41, 43].

The ratio of the two tautomeric forms that is observed in the gas phase by mass spectrometry probably reflects the true position of equilibrium in the absence of solvation and intermolecular interactions: whereas 1-alkanoyl-5-hydroxypyrazolidines exist even in the gas phase mainly in cyclic form, in the case of aroylpyrazolidines the amount of the linear form reaches 50% [47].

The main criteria for assignment of the cyclic or linear structure of the compounds are the data of ^1H and ^{13}C NMR spectroscopy: for the cyclic form, peaks of the hemiacetal carbon atom at 80-100 ppm and the proton at this atom in the region

of 5-6 ppm are characteristic, and, for the linear form, peaks of the carbonyl carbon atom at 180-200 ppm are characteristic [7, 43, 45, 46]. The presence of a linear isomer has also been observed in the IR spectra of the compounds ($\nu_{C=O}$) [32, 33].

2. SYNTHESIS OF FUNCTIONALLY SUBSTITUTED 1,2-AZOLIDINES

In most cases, the methods for synthesis of azolidines containing functional groups at the carbon atoms are a modification of known methods for construction of isoxazolidine and pyrazolidine rings. The synthesis methods described in the literature can be divided into four main groups: 2.1. Reactions including complete construction of an azolidine ring with formation of C–C and C–X bonds; 2.2. Syntheses based on derivatives of hydroxylamine and hydrazine with formation of C–N and C–X bonds; 2.3. Isomerization of the carbon skeleton of other classes of compounds; 2.4. Syntheses based on derivatives of azolidines and azolidones.

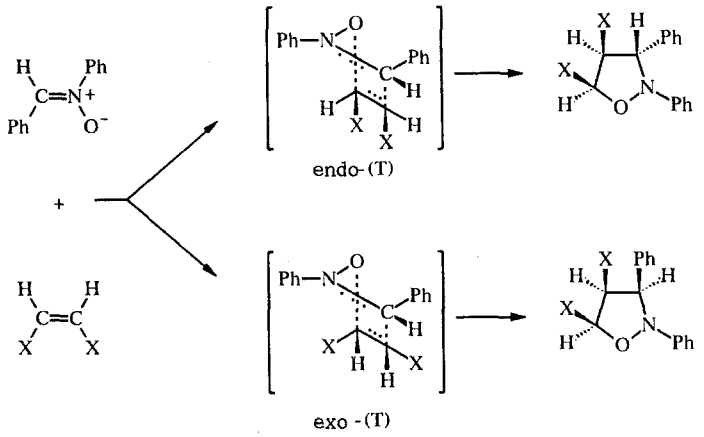
These synthesis methods have been studied to different degrees. Thus, e.g., among the publications on the synthesis of isoxazolidines, more than 85% are on investigations of 1,3-dipolar cycloaddition of nitrons to substituted alkenes, but publications on other methods are, as a rule, scattered communications, often not having as their purpose the development of methods for synthesis of functionally substituted azolidines. Syntheses of pyrazolidine derivatives are mainly included in types 2.2 and 2.4.

2.1. Synthesis of Azolidines by 1,3-Dipolar Cycloaddition

A number of reviews [48-52] have been devoted to this most widely used method for synthesis of functional derivatives of isoxazolidine [48-52], and a collection of articles has recently been published that covers the literature on this topic up to 1983 [53]; therefore in this review, we shall not mention the theory of cycloaddition and consider in detail the regio- and stereochemical characteristics of this reaction, but we shall mention only some recent publications in this field.

The reaction of nitrons with dipolarophiles can afford 5-substituted isoxazolidines (for electron-enriched dipolarophiles, these are butyl vinyl ether [54, 55], alkyl vinyl ethers [56, 57], aryl vinyl ethers [58], and vinyl acetate derivatives [59, 60]; for most of the 1,1-disubstituted ethylenes, these are methyl α-methacrylate [61, 62], α-methacrylonitrile [54, 62], ketene acetal [60, 63, 64], diketene [65], enamines [66-68], and sulfones [69]) or the corresponding 4-regioisomer. The amount of the 4-isomer in the reaction mixture increases with increasing electron-acceptor nature of the dipolarophile substituent [62, 70-73] and decreasing ionization potential of the nitron [70, 74-77]. As a rule, the reaction of nitrons with vinyl sulfones [73, 78-80] and phosphonates [72, 81, 82] affords 4-substituted isoxazolidines. At the same time, communications have recently appeared that the reaction of diphenylvinylphosphine with some nitrons affords exclusively 5-substituted isoxazolidines [83] and that 5-substitution predominates in the reaction with methylvinylphosphine oxide [84]. In reactions with 1,2-disubstituted ethylenes (dibenzoylethylene [85], maleic anhydride [86], maleimide [87], N-phenylmaleimide [88, 89], crotonates [54, 61, 90, 91], crotonitrile [54], β-nitrostyrene [86, 92], and others [81, 93-95]) the more electron-acceptor substituent of the dipolarophile occupies the 4 position. The presence of an allyl oxygen atom in the alkene also promotes the formation of 4-substituted isoxazolidines [96]. The direction of the reaction is also affected by steric factors [97], and, when the process is reversible, the direction of addition is governed by the conditions of kinetic or thermodynamic control [56, 98-101]. The rate of the 1,3-dipolar cycloaddition of nitrons increases with increasing acceptor nature of the dipolarophile substituent [58, 102] and with increasing length of the conjugation chain of the nitron [58, 103], and it virtually does not depend on the solvent [103, 104], which confirms the accuracy of consideration of 1,3-dipolar cycloaddition as a consistent process of interaction of molecular orbitals [49, 64, 70, 74, 105-109], but it agrees poorly with Firestone's assumption that the reaction occurs via a biradical intermediate [110-112].

