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Unusual transformations of 2-isoxazolines

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Abstract. The data on unusual transformations of 2-isoxazolines observed in both their preparation by traditional methods and various reactions, mostly with nucleophilic reagents, are considered systematically. Possible mechanisms of these reactions are discussed. Special attention is given to the transformations of 2-isoxazolines under the action of complex organometallic compounds. The bibliography includes 78 references.

I. Introduction

Isoxazoles and their dihydro derivatives, 2-isoxazolines (hereinafter, isoxazolines), are synthetic precursors of various acyclic compounds. They are widely used in organic synthesis for obtaining β-hydroxy ketones and β-diketones, γ-amino alcohols, enoximes, enones, and β-amino enones. Owing to the versatility of the nitrile oxide method of preparing isoxazoles and isoxazolines and the latent bifunctionality of the isoxazole heterocycle, the so-called 'isoxazoline pathway' [1] developed in the last two decades has become a recognized procedure for the total synthesis of natural compounds, including antibiotics, nucleosides, alkaloids, vitamins, steroids, and prostanoids.

The use of isoxazoles in a total chemical synthesis of natural compounds and the related aspects of the preparation and transformations of isoxazoles and isoxazolines have been surveyed in a number of reviews.[1–5]

The main attention in these reviews has been concentrated on the reductive cleavage of the heterocycle at the N—O bond. This reaction is a traditional method of realisation of the latent bifunctionality of the isoxazole ring. At the same time, after the discovery of selective reductive cleavage of the heterocycle, the reactions of isoxazolines with nucleophilic reagents, which had been earlier the subject of intense studies of the properties and transformations of the isoxazole ring, failed to attract further attention of investigators, since they did not find wide synthetic application, except for the cleavage of 3-non-substituted isoxazolines into hydroxy nitriles [6] and of 3-substituted isoxazolines into enoximes.[7]

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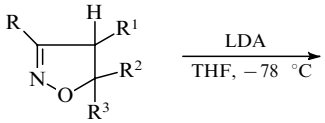
However, recently considerable attention has again been expressed in the transformations of isoxazolines under the action of nucleophilic reagents. The reason for this is, first and foremost, the application in modern organic synthesis (including the isoxazoline chemistry) of new reagents, in particular complex organometallic systems. The use of organometallic reagents, in which the reductive capacity is combined with their properties as bases, has led to the discovery of transformations, which are unusual for isoxazoline compounds. Information about the state-of-the-art of these unusual reactions of isoxazolines is systematised and considered in the present review.

II. Interaction of 2-isoxazolines with bases

The molecule of 2-isoxazoline (**1**) having two heteroatoms with lone electron pairs and an unsaturated C=N bond is characterised by an uneven distribution of the electron density over the ring and by the presence of potentially mobile ('acidic') hydrogen atoms at C(3), C(4), and C(5). Under the action of a base, deprotonation can occur, which is accompanied by the generation of one of the possible cyclic carbanions (**2a**–**e**) (Scheme 1).

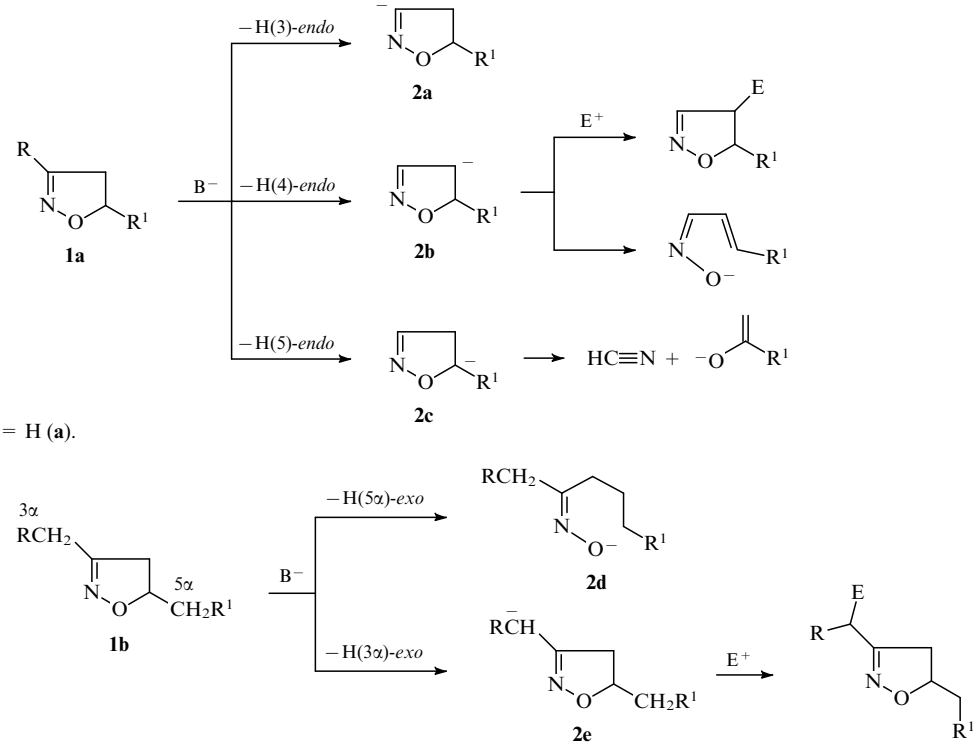
3- or 4-Non-substituted isoxazoline derivatives undergo cleavage under the action of bases. It is the protons at these carbon atoms that are the most 'acidic' as regards the distribution of electron density in the isoxazoline molecule. Thus, the interaction of C(3)- non-substituted isoxazolines with bases gives the isoxazolinium anion **2a**. Upon subsequent cleavage of the N—O bond, the isoxazoline derivative is transformed into a compound with a hydroxynitrile group.[6,8–10]

The 3-substituted 2-isoxazolines **3** are cleaved only in the presence of strong bases. This reaction has been extensively and systematically studied by Jager et al.[2,7,11–13] In the first step, a strong base abstracts the proton from the C(4) atom (4-*endo*-deprotonation) with the formation of an isoxazolinium anion of the type **2b** (Scheme 1), which is stable at −60 °C to −80 °C and cleaves at room temperature to give a non-cyclic enoximate anion and then the enoxime **4**.

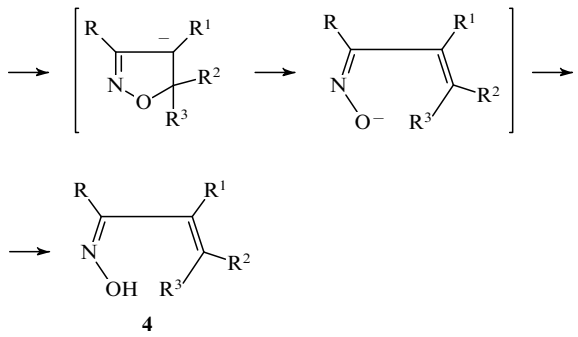


3

Scheme 1



R = H (**a**).



4

Various preparative methods have been developed for the cleavage of isoxazolines into unsaturated oximes with lithium diisopropylamide (LDA)[7,14] and dimsylsodium.[15] These methods have found wide application in the synthesis of polyfunctional organic (including natural) compounds.[3,16–18]

If the isoxazoline contains alkyl substituents, 4-*endo*-deprotonation competes with *exo*-deprotonation; however, it has been established that the 4-*endo* proton possesses a higher acidity and is the first to be deprotonated under standard conditions for this reaction (−78 °C, LDA).[18] With respect to the ease of abstraction by bases, the hydrogen atoms of *C*-alkyl-2-isoxazolines can be arranged in the following order: 3-*endo* > 4-*endo* > 3-*exo* > 5-*endo*.

Jager[12] has proposed a generalised scheme, which includes four possible pathways of transformations of the 3-substituted isoxazoline heterocycle under the action of bases (see Scheme 1). The mobility of the H(4) protons of the isoxazoline ring can be employed for the introduction of substituents into the isoxazoline molecule using the so-called 'Jager alkylation' method.[7,11–13,17–19] Alkylation of the anions **2b** and **2e** by electrophiles is used for the modification of the heterocycle and subsequent generation of a functionalised acyclic compound from the isoxazoline derivative.[2,3]

Analysis of a great number of publications has revealed that an unambiguous result can hardly be achieved in reactions with bases due to a number of factors intervening. The main factors are the structure of the substrate and the nature of the base interacting with it. The direction and ease of the isoxazoline ring cleavage depend on the particular structure of the isoxazoline derivative, in the first place, on the distribution of electron density in the molecule.[20,21] The presence or the absence of substituents at the carbon atoms of the heterocycle and their electronic effect on the ring eventually determines the site of deprotonation under the action of the base. Clearly substituents having polarised bonds, heteroatoms, etc., can influence critically the direction of the reaction. Such situations will be the subject of our further consideration.