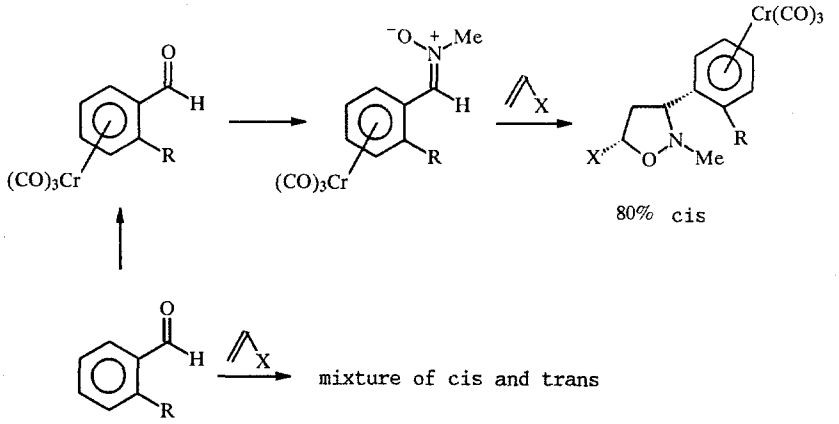
The stereochemistry of the dipolarophile in the resulting isoxazolidine is preserved, and the addition is stereospecific (cis) with respect to it. But the $C_{(3)}$ configuration depends on the degree of preference of the transition state [71, 91], which is governed by the presence [21, 71, 113, 114] or absence [57] of secondary nonbinding interactions, steric hindrances [73, 115], or thermodynamic conditions [116].



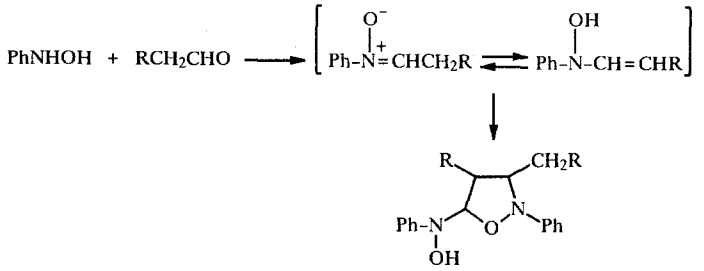
Asymmetric addition is also possible because of the presence of an optically active substituent in the nitron or dipolarophile molecule [60, 117]. High stereoselectivity of cycloaddition is also achieved during the formation of complexes of nitrons with chromium carbonyls [114], which is also due to the existence of additional interactions of substituents with aryl in the transition state.

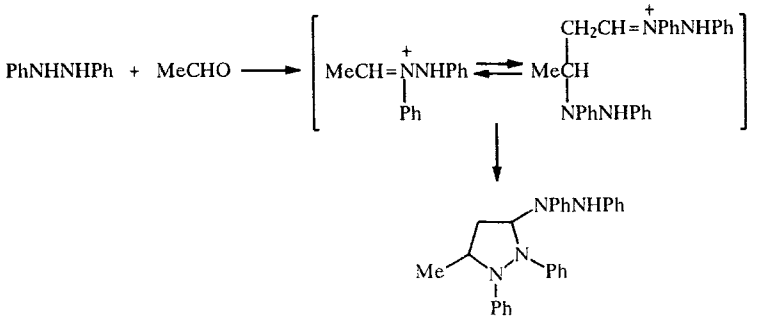
The presence of a β-oxygen atom at the N nitrogen atom in the nitron increases the diastereoselectivity of cycloaddition because of the presence of a kinetic anomeric effect in this case [118].

Similar patterns are observed for silyl [119, 120] and alkyl [22, 24, 121] ethers of nitrons, the reaction of which with alkenes affords N-alkoxyisoxazolidines.

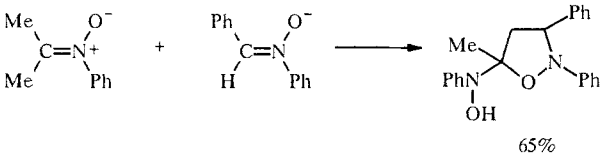


A particular case of 1,3-dipolar cycloaddition is dimerization of nitrons, affording 5-hydroxylamino-substituted isoxazolidines [34, 122-126], and similar dimerization of hydrazonium salts [127, 128].





Also possible is the crossed reaction of various nitrons with formation of an isoxazolidine ring [129].



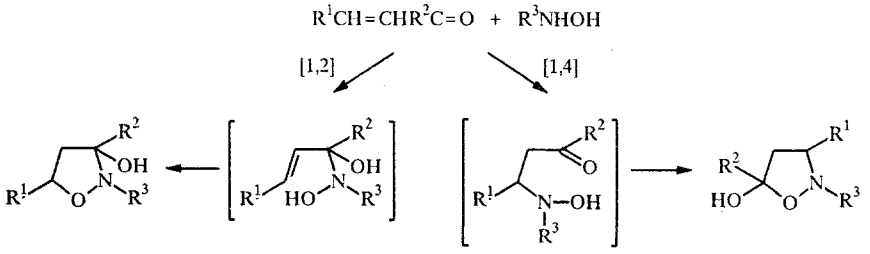
65%

The 1,3-dipolar cycloaddition reactions have found wide use in the synthesis of isoxazolidines because they are simple in an experimental sense and give good yields. This method can be used to obtain alkoxy-, acyloxy-, nitro-, amino-, sulfonyl-, phosphonyl-, cyano-, carbethoxy-, and acylisoxazolidines with substituents in the 4 and 5 positions. However, 3-functionally substituted isoxazolidines remain unobtainable.

2.2.1. Synthesis of 1,2-Azolidines by the Michael Reaction

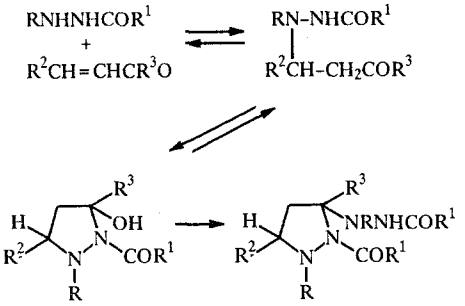
The reaction of derivatives of hydrazine and hydroxylamine with α,β-unsaturated carbonyl compounds is a widely used method for synthesis of Δ^2- [130] and Δ^3-azolines [131, 132]. The formation of corresponding hemiaminal structures as intermediate compounds has been postulated [133] and has also sometimes been observed by spectral methods [37, 134-136]. Comparatively recently this reaction has begun to be used as a method for synthesis of 3- and/or 5-hydroxyisoxazolidines [34, 35, 120, 134, 137] and 5-hydroxypyrazolidines [7, 43, 138, 139].

The reaction mechanism depends on the reaction conditions. In the case of isoxazolidines, it is considered that under neutral conditions first there is attack of the multiple bond by the nitrogen atom of the hydroxylamine with subsequent cyclization of the resulting addition product [36, 137], with the possible formation of two regioisomers.



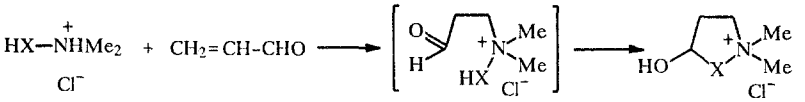
Indeed, 5-hydroxyisoxazolidines are formed in the reaction of N-alkyl- and N-arylhydroxylamines with α,β-unsaturated aldehydes and ketones [34, 36, 41, 42, 137, 140], and 3-hydroxyisoxazolidine is formed in reactions with hydroxyurea [35]. Isoxazolidine derivatives obtained from ketones (phorone [137], methyl vinyl ketone [34, 35, 42], phenyl vinyl ketone [35], and mesityl oxide [36, 37, 134, 140]) are somewhat more stable. The presence of electron-acceptor substituents in the ketone molecule facilitates the reaction and results in an increase of the yields of 5-hydroxyisoxazolidines to 80% [141, 142].

Hydroxy derivatives of pyrazolidines have been obtained by Michael reactions (this is virtually the only preparative route for their synthesis) only with the use of β-alkyl(aryl)hydrazides of acids; therefore, the addition always occurs regioselectively [7, 138].



Adducts of alkenals have a cyclic structure, although there is ring-chain tautomerism in the case of aroyl derivatives (R_1 = Ar) [43, 139]; but adducts of methyl vinyl ketone are completely linear, and the reaction could not be carried out with the remaining ketones [143]. In the case of β-arylhydrazides, hydroxy compounds are kinetic reaction products; during long-term heating, the more thermodynamically stable 5-hydrazino derivatives are formed [7]. The formation of 5-hydroxypyrazolidines occurs stereoselectively, with the formation of only one of two possible pairs of diastereoisomers with trans arrangement of the substituents in the 3 and 5 positions [7, 31].

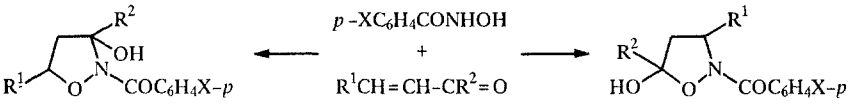
Recently it has been shown [144] that a similar reaction is possible for salts of acylhydrazine and hydroxylamine, with the obtained hydroxy compounds existing only in the cyclic form.



X=O, AcN

The reaction of N-acyl derivatives of hydroxylamine with alkenals in the presence of bases can occur with the formation of 3-hydroxyisoxazolidines [137, 145]. It has been hypothesized that in this case an O-anion of hydroxylamine is formed, and this O-anion reacts further with an α,β-unsaturated carbonyl compound by 1,4-addition [137], but, because of the relative instability of the resulting compounds, Ly et al. [137] were unable to recover the 3-hydroxy-substituted isoxazolidine.

Recently a method has been developed for synthesis of hydroxyisoxazolidines by the reaction of hydroxamic acids and α,β-unsaturated carbonyl compounds with catalysis by triethylaminoethyl cellulose [41, 42]. It has been shown that the direction of the reaction depends on the donor nature of the substituent in the aromatic ring of the hydroxamic acid [41].

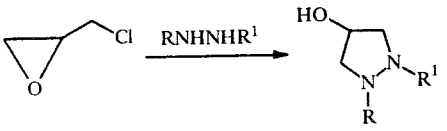


X=H, Br, NO_2 $\quad$ R^1, R^2=H, Me $\quad$ X=Me, MeO

Just as α-substituted aldehydes, alkylhydroxamic acids do not react under these conditions. The direction of addition of arylhydroxamic acids to α,β-unsaturated carbonyl compounds on the surface of adsorbents in the absence of a solvent and the stereochemistry of the resulting reaction products are governed not by the nature of substitution in the hydroxamic acid, but by the properties of the sorbent. It has been shown that the use of silica gel affords 3-hydroxyisoxazolidines, and the use of diethylaminoethyl and triethylaminoethyl cellulose affords 5-hydroxyisoxazolidines regardless of the substituents of the aromatic ring of hydroxamic acid [146, 147]. The only reliable criterion for assignment of the position of the hydroxy group of isoxazolidines is the ^{13}C-NMR spectral data: 3-hydroxyisoxazolidines have chemical shifts in the region of 79-82 ($C_{(3)}$ atom) and 68-76 ppm ($C_{(5)}$ atom), and regioisomeric 5-hydroxy derivatives have chemical shifts in the region of 97-99 ($C_{(5)}$ atom) and 44-69 ppm ($C_{(3)}$ atom) [41]. Investigation of the kinetics of formation of addition products on diethylaminoethyl cellulose suggests that in this case the formation of regioisomers occurs in parallel and is subject to kinetic and thermodynamic control: the kinetic reaction product is the 3-isomer, and the thermodynamic reaction product is 5-substituted isoxazolidine [146]. These data suggest that although the formal result of the reaction in the solution depends on the donor nature of the substituent of hydroxamic acid, in any case because of the reversibility of addition, we are probably dealing with simultaneously occurring concurrent reactions involving undissociated molecules and O-anions of hydroxamic acid.