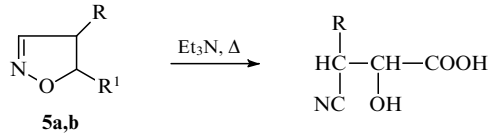
III. 1,4-Cycloreversion of 2-isoxazolines

Cycloreversion of isoxazolines (degradation of the heterocycle at two bonds) often interferes with normal (usual) isoxazoline ring cleavage under the action of basic (as well as organometallic and some other) reagents normally occurring at one of the bonds of the N–O–C fragment. Two types of ring fission (in accord with the number of C–C bonds present in the heterocycle) are known for isoxazolines, *viz*., 1,3- and 1,4-scission.

Ring fission always occurs with rupture of the bond between the heteroatoms, since this bond is the weakest in the ring. Most probably, it is the C=N–O fragment of the ring, that interacts with the reagent. For example, it has been noted that chelation of various reducing reagents (e.g., complex metal hydrides, hydrogenation catalysts, etc.) in reductive cleavage reactions occurs with the involvement of this particular fragment of the isoxazoline molecule.[18] The site of the second ring fission is one of the two C–C bonds, namely: C(3)–C(4) in the case of 1,3-cycloreversion and C(4)–C(5) in the case of 1,4-cycloreversion. In the reaction with a nucleophile (with a base), the reaction center is the carbon atom carrying the most acidic proton. The site of the second fission of the ring is largely determined by the specific structure of the isoxazoline molecule, e.g., by the presence of substituents, which can affect the distribution of electron density at the ring atoms.

Thus, cycloreversion, which normally accompanies the main (usual) direction of the reaction, poses the problem of practical synthesis of hydroxynitriles from isoxazolines. The highly stereoselective reaction of isoxazoline cleavage into hydroxynitriles was

first described by Huisgen et al.[6] for isoxazoline-5-carboxylic acid (**5a**) and 4-methylisoxazoline-5-carboxylic acid (**5b**), which produced quantitatively 3-cyano-2-hydroxypropionic and 3-cyano-2-hydroxybutyric acids upon treatment with triethylamine.[6]

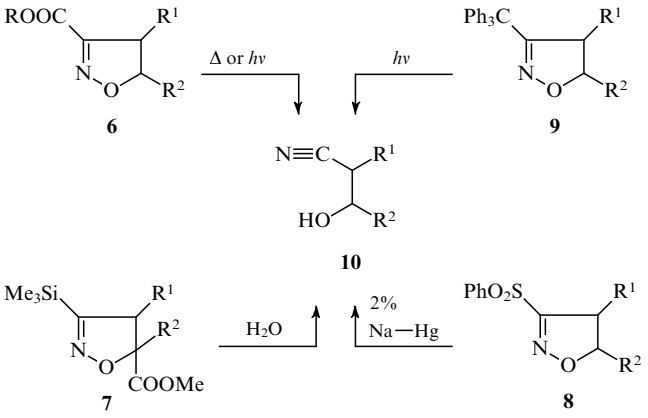


5a,b

R = H (**a**), CH_3 (**b**); R^1 = COOH.

Cleavage of other 3-non-substituted isoxazolines under the action of bases occurred in a similar way.[22,23] Consecutive 1,3-dipolar cycloaddition of nitrile oxides to alkenes and basic cleavage of 2-isoxazolines thus formed is a rather simple, versatile and stereospecific method for preparing vicinal hydroxy nitriles.

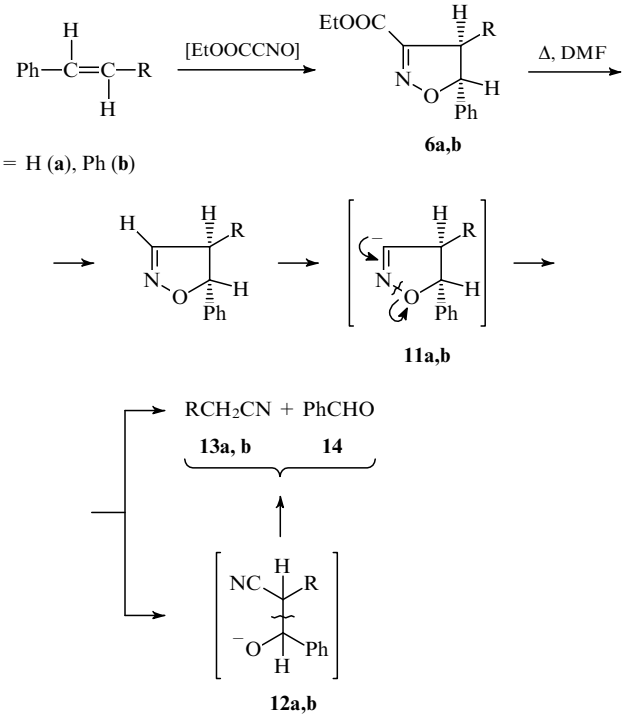
The scope of this method has been expanded with to the use of 3-substituted 2-isoxazolines **6**–**9,** which could generate under certain conditions either the 3-non-substituted isoxazolines **5** or the corresponding anion or radical. Thus, the photolytic or pyrolytic decarboxylation of isoxazoline-3-carboxylic acids and their derivatives **6** was accompanied by simultaneous cleavage of the heterocycle to give the β-hydroxynitriles **10**.[24–26] 3-Triphenylmethyl-2-isoxazolines **9**,[27] 3-trialkylsilyl-2-isoxazolines **7,**[28] and 3-phenylsulfonyl isoxazolines **8**[22,25] underwent similar cleavage. These methods turned out to be useful in the solution of a number of synthetic problems and are now widely used in the synthesis of polyfunctional compounds.[6,10,25,28–33] Compounds **5**–**9** behave similarly in the above reactions and, as will be shown below, the mechanisms of cleavage (cyclodegradation) of the isoxazoline heterocycle are identical. Therefore, all these reactions including the interaction with nucleophilic reagents, as well as pyrolytic and photolytic degradation, are considered in the same section.



6 **9** **10** **7** **8**

Pyrolytic decarboxylation of isoxazoline-3-carboxylic acid derivatives devoid of aromatic substituents gives the β-hydroxynitrile **10** in a quantitative yield. However, in many cases other products form in addition to the hydroxynitriles **10**. Heating of ethyl 5-phenylisoxazoline-3-carboxylate **6a** at 120–130 °C results in the hydroxynitrile **10** (R^1 = H, R^2 = Ph) (65%–90%) and trace amounts of benzaldehyde. Ethyl isoxazoline-3-carboxylate **6b** (R = Ph) prepared from *trans*-stilbene gives quantitatively under identical conditions a 1 : 1 mixture of phenylacetaldehyde (**13**) and benzaldehyde (**14**), the products of cyclodegradation at the N–O bonds (the anion **11b**) and C(4)–C(5) (the alkoxide ion **12b**) (Scheme 2).[26]

Scheme 2



6a,b

R = H (**a**), Ph (**b**)

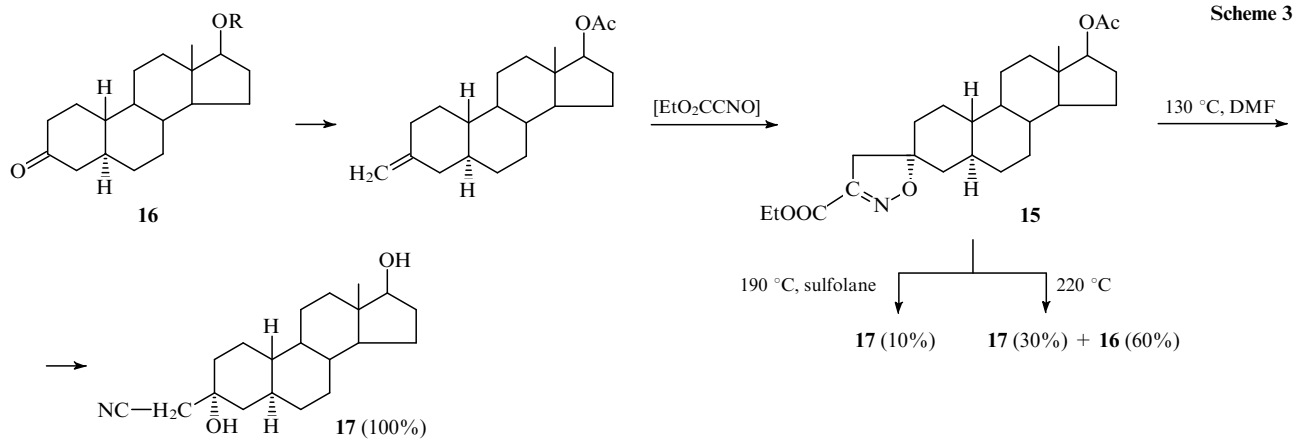
11a,b

12a,b

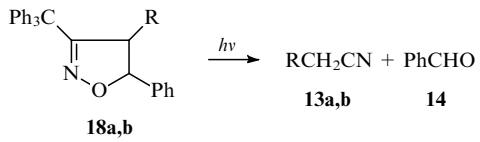
The steroid isoxazoline **15** obtained from the ketone **16** gives quantitatively the hydroxynitrile **17** (1 h, 130 °C, DMF). However, at 220 °C the yield of the hydroxynitrile **17** is 30% and the yield of the ketone **16** is 60%, while in sulfolane (190 °C, 30 min) the yield of the hydroxy nitrile is as low as 10% (Scheme 3).[26]