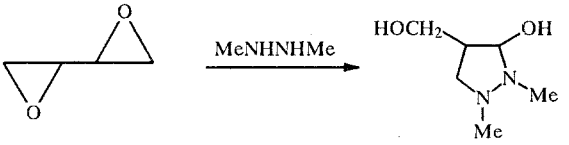
2.2.2. Cyclization of Bifunctional Compounds

Generation of a trifunctional hydrocarbon fragment is necessary for the synthesis of 4-functionally substituted compounds. Hydrazine itself [148] and also alkyl- and arylhydrazines [148-153] facilely react with epichlorohydrin with formation of 4-hydroxypyrazolidines.

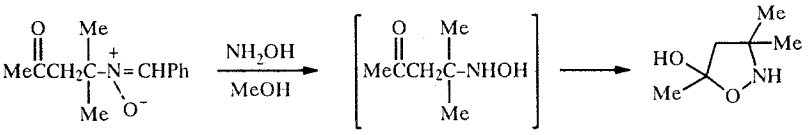


30...75%

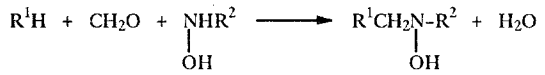
The reaction with butadiene dioxide is more interesting [154]:

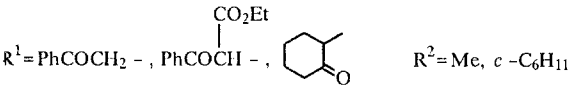


Similar cyclization to 4-hydroxyisoxazolidines is observed for a-chlorohydrins obtained from α-oxides [155, 156]. N-Substituted hydroxylamines cyclizing to isoxazolidines can be obtained from nitrons [157]



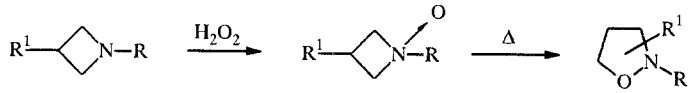
or by the Mannich reaction [158]:





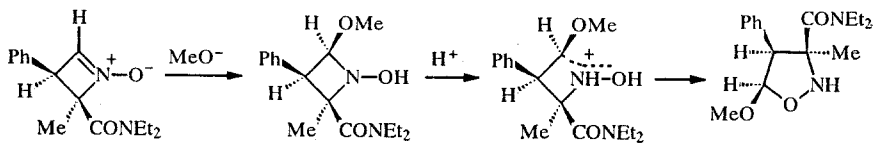
2.3. Syntheses of Azolidines by Isomerization of the Carbon Skeleton of Other Classes of Compounds

Azetidine N-oxides containing hydroxyl or alkoxy substituents in the ring undergo isomerization to isoxazolidines during heating, with 4- and 5-substituted isoxazolidines being formed in virtually equal amounts [159, 160].



R=Alk, *c*-Alk, CH_2Ph R^1=OH, OAlk, OAr, OCH_2Ar

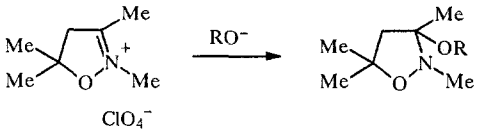
In an alkaline medium, four-membered cyclic nitrons add a water or alcohol molecule with subsequent cyclization to hydroxy(alkoxy)isoxazolidines [161]:



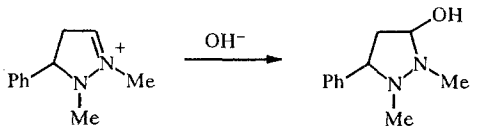
Compounds containing a substituent other than hydrogen (Me or Ph) at the double bond of the nitron do not participate is this reaction [161]. Thus far, the occurrence of such isomerization has been shown with a single example; therefore, this method is more of theoretical than practical interest.

2.4.1. Addition of Nucleophiles to Multiple Bonds of Azolines

In most cases, the polarization of the C=N bond in molecules of Δ^2-1,2-azolines is weak for nucleophilic attack at the $C_{(3)}$ atom [162], but salt formation at one of the heteroatoms of the ring is sufficient for activation [163, 164]. When an alkali or an alcoholate reacts with Δ^2-pyrazolinium salts, 3-hydroxy or alkoxy derivatives can be obtained [36, 165]. For methoxyisoxazolidines, the reaction is preparative.

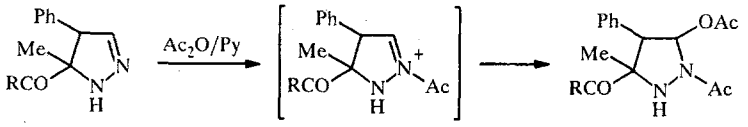


[36, 165]



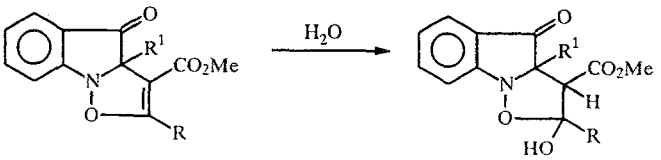
[166, 167]

However, for functionally substituted pyrazolidines and hydroxyisoxazolidines, this method still cannot be considered preparative because the authors give only spectral data, probably because of the lability of the obtained compounds. There are a number of communications (see, e.g., [168] and [169]) where the authors assume, without sufficiently cogent reasons, the formation of addition products at the C=N bond, and the formation of these products is not confirmed in further communications. Exceptions are syntheses of stable compounds gem-substituted in the 5 position that have at least one acceptor substituent in this position [143, 170, 171].



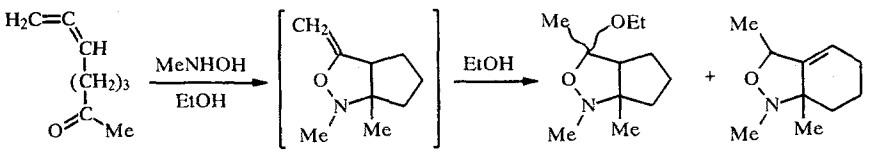
R=CHN$_2$,OAlk

Not requiring activation, Δ^4-isoxazolines are hydrated more facilely, and adducts with methanol are formed during acid catalysis [50, 172-174].



R=CO$_2$Me,Ph; R^1=H,Ph

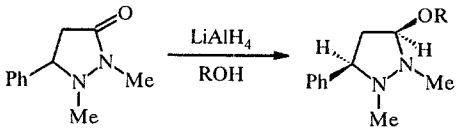
Similar to this is the process of formation of isoxazolidines as a result of addition of a nucleophile at the exocyclic double bond that forms during the reaction of a nitron with an allene [173, 175].



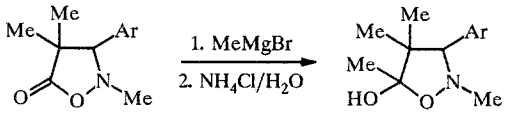
60 : 40

2.4.2. Reduction of Azolidones

At first glance, the most convenient method for synthesis of hydroxyazolidines is the reduction of facilely obtainable 3- and 5-azolidones. However, although some successful experiments have been published, the method is not preparative. The corresponding 3-hydroxy and 3-methoxy compounds have been obtained in the reduction of 3-pyrazolidone: these compounds have definite stereochemistry [166], but they have been obtained in trace amounts [136, 166, 167].



The addition of methylmagnesium bromide to the exocyclic C=O bond of 5-isoxazolidinone after mild decomposition by an ammonium chloride solution affords 5-hydroxyisoxazolidine [176].



Ar = Ph, C_6H_4Cl-*p*

Unlike in the case of reactions with other reducing agents (see Section 3.3), in this case cleavage of the N–O bond does not occur, and the isoxazolidine ring is preserved.

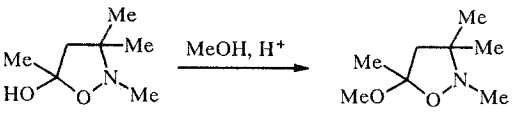
3. PROPERTIES OF FUNCTIONALLY SUBSTITUTED 1,2-AZOLIDINES

The physical and chemical properties of functionally substituted azolidines (tautomerism, dehydration, substitution, reduction, oxidation, etc.) are mainly governed by the presence of a reactive substituent in the molecule. The only property that is characteristic of the isoxazolidine fragment itself and, therefore, any of its derivatives is reductive cleavage of the N–O bond with formation of amino alcohols.

3.1. Reactions of Azolidines with Preservation of the Five-Membered Ring

This type of reactions includes nucleophilic-substitution and elimination reactions and modification of functional groups of azolidines.

The preparation of 5-alkoxy derivatives by the reaction of 5-hydroxyisoxazolidines with an alcohol in an acid medium has been described in [36], [140], and [177]:

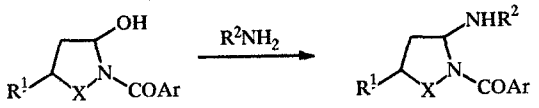


Because ring-chain tautomerism is characteristic of hydroxyisoxazolidines, Belly et al. [140] have assumed that substitution in this case occurs via the formation of an open hemiacetal of the linear form of isoxazolidine.

Recently, preparative methods have been developed for the preparation of 3- and 5-alkoxyisoxazolidines and 5-alkoxypyrazolidines having an N-acyl substituent using phase-transfer acid catalysis, and these methods have enabled preparation of these compounds in high yields [44, 45]. Nucleophilic substitution in the series of 3,5-disubstituted isoxazolidines occurs with formation of a mixture of diastereomeric pairs in unequal amounts. X-ray diffraction analysis and NMR methods using the nuclear Overhauser effect have shown that the formation of cis-3-methoxy-5-methyl-2-benzoylisoxazolidine (cis:trans ratio ~2:1) and trans-5-methoxy-3-methyl-2-benzoylisoxazolidine (cis:trans ratio ~1:4) is preferred [30], which agrees well with the effect of stereoelectronic and steric factors.

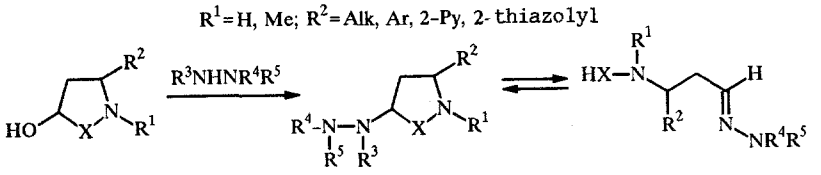
Substitution of one alkoxy group by another one occurs under similar conditions, but with significantly greater difficulty [44]. The reaction is complicated by the fact that an increase of the contact time of the reacting compounds leads to quantitative isomerization of 3-alkoxyisoxazolidines to 5-alkoxy derivatives that are regioisomeric to them [178].

Hydroxyazolidines also react facilely with amines, hydrazines, and hydroxylamines with the formation of amino, hydrazino, and hydroxylamino derivatives, respectively [44, 45, 179, 180].