Upon photolysis, 5-phenyl-3-triphenylmethylisoxazoline (**18a**) and 4,5-diphenyl-3-triphenylmethylisoxazoline (**18b**) prepared from styrene and *trans*-stilbene, respectively, gave different amounts of benzaldehyde. Under these conditions, the steroid isoxazoline **19** was converted (via the radical **20**) into a mixture of the ketone **22** (up to 48%) and the hydroxy nitrile **21** (up to 5%).[27]

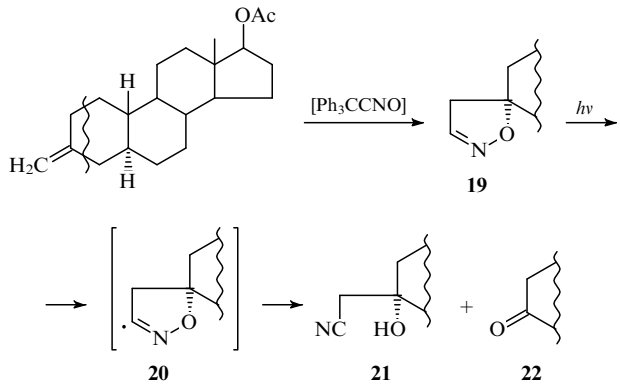
Scheme 3



16 **15**

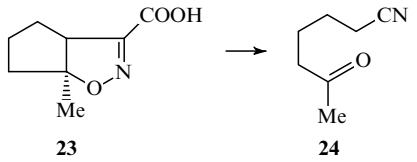


R = H (**a**); R = Ph (**b**).



The mechanism of cyclodegradation proposed by Kaufmann and Kalvoda[26,27] involves generation of a cyclic carbanion **11**. Subsequent cleavage of the weakest N—O bond gives either the acyclic alkoxide ion **12** or the nitrile **13** and the aldehyde **14** as a result of synchronous heterocycle fragmentation, depending on the strength of the C(4)—C(5) bond. Thus, the cycloreversion of the carbanion **11** may occur either consecutively: **11** → **12** → **13** + **14**, or synchronously: **11** → **13** + **14** (see Scheme 2). Apparently, the degradation of the photolytically generated radical **20** occurs by an analogous scheme.

The result of conversion of the 3-phenylsulfonylisoxazolines **8a**–**h** depends on the structure of the substituents at the C(4) and C(5) atoms of the heterocycle (Table 1). Thus, the reaction of phenylsulfonyl derivatives **8a**–**f** with sodium amalgam gives 86%–94% of the corresponding hydroxy nitriles as the sole diastereomers. It is worthwhile noting that the 3-phenylsulfonyl derivative **8f** is cleaved into the corresponding hydroxy nitrile (**10f**), while the isoxazoline-3-carboxylic acid (**23**) gives upon decarboxylation only 6-oxoheptanonitrile (**24**), the product of the cyclodegradation at the C(4)–C(5) bond:[25]

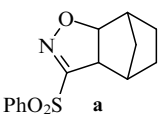
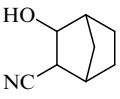
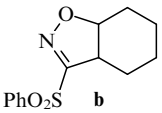
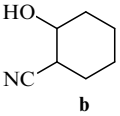
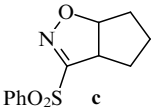
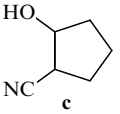
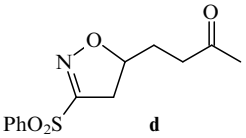
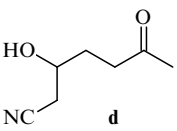
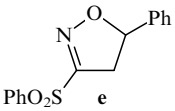
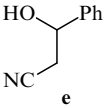
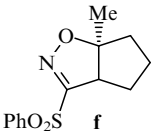
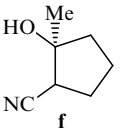
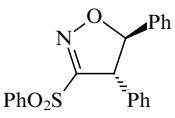
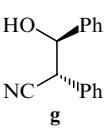
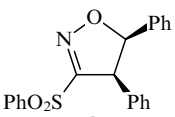
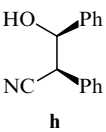


Upon treatment with sodium amalgam, 3-phenylsulfonyl-4,5-diphenylisoxazolines **8g**,**h** give the same cycloreversion products, **13b** and **14**[22,23] as those formed upon decarboxylation of 4,5-diphenylisoxazoline-3-carboxylic acid.[26] The composition of the base-induced cleavage products also depends on the pH of the reaction medium: in a phosphate buffer, a mixture of hydroxy nitrile, benzyl alcohol (the product of subsequent reduction of benzaldehyde with sodium amalgam), and phenylacetaldehyde is formed. It has been noted that at pH > 10 the cycloreversion products form predominantly, whereas at pH < 9 hydroxynitriles form (in this case, the conversion is insignificant). Since in an aqueous sodium hydroxide solution the conversion of the hydroxy nitriles prepared from the isoxazolines **8g**,**h** into benzaldehyde and phenylacetaldehyde was completed within several minutes, it may be supposed that the latter are the products of the retroaldol reaction of the hydroxy nitrile, since the latter is alkali-labile. However, it is very likely that both the N—O cleavage of the isoxazoline ring into the hydroxy nitrile and the competing process of cycloreversion occur by the same mechanism, in which the cycloreversion is one of the pathways of stabilisation of the cyclic carbanion **11** or the acyclic alkoxide ion **12**.

The anion **11,** which has been postulated for the cyclodegradation of the isoxazoline-3-carboxylic acids **6**,[26,27] seems to be the intermediate product in the cleavage of 3-non-substituted (**5**),[6] 3-phenylsulfonyl- (**8**),[22] and 3-trimethylsilylisoxazolines (**7**),[28] although direct evidence in favour of this mechanism has not been obtained yet. The generation of the isoxazolinium anion **11** from 3-phenylsulfonyl-, 3-trimethylsilyl-, and 3-carboxyisoxazolines occurs by the cleavage of the C(3)—X (X = S, Si, C) bond. It is worth noting that the identity of the products of the above reaction points to the common intermediate, which can be represented by the corresponding 3-non-substituted isoxazoline generating the anion (or the radical). If the C(4)—C(5) bond cleavage occurs and the β-hydroxy nitrile is thermally stable under the given reactions conditions, one may postulate the cyclodegradation as occuring via the intermediate formation of the acyclic alkoxide ion **12**.[26] An alternative mechanism of this reaction is the concerted cycloreversion of the carbanion **11** with the formation of compounds **13** and **14**.[25]

The cleavage of the alkoxide ion **12** must be very rapid and compete with protonation. Thus, the observed conversion of the β-hydroxy nitrile **10f** into the oxonitrile **24** under the action of a

Table 1. Cleavage of 3-benzenesulfonylisoxazolines **8a**–**h** by sodium amalgam into hydroxy nitriles **10a**–**h**.[21]

3-Benzenesulfonylisoxazolines (**8**)	β-Hydroxy nitriles (**10**)	Yield (%)
 **a**	 **a**	91
 **b**	 **b**	94
 **c**	 **c**	89
 **d**	 **d**	86
 **e**	 **e**	83
 **f**	 **f**	93
 **g**	 **g**	0
 **h**	 **h**	0

base (170 °C) is in accord with the rapid cleavage of the C(4)–C(5) bond in the alkoxide ion.[22] Presumably, in the course of decarboxylation the alkoxide anion **12** is originally generated in an excited state; such a 'hot' alkoxide ion undergoes fragmentation more easily.

If isoxazolines are considered as a latent form of β-hydroxy ketones and the process of the formation of isoxazolines and their cleavage into hydroxy ketones as the equivalent of the aldol condensation, the 1,4-cycloreversion represents, in effect, a retroaldol degradation.