[44]

R^1=H, Me; R^2=Alk, Ar, 2-Py, 2-thiazolyl

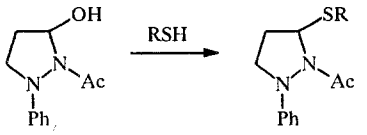


[46, 179]

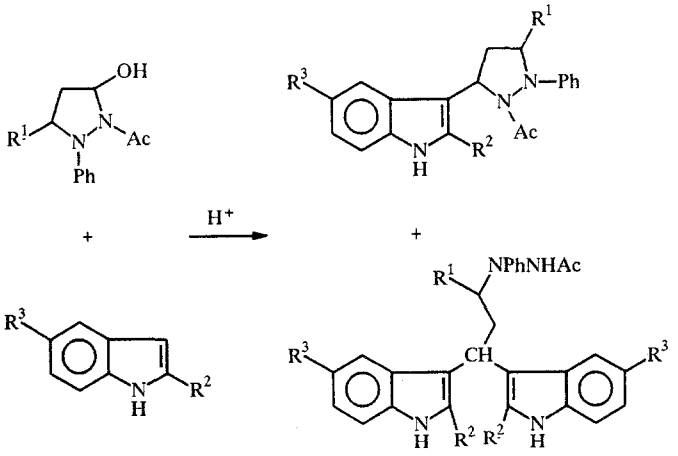
X = O, NR

The presence of a substituent other than hydrogen in the 3 position of pyrazolidine significantly retards the reaction with amines. The reaction rate and the yields of aminoazolidines increase with increasing nucleophilicity of the amine [44], and when the isoxazolidine molecule contains two aromatic rings with acceptor and donor substituents the formation of a charge-transfer complex is possible [181].

Substitution by a mercapto group occurs similarly under noncatalytic conditions [182].

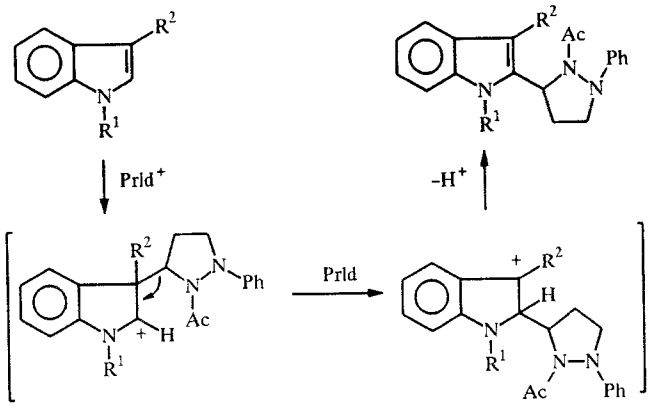


The possibility of introduction of an azolidine molecule into the heterocycle ring is very promising in synthetic terms. The reaction of hydroxypyrazolidines with 3-unsubstituted indole affords products of substitution at the most nucleophilic β-position of indole, i.e., 3-pyrazolidinylindoles [182]:



R^1, R^2, R^3=H, Me

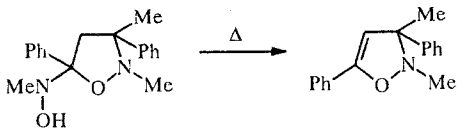
The second direction of these reactions is the formation of bis derivatives, which can be obtained from a linear tautomer of hydroxypyrazolidines. The amount of the bis derivatives increases with retardation of the main process. Reactions of hydroxypyrazolidines with indoles having an alkyl or aryl substituent in the 3 position, but a free 2 position, occur regioselectively with formation of 2-pyrazolidinylindoles. The formation of 2-pyrazolidinylindoles is preceded by ipso attack of the 2-pyrazolinium cation at the 3 position with subsequent migration of pyrazolidine to the 2 position according to the scheme of the Plancher rearrangement, which is well known in the indole series:



R^1=H, Me; R^2=Me, Ph

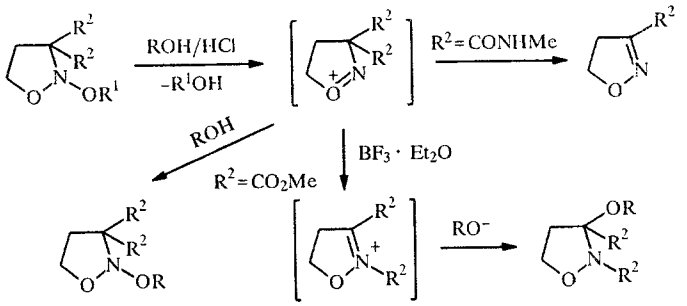
A confirmation of this is the reaction with 3-benzylindole, where it is also possible to detect a significant amount of the product of migration of a second radical, benzyl [182]. The reaction of hydroxypyrazolidine with 2-benzyl- and 2-phenylindoles occurs in an even more complex manner. Instead of the expected 3-pyrazoliadinyl derivatives, only products of the Wagner–Meerwein double rearrangement, isomeric 2-pyrazolidinyl-3-substituted indoles, are recovered. The driving force of the process is probably the high stability of 2-pyrazolidinylindoles.

Elimination reactions also occur with preservation of the azolidine ring. Thus, 3- and 5-hydroxyazolidines and 5-(hydroxylamino)isoxazolidines easily lose a water or hydroxylamine molecule in an acid medium or during heating, undergoing conversion to $\Delta^3(\Delta^4)$-azolines [36, 134, 135, 165, 183, 184].



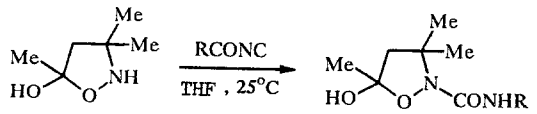
[183]

Isoxazolidines containing N-siloxy [120] or alkoxy groups [185] undergo a similar conversion under the same conditions:

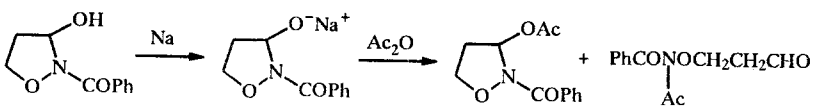


When $BF_3 \cdot Et_2O$ acts on N-alkoxyisoxazolidines, the substituents of the isoxazolidine ring migrate via intermediate formation of a similar isoxazolinium salt [185].

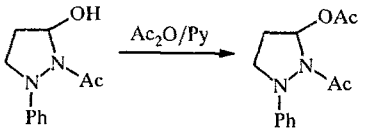
In some cases, it is possible to modify the functional groups of azolidines by acylation [177, 181, 182]:



[177]



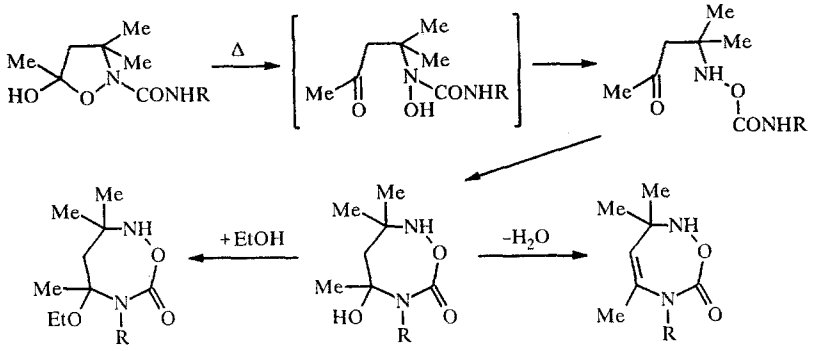
[181]



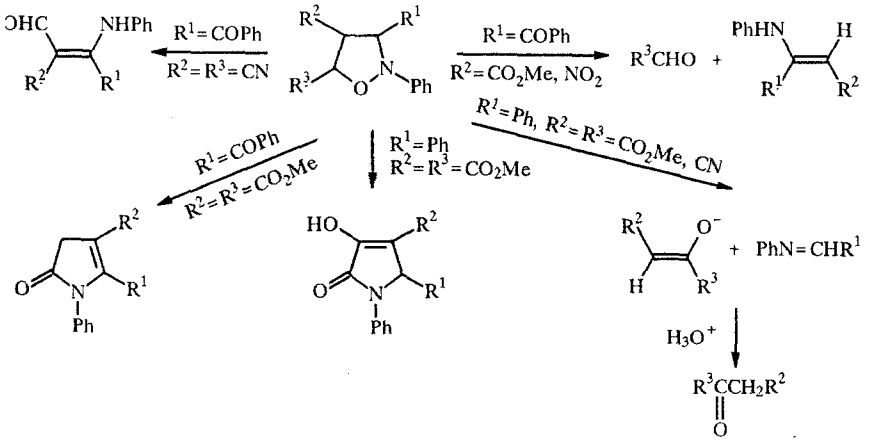
[182]

3.2. Reactions Accompanied by Cleavage of the Azolidine Ring

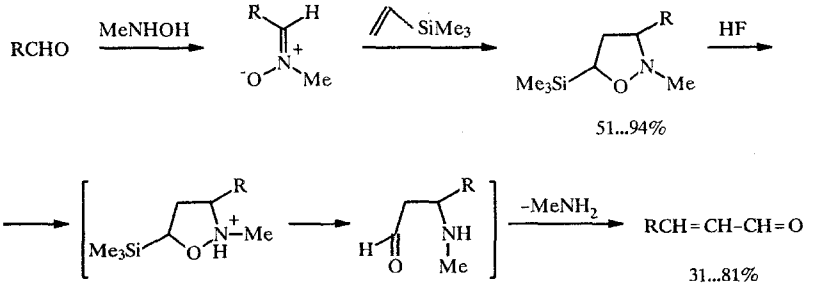
Under thermal conditions, some hydroxy- [177], hydroxylamino- [186], and ω-carbomethoxypolymethyleneisoxazolidines [95] undergo cleavage of the N−O bond with subsequent formation of a new ring.



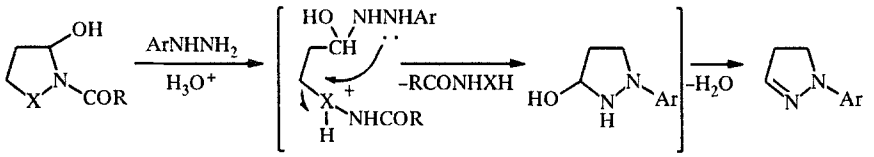
Opening of the azolidine ring of functionally substituted isoxazolidines can also be caused by the action of bases [187] and can lead to the formation, from 5-alkoxyisoxazolidines, of linear esters of acids and enamines of lactams, enols of lactams, or anils or to epimerization in relation to the substituents of the isoxazolidine ring [188] in the case of 3,4,5-trisubstituted isoxazolidines.



Recently, DeShong and Leginus [189] have proposed an interesting method for synthesis of α,β-unsaturated aldehydes from saturated compounds with lengthening of the carbon chain, based on the opening of the isoxazolidine ring in the presence of acids.