Apart from the above examples of 1,4-cyclodegradation of the isoxazoline ring, when the generation of the isoxazolinium anion of type **2a** proceeds with the participation of nucleophilic reagents, an alternative way of 1,4-cycloreversion of isoxazolines is known, which represents the degradation of the isoxazoline ring without deprotonation and is accompanied by the formation of two carbonyl compounds. Such a cyclodegradation was observed as a competing process in the cleavage of isoxazolines by metal polycarbonyls.[34–38]

In 1984–1987, preparative methods were developed for thermolytic and photolytic degradation of isoxazolines into β-hydroxy ketones in the presence of metal polycarbonyls.[34, 35, 37] This interaction is not unambiguous, however. Thus, in the case of phenyl-substituted isoxazolines **25a,b,** the aldehydes **26** and the ketones **27** form, which are the products of retroaldol degradation of the heterocycle at the N–O and C(4)–C(5) bonds (Scheme 4). The isoxazolines containing no substituents at C(5) give, in addition to the 1,4-cycloreversion products, the corresponding β-hydroxyketones **28** or aminoenones. It was also found that 1,4-cycloreversion is the main pathway of the cleavage of isoxazolines with $Mo(CO)_6$ in anhydrous media.[37]

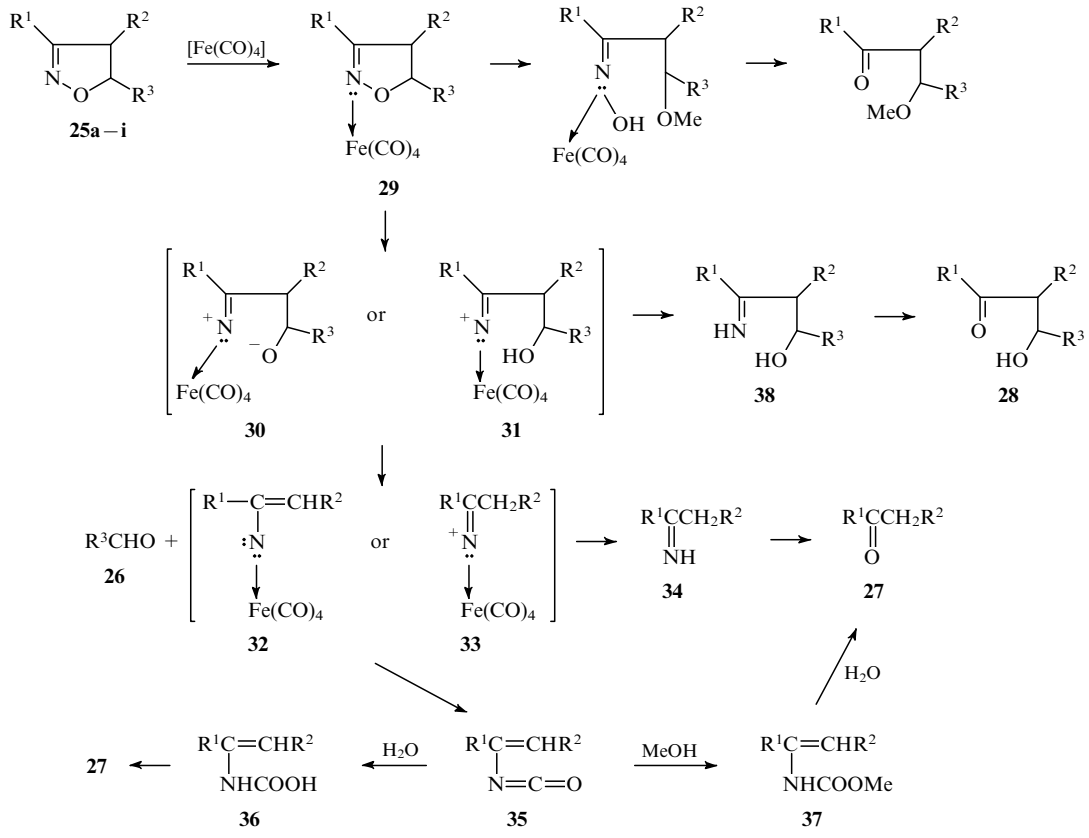
The yields of the products of photolytic [under the action of $Fe(CO)_5$] and thermal [under the action of $Fe_2(CO)_9$] cleavage of the isoxazolines **25a–i** are listed in Table 2.[34] The results presented can be explained within the framework of the mechanism of cyclodegradation depicted in Scheme 4. The most probable mechanism is the degradation via the intermediate **29** and its cleavage with the formation of a bipolar complex **30**, the rapid hydrolysis of which gives the β-hydroxy ketone **28**. In anhydrous media, the cleavage occurs at the C(4)-C(5) bond. An *n*-donor complex **29** of isoxazoline with $Fe(CO)_4$ generated photochemically from $Fe(CO)_5$ or thermally from $Fe_2(CO)_9$ cleaves to give the intermediates **30** or **31,** which undergo further degradation to yield the aldehyde **26** and the vinylnitrene complex **32** (or its protonated form **33**). Obviously, the factor facilitating the easy cleavage of the N-O bond is the delocalisation of the π-*d* electrons from Fe to the π*-orbital of the C=N–O fragment of the heterocycle. In methanol (or in the presence of water), the complex **32** undergoes reduction to give the imine **34** (major pathway) or insertion of the carbonyl occurs with the formation of the vinyl isocyanate **35** (minor pathway). The isolation of a stable methyl mesyl ketimine in the case of the isoxazoline **25g** is evidence for the intermediate formation of the corresponding imine **34**. In the presence of water,

Table 2. Photolytic cleavage of 2-isoxazolines by iron polycarbonyls during photolysis.[34]

Compounds **25**	R^1	R^2	R^3	Time /h	Yield (%) **26**	**27**	**28**
a	Ph	H	Ph	24	57	69	–
a [a]	Ph	H	Ph	6	73	81	–
b	Ph	Ph	Ph	10	62	96	–
b [a]	Ph	Ph	Ph	3	42	84	–
c	Ph	H	Hexyl	24	52	86	–
c [a]	Ph	H	Hexyl	4	–	53	30
d	Me	H	Ph	2	53 [b]	57 [b]	–
e	Me	H	Hexyl	6	61 [b]	54 [b]	–
f	Ph	H	Vinyl	24	54 [b]	78 [b]	–
g	Mesyl	H	Ph	6	6	58	91
h	Ph	H	H	19	see [c]	35	60
i	Ph	Me	H	5	see [c]	45	40

[a] Thermal treatment; [b] isolated as 2,4-dinitrophenylhydrazone; [c] not isolated.

Scheme 4



the vinyl isocyanate **35a** (R^1 = Ph) dissociates into the ketone **27a** via the intermediate acid **36**, and in methanol it gives 1-phenylvinylcarbamate **37a**. The imine **34a** is hydrolysed when treated with water (or in the presence of water) to give the ketone **27a**. Thus, the intermediates **32** (or **33**) are very labile in protic media or in the presence of trace amounts of water. The carbamate **37** can also undergo hydrolysis into the ketone **27.** The formation of the latter can also occur through consecutive transformations of the intermediates **32** (or **33**) into the imine **34**.[34]

The nature of the substituent at the C(3) atom does not apparently influence appreciably the course of the reaction. Thus, for 3-methyl- (**25e**) and 3-phenyl-substituted (**25a**) isoxazolines the results of the reaction are comparable (Table 2). Obviously, the substitution at C(5) is the most important for the cleavage of the C(4)–C(5) bond. The absence of substituents at C(5) prevents this cleavage. Thus, for the C(5)- non-substituted 2-isoxasolines **25h**,**i,** the yield of the aldol degradation products, *viz*., acetophenone **27h** and propiophenone **27i**, was about 40%, whereas the corresponding hydroxyketones **28h**,**i** were obtained with the yields of about 50%. Apparently, in these cases the energy barrier for the C(4)–C(5) bond cleavage is higher than that for the 3-substituted isoxazolines **25a**–**g,** and the degradation of the **30** (**31**) → **26** + **32** (**33**), type involving the elimination of the aldehyde molecule, competes with the cleavage via the hydroxy imine **38** into the hydroxyketone **28**. Irradiation of the isoxazolines **25h**,**i** with $Fe(CO)_5$ in methanol does not cause the aldol-type reversion.

Reactions of isoxazolines **39a**–**c** having acetoxy, ethoxy, or amino groups at C(5) with metal polycarbonyls give β-amino enones **40a**–**c** in good yields under identical conditions (Table 3).[34, 36] The enamino ketone **40** can form from the complex **41** by cleavage at the N–O bond and subsequent elimination of the AcO- or EtO-groups to give the vinylnitrene complex (pathway *A*, Scheme 5) similar to the complex **31**. An alternative pathway for obtaining the enamino ketones **40**[33] (pathway *B*, Scheme 5), through elimination of AcOH and EtOH from isoxazolines with the intermediate formation of the corresponding isoxazoles **42** and their degradation by metal polycarbonyls has been described.[39] This pathway seems to be analogous to aromatisation of isoxazolines, which will be considered below. The pathway *C* depicted in Scheme 5 is analogous to the degradation of isoxazolines **25a**–**g** and involves the elimination of the aldehyde **26** with the formation of the vinylnitrene complex **43**, which is further converted into the ketone **44**. In the case of isoxazoline **39c** having a pyrrolidino substituent at C(5), the products of conversion by both the pathway *A* and the pathway *C* have been isolated. The direction of this reaction is also affected by the substituents at C(4) of the heterocycle. For 4,4-dimethyl-5-(pyrrolidino-2-isoxazoline (**39d**), only one pathway *C* resulting in the formation of the ketone **44d** is realised, since for $R^1 \neq H$, the elimination of the tertiary amine molecule is unlikely.

Scheme 5

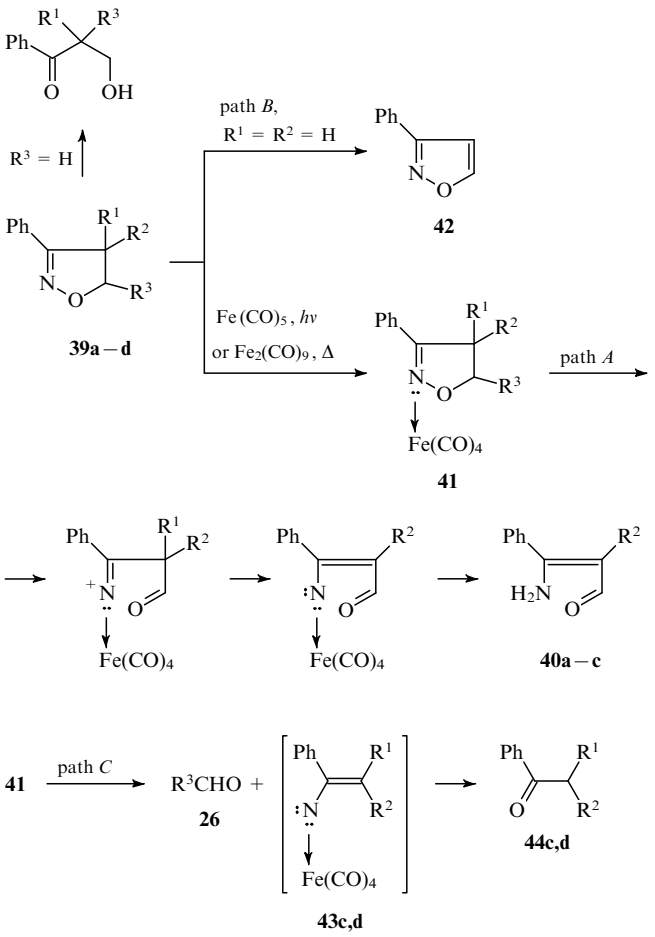
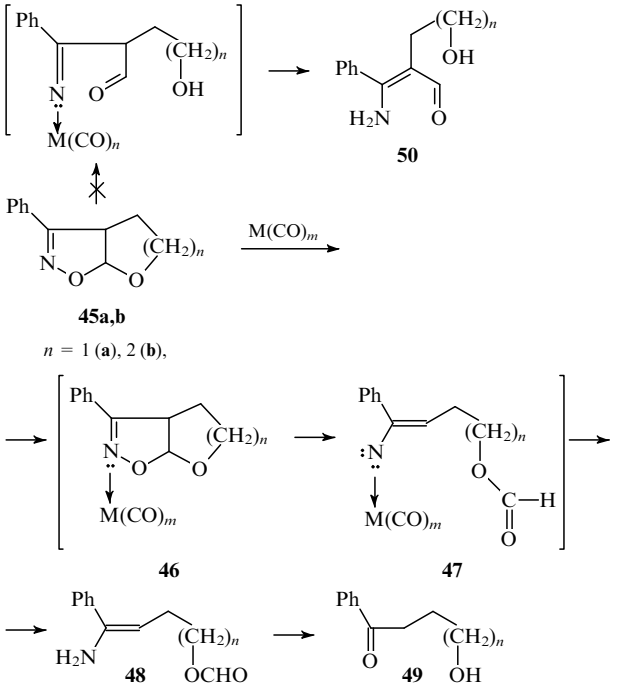


Table 3. Photolytic cleavage of the 2-isoxazolines **39a**–**d** by iron polycarbonyls during photolysis.[34]

Compounds **39**	R^1	R^2	R^3	Time /h	Yield (%) **44**	**40**
a	H	H	OAc	6	80	0
a [a]	H	H	OAc	3	79	0
b	H	H	OEt	24	76	0
c	H	Et	$-N(-CH_2-)_4$	24	35	51
d	Me	Me	$-N(-CH_2-)_4$	20	0	72

[a] Thermal treatment.

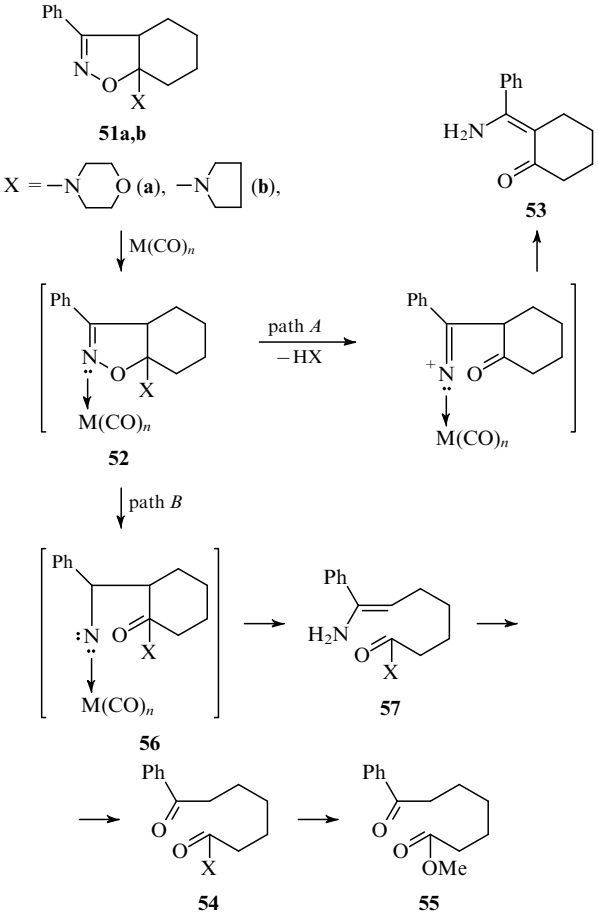
In the reactions of fused isoxazolines, *viz*., 3-phenyl-3*a*,4,5,6*a*-tetrahydrofuro- (**45a**) and 3-phenyl-3*a*,5,6,7*a*-tetrahydro-4*H*-pyrano[3,2-*d*]isoxazoles (**45b**) with metal polycarbonyls, cycloreversion is the major transformation.[35, 36]



The degradation proceeds via the *n*-donor complex **46**, which is cleaved to give a nitrene complex **47**; its further reduction results in the enamine **48**, which is hydrolysed under the reaction conditions into the hydroxyketone **49**. An alternative pathway with the formation of the enamino ketone **50** resulting from the cleavage of the N—O bond of the isoxazoline and the C—O bond of pyran does not take place, in contrast to the cleavage of 5-ethoxy- or 5-acetoxyisoxazolines.

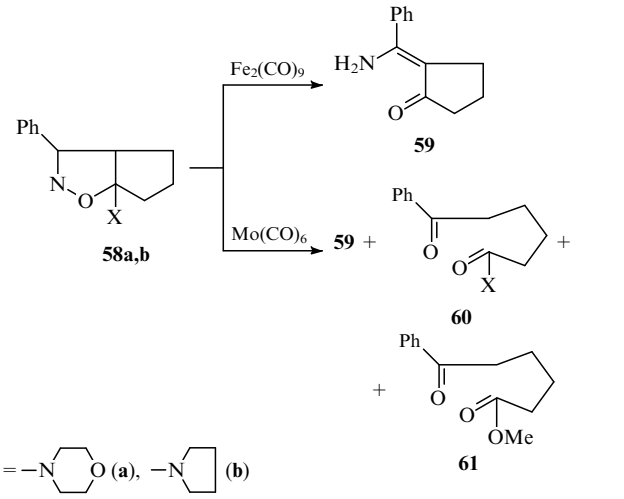
Similar reactions with 7*a*-morpholino- (**51a**) and 7*a*-pyrrolydino-3-phenyl-3*a*,4,5,6,7,7*a*-hexahydrobenzo[*d*]isoxazoles (**51b**) give the products **53** and/or **55**, depending on experimental conditions. With $Fe_2(CO)_9$ (thermolysis) or $Fe(CO)_5$ (photolysis), the degradation follows predominantly pathway *A* (Scheme 6) to give the enamino ketone **53** formed as a result of cleavage of the N—O bond and the elimination of the amine HX. Treatment of isoxazolines **51** with molybdenum hexacarbonyl in methanol gives, in addition to the products **53** and **55**, also a small amount of the oxo amide **54**. The degradation of the intermediate complex **52** at the N—O and C(3*a*)-C(7*a*) bonds can also occur via the intermediate **56,** the reduction of which and subsequent hydrolysis gives the enamino amide **57** (pathway *B*, Scheme 6). The derivative **55** is the product of methanolysis of the amido group in the compound **54**.[35]