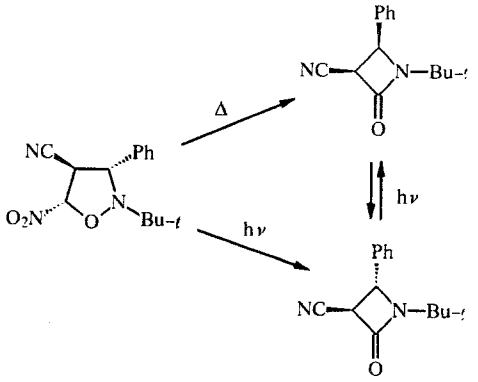
The reaction of 3-hydroxyisoxazolidines and 5-hydroxypyrazolidines [178, 182] with phenylhydrazine in acid catalysis also occurs with opening of the azolidine ring and subsequent recyclization to Δ^2-pyrazoline:



X=O, NR^1

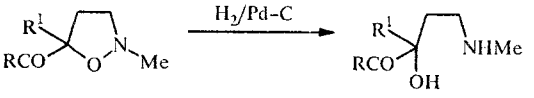
The isomerization of alkoxyisoxazolidines in an acid medium [178] also probably occurs by a similar mechanism [178] (see Section 3.1).

Thermal isomerization of 5-nitroisoxazolidines to β-lactams is also known [94, 190]:



3.3. Reduction of Azolidines

The reduction of isoxazolidines with cleavage of the N−O bond and formation of γ-amino alcohols is now the only property that is characteristic of the isoxazolidine fragment as such regardless of the type of substituents present in the ring [119, 191-194].

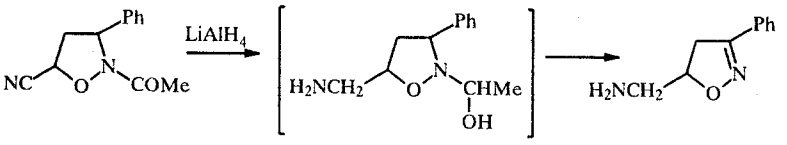


[195]

R^1=H, Alk, Ar; R=Me, Ph, OEt

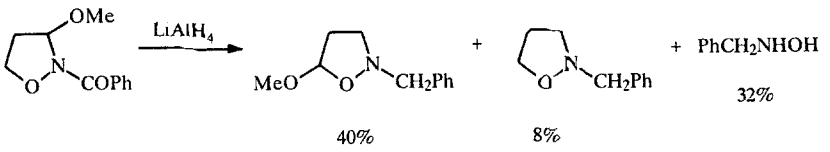
Sometimes the reaction does not stop in the stage of formation of the γ-amino alcohol, but is accompanied by ejection of a molecule of an amine [196] or an alcohol [191, 197]. The reducing agents for hydrogenolysis are usually zinc in acetic acid [15], borohydrides [119], and hydrogen over a nickel [191, 197] or palladium catalyst [195, 196].

The reduction of lithium aluminohydride occurs more mildly and, as a rule, is not accompanied by cleavage of the N−O and N−N bonds. Here functional groups of an azolidine undergo reduction [191, 198, 199].

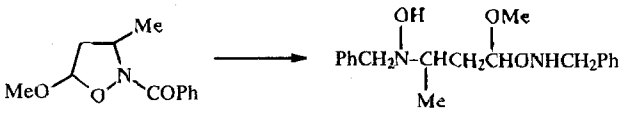


[35]

The reduction of 3-alkoxyisoxazolidines by lithium aluminohydride occurs with partial ring cleavage and is accompanied by isomerization [181] (see Section 3.2).

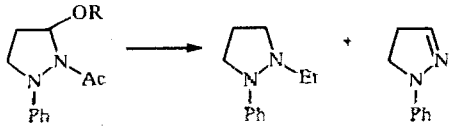


Under these conditions, methoxyisoxazolidines having another alkoxy substituent in the ring are reduced with formation of acyclic products of addition of a fragment of the starting isoxazolidine molecule (benzohydroxamic acid or benzylhydroxylamine) to another isoxazolidine molecule.



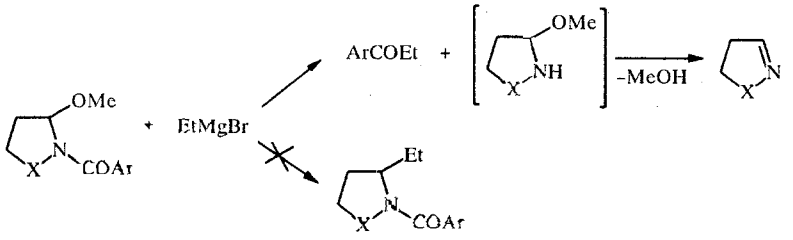
[181]

Under these conditions, 5-hydroxy- and 5-alkoxypyrazolidines react both at the aminal center and at the amide center [182]:



87 : 13

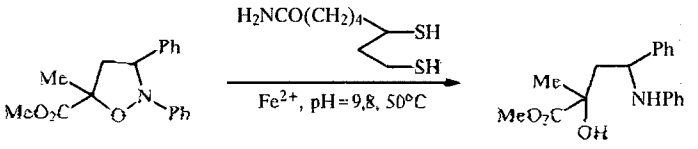
In the reaction of ethylmagnesium bromide with N-acylalkoxyazolidines, two directions of the reaction are possible: at the hemiaminal carbon atom and at the carbonyl group of the N-acyl substituent:



X=O, NAr[1]

It has been shown that pyrazolidine derivatives and alkoxyisoxazolidines react at the carbonyl group [181, 182].

Recently, an interesting communication has appeared on a new method for selective reduction of isoxazolidines by a dihydrolipoamide-Fe(II) complex [200] with formation of γ-amino alcohols:



81%

It is of interest that this reaction occurs without side processes of elimination, cyclization, and hydrolysis,, and also that the multiple bonds contained in the molecule of the starting compound are not affected during reduction [200].

Thus, there is now a rather wide range of available methods for synthesis of functionally substituted 1,2-azolidines, which makes it possible to use this fragment as a synthon in organic synthesis.

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