Scheme 6



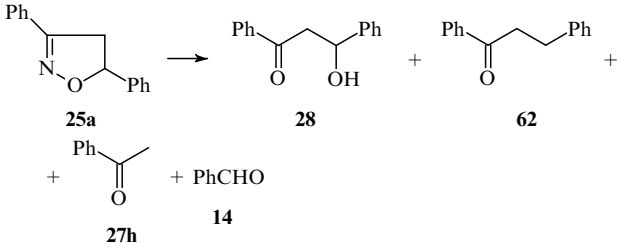
On the other hand, the reaction of 6*a*-morpholino- (**58a**) and 6*a*-pyrrolidino-3-phenyl-3*a*,5,6,6*a*-tetrahydro-4*H*-cyclopenta[*d*]-isoxazolines **58b** with $Fe_2(CO)_9$ is a very slow process, and the β-enamino ketones **59** are isolated along with large quantities of the original isoxazolines. At the same time, the enamino ketone **59**, the amide **60,** and the ester **61** are readily formed with $Mo(CO)_6$.[35]

In the above examples, a dependence emerged between the direction of isoxazoline degradation and the length of the



4,5-polymethylene chain. Presumably, the composition of the products does not depend on the structure of the leaving group X. However, the cleavage of the N—O bond with simultaneous elimination of the heterocyclic amine and the formation of the enamino ketones **59** becomes the major pathway for the fused isoxazolines **58**.

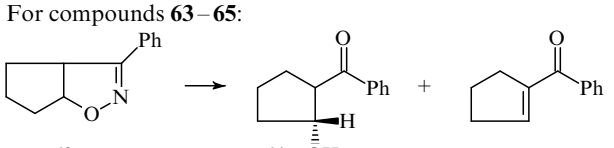
It should be noted that the cycloreversion, which interferes with the degradation of 3-phenyl-substituted isoxazolines, is not characteristic of 3-alkyl-substituted ones. In the latter case, the degradation of the heterocycle under the action of metal polycarbonyls follows a traditional pattern with the formation of the corresponding hydroxy ketones and enones. A modified procedure has been proposed to block the cycloreversion, which occurs in the reaction of the 3,5-diphenyl-substituted 2-isoxazolines **25** with metal polycarbonyls, in which the reagent is the $Mo(CO)_3(MeCN)_3$ complex.[38] In this case, the proportion of the cycloreversion products **14** and **27h** formed upon cleavage of the 3,5-diphenyl-2-isoxazoline **25a** diminishes from 40% down to 4%.



	Method	Recovery of the starting material (%)	Yield (%)			
			28	**62**	**27h**	**14**
25a	A [a]	27–30	21–39	16–27	2	2
	B [b]	—	16	20	25	13

[a] A — $Mo(CO)_3(MeCN)_3$. [b] B — $Mo(CO)_6$, MeCN, H_2O, 1.5 h.

For compounds **63**–**65**:

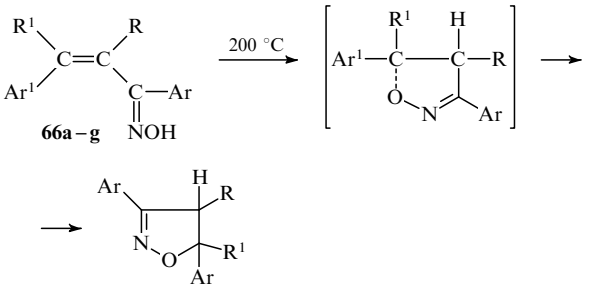


	Method	Recovery of the starting material (%)	Yield (%)	
			64 (*cis* : *trans*)	**65**
63	A	45–52	27–38 (1.5)	10–17
	B	32	24 (5)	10

IV. 1,3-Cycloreversion of 2-isoxazolines

If the 1,4-cycloreversion of 2-isoxazolines considered above represents a retroaldol degradation, the 1,3-cycloreversion is a process which is the opposite of intramolecular cycloaddition. The reaction of retro-1,3-dipolar intramolecular cycloaddition takes place primarily in the synthesis of isoxazolines from oximes.

Thus, Shotter et al.[40] observed 1,3-cycloreversion of isoxazolines in the studies of thermal cyclisation of the oximes **66a – g**. At temperatures around 300 °C, oximes yield compounds, which can be regarded as products of fragmentation of the intermediate isoxazolines undergoing 1,3-cyclodegradation.[40] These isoxazolines were isolated if the cyclisation of the oximes **66a**,**b** was carried out at 200 °C, and then at 300 °C they decomposed into the same products as those obtained upon thermal cyclisation of oximes at 300 °C.



66a – g **25a, 67b – g**

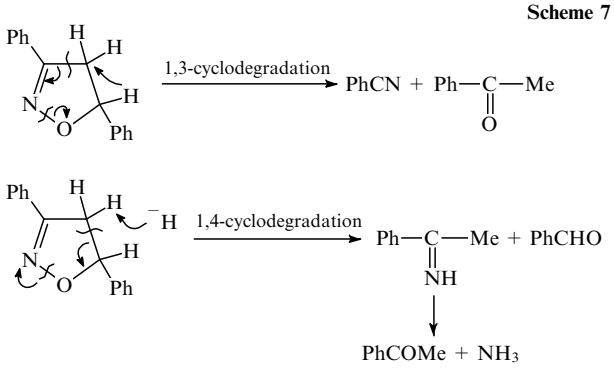
Ar = Ar^1 = Ph: R = R^1 = H (**a**); R = Br, R^1 = H (**b**);
R = H, R^1 = Me (**c**); R = Me, R^1 = H (**d**);
R = R^1 = H: Ar = *p*-MeOC$_6$H$_4$, Ar^1 = Ph (**e**);
Ar = Ph, Ar^1 = *p*-MeOC$_6$H$_4$ (**f**);
R = Me, R^1 = H, Ar = Ph, Ar^1 = 2-thienyl (**g**).

Thus, upon heating at 280 °C, the benzalacetophenone oxime **66a** gives 36% of benzonitrile, 30% of acetophenone, 4% of benzaldehyde, 6% of ammonium benzoate, water, and ammonia. At first, 3,5-diphenylisoxazoline **25a** is formed from this oxime at 200 °C; further heating up to 280 °C gives the products of 1,3- (benzonitrile and acetophenone) and 1,4-cyclodegradation (benzaldehyde and acetophenone imine). The latter undergoes easy hydrolysis into acetophenone and ammonia. It is thus supposed that pyrolysis of oximes proceeds through the intermediate formation of isoxazolines with their subsequent cyclodegradation by two pathways. A scheme has been proposed for the 1,3-cycloreversion, which involves a hydride shift. It is believed that 1,4-cyclodegradation is a reductive process consisting in the transfer of the hydride ion; however, the donor of this ion has not been identified (Scheme 7). The isolation of the isoxazoline **67c** in 65% yield and the absence of cyclodegradation products in the pyrolysis of the oxime **66c** are evidence in favour of the proposed mechanism. Probably, in this case the postulated hydride shift is impossible. The reaction with the oxime **66d** gave benzonitrile (50%) and propiophenone (56%), the products of 1,3-cyclodegradation of the intermediate, isoxazoline **67d**, and its aromatisation product, 3,5-diphenyl-4-methylisoxazole. There was no 1,4-cyclodegradation under these conditions.

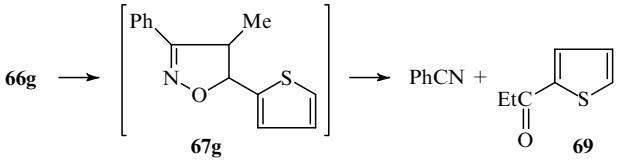
By analogy with the behaviour of other five-membered heterocyclic systems, the authors assumed that the both pathways of cyclodegradation (1,3 and 1,4) are cases of retro-1,3-dipolar cycloaddition. However, the dipolar ion, $^+CH_2-CH(Ph)-O^-$, formed upon 1,3-cyclodegradation, is devoid of the four π-electrons in the C–C–O bond system necessary for its conversion into an alternative canonical structure, $^-CH_2-CH(Ph)-O^+$, while in the case of the vinylnitrene **68**, the original product of 1,4-cycloreversion, such an isomerisation is very likely:

$$^-N=C(Ph)-CH_2^+ \longrightarrow :N-C(Ph)=CH_2\ (\mathbf{68}) \longrightarrow \longrightarrow {}^+N=C(Ph)-CH_2^-.$$

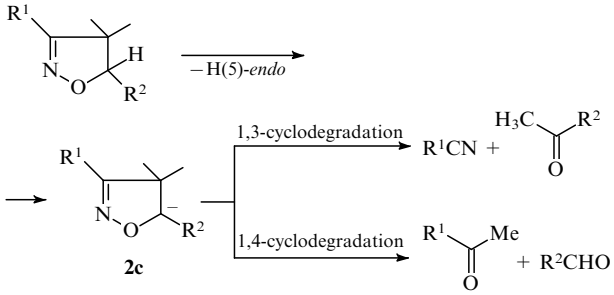
Scheme 7



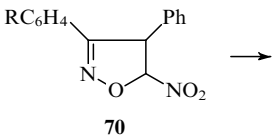
For 2-methyl-1-phenyl-3-(2-thienyl)prop-2-en-1-one oxime **66g**, the corresponding intermediate product, isoxazoline **67g**, could not be isolated under the conditions of thermal cyclisation,[40] apparently due to the high susceptibility of the latter to cyclodegradation. This reaction gave only benzonitrile and the corresponding ketone **69**.



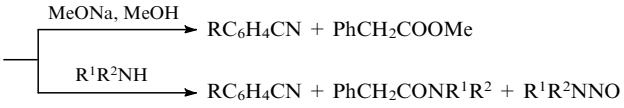
It should be noted that benzonitrile oxide and alkene, the products of cycloreversion by the third possible pathway (the so-called '3,5-retro-Grunanger addition'), were not identified among the products of oxime pyrolysis. Such a process did not take place in other cases either. Obviously, this process is hardly likely due to the energy gain in the direct reaction. Studies of the interaction of 3-substituted isoxazolines with bases did reveal cases of 1,3-cycloreversion. 1,3-Cycloreversion of isoxazolines under the action of bases is associated with the possibility of generating an anion at C(5) of the isoxazoline. It is known that the most acidic protons are the proton at C(3) in 3-nonsubstituted isoxazolines and the proton at C(4) in 3-substituted isoxazolines.[7,18] 5-*endo*-Deprotonation is not usual in this case; it can occur only in isoxazoline structures in which deprotonation at other carbon atoms is hindered, on the one hand, and which contain substituents at C(5) able to stabilise the anion formed, on the other hand.Thus, a significant increase in the proton H(5) acidity can be invoked by electron-acceptor substituents at C(5).[41] Indeed, isoxazolines carrying electron-acceptor substituents turned out to be highly susceptible to such a cyclodegradation. The degradation of the cyclic carbanion **2c** generated as a result of C(5) deprotonation by the nucleophile can further proceed in accordance with the scheme:



Baranski and Cholewka [42] observed 1,3-cycloreversion under conditions of the Nef reaction. This is the first example of such reaction. Treatment of 3,4-diaryl-5-nitroisoxazolines **70** with a stoichiometric amount of NaOMe in absolute methanol resulted in the aromatic nitrile and methyl phenylacetate; an analogous reaction with Et$_3$N or cyclic amines in aprotic solvents results in the nitrile and the corresponding amides.[42]

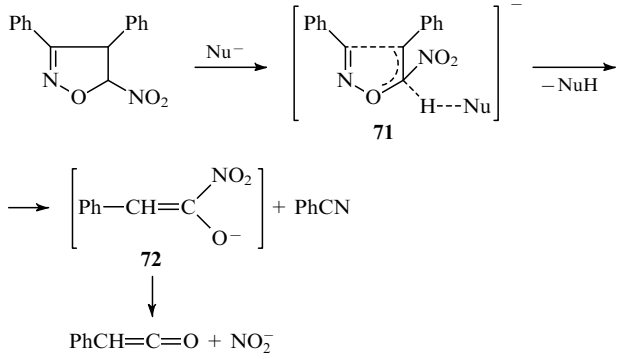


70



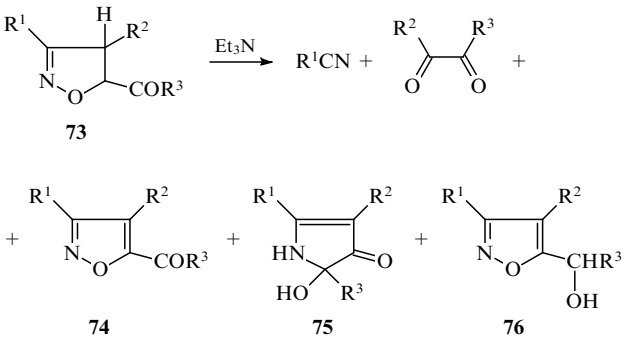
Since it had been known that 5-nitroisoxazolines easily eliminate nitrous acid to give the corresponding isoxazoles[43–46] (see also Section V), it has been postulated that cyclodegradation is preceded by the aromatisation of the heterocycle through the elimination of nitrous acid. The isoxazoles formed thereby can undergo further degradation by the nucleophile. However, the composition of the reaction products excluded the intermediate formation of isoxazoles. Furthermore, unlike 4-nitro-2-isoxazolines, 5-nitroisoxazolines were not subjected to aromatisation by MnO_2.[47]

The most likely mechanism of the 1,3-cycloreversion of nitroisoxazolines is believed to be the synchronous E_2-process with transfer of the H(5) proton to the nucleophile, the cleavage of the N–O and C(3)–C(4) bonds in the intermediate **71**, and the changes in the order of the C=N and C(4)–C(5) bonds. Further transformations of the acyclic anion **72** consist in the elimination of the nitrite anion and the formation of ketene.[42]



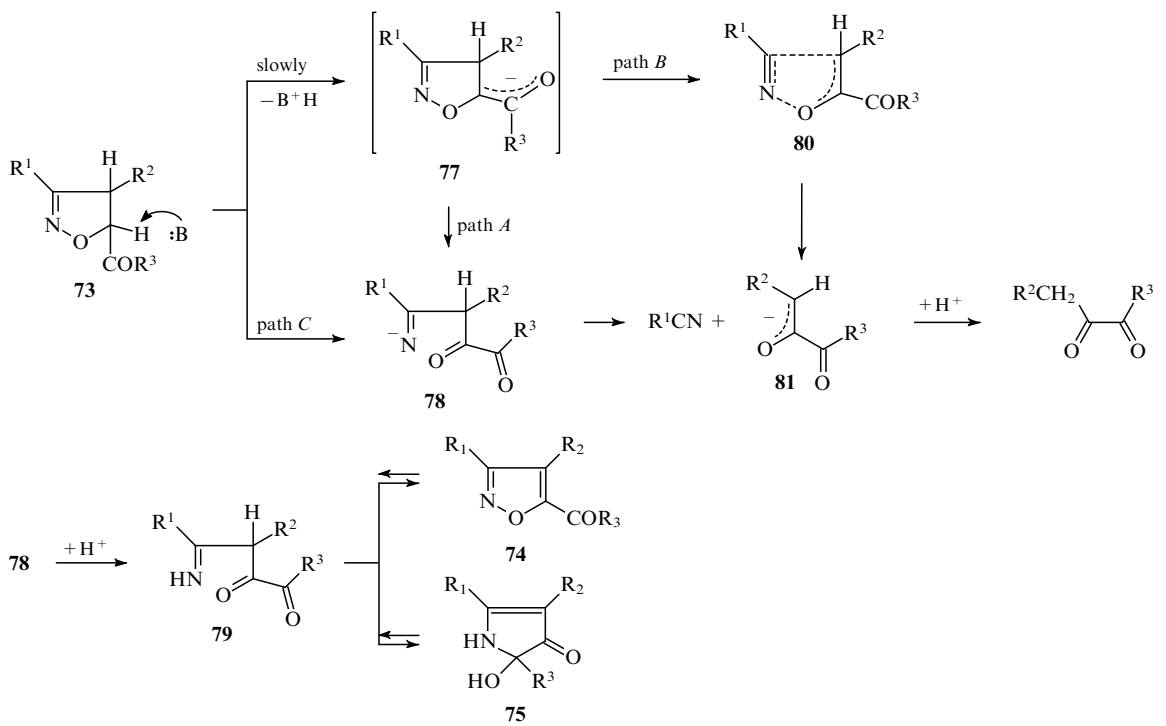
It has to be noted that a final choice in favour of one of the proposed alternative mechanisms is difficult to make, because it is not easy to draw a demarkation line between the ability of 5-nitroisoxazolines for aromatisation and their susceptibility to cyclodegradation. Apparently, aromatisation and cyclodegradation are competing processes, and the composition of the products is determined by both the particular structure of the substrate and the nature of the nucleophile used.

The 5-acylisoxazolines **73**, which decompose into nitriles, α-diketones, isoxazoles **74** and **76**, as well as Δ^2-pyrrolin-4-ones **75** under the action of bases, are also susceptible to C(5)-deprotonation.[41,48] 5,5-Disubstituted isoxazolines are stable under these conditions due to the impossibility of C(5)-deprotonation.[41]



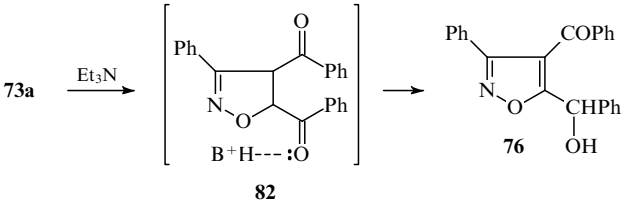
In methanol, C(5)-deprotonation of 5-acylisoxazolines **73** gives approximately 8% of the isoxazoles **74** and **75**, whereas in benzene their yield is as high as 70%. The mechanism of formation of 5-hydroxy-2-pyrrolin-4-one **75** can be represented by Scheme 8. In the presence of bases, C(5) deprotonation of isoxazoline **73** occurs with the formation of the anion **77**; this is followed by its cleavage at the N–O bond to the anion **78** and reprotonation give the equilibrium mixture **74** ⇌ **79** ⇌ **75**. The fragmentation products, the nitrile and the α-diketone, form by the same scheme either by pathway *A* or *B*. Pathway *A* seems to be more preferable than pathway *B*, for it includes a symmetrical cycloreversion via the activated complex **80**. However, it is difficult to make a choice between these pathways, since both of the corresponding transition states for **78** and **80** have similar energy.[48]

Scheme 8

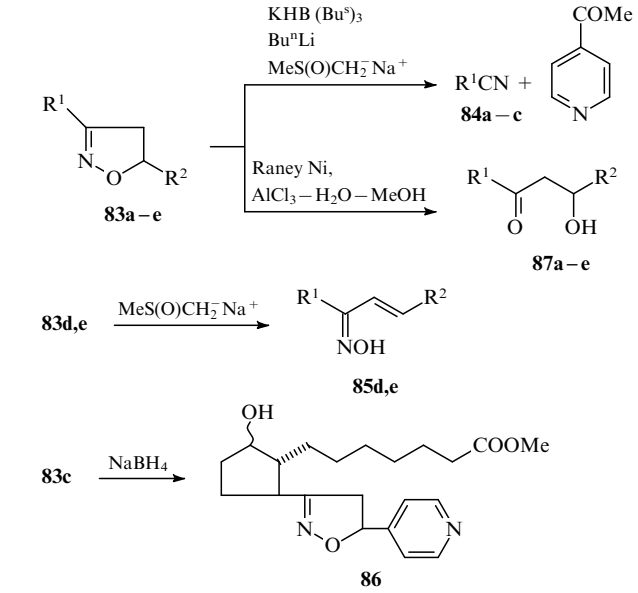


No deuterium exchange occurs on addition of triethylamine to a solution of isoxazolines **73** in D_2O (^1H NMR data); therefore it can be suggested that the equilibrium **73** ⇌ **77** does not exist and deprotonation is the slowest stage of the process. The lack of direct evidence for the formation of the anion **77** allows one to suggest that degradation via pathway *C* is not unlikely. On the other hand, ignoring pathway *B* and considering pathway *A* to be the only one possible, the degradation of the isoxazoline ring to the imino diketone **79** must be more effective in benzene than in methanol, since the transition complex **78** contains a contact ion pair with triethylamine (Scheme 8).

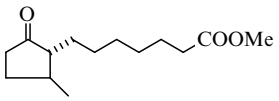
In conformity with this assumption, the formation in a high yield of the isoxazole **76** upon the cyclodegradation of 4,5-dibenzoyl-3-phenyl-2-isoxazoline (**73a**) ($R^1 = R^3 = Ph$, $R^2 = COPh$) in the reaction with triethylamine can best be explained by the transition state **82**:[48]



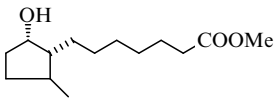
1,3-Cycloreversion of the 3-R-5-(4-pyridyl)isoxazolines **83a–c** resulting in the nitriles **84a–c** and 4-acetylpyridine occurs on the interaction of these isoxazolines with bases (butyllithium and dimsylsodium) and potassium selectride,[49, 50] whereas their analogues **83d,e** interact in accordance with the known schemes to give enoximes **85d,e**.[2, 3, 15, 51]



R^1 = $-C_6H_3(OMe)_2$ (**a**), $-(CH_2)_4COOMe$ (**b**),



(**c**, **d**, **e**),



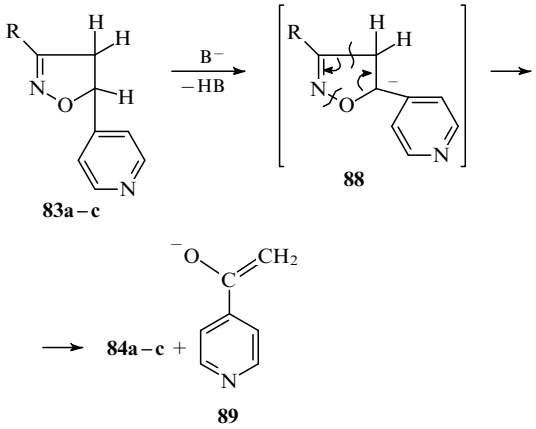
(**84**);

R^2 = pyridyl-4 (**a–c**), Ph (**d**), $-CH_2OPh$ (**e**).

It is noteworthy that the reduction of the isoxazoline **83c** with sodium tetrahydroborate results in the formation of the carbonyl-group reduction product, **86**. Upon reductive cleavage (Raney Ni, $AlCl_3$, $MeOH-H_2O$), 5-pyridylisoxazolines **83a-c** and 5-phenyl(phenoxymethyl)isoxazolines **83d,e** give the β-hydroxy ketones **87,** which is typical of isoxazoline cleavage by reagents of this type.[1, 3]

The formation of different products in the reaction with nucleophilic agents from the 5-pyridylisoxazolines **83a–c** and from the 5-phenylisoxazolines **83d**,**e** points to the involvement of the substituent at C(5). In the case of the derivatives **83a–c,** the products of the cyclodegradation of the isoxazoline fragment form, and the ketone-nitrile 1,3-cycloreversion of 5-(4-pyridyl)-2-isoxazolines observed is similar to the cycloreversion of 5-acyl- and 5-nitro-2-isoxazolines and seems to proceed in accordance with Scheme 9:

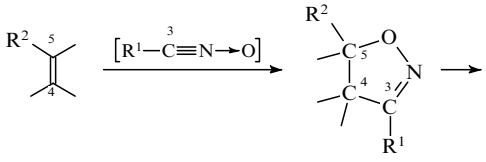
Scheme 9

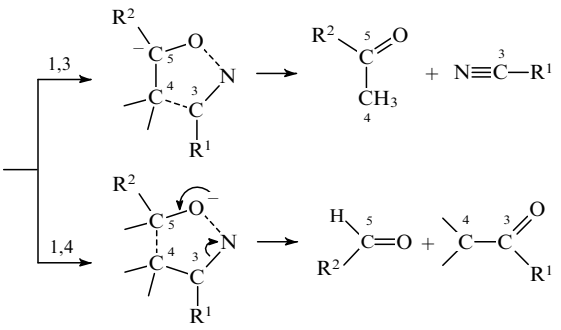


The first step in the 1,3-cyclodegradation of 5-pyridyl-2-isoxazolines **83a–c** is the generation of the anion **88** under the action of the base. Subsequent redistribution of the electron density in the isoxazoline fragment results in the cleavage of the N–O and C(3)–C(4) bonds. The formation of a stable molecule of the corresponding nitrile **84** from the N–C(3)–R fragment is the driving force of this cyclodegradation. The C(4)–C(5)–O fragment carrying originally a negative charge undergoes cyclodegradation to give the enolate anion **89** and then acetylpyridine. It should be noted that all the cases of 1,3-cycloreversion observed previously in reactions with bases seem to occur with the participation of the isoxazolinium anion, the stabilisation pathways of which depend on the specific reaction conditions and the reagents used.

The interaction of the compounds **83d**,**e** with butyllithium and dimsylsodium occurs via the intermediate formation of the anion of the **2b** type (see Section II), which, depending on conditions, can regenerate the original isoxazoline (BuLi, −78 °C) or can be cleaved at the C(5)–O bond to form the stable enoxime **85** (dimsylsodium, 20 °C).

It should be noted in conclusion that the sequence: [2 + 3]-cycloaddition ⇌ deprotonation ⇌ [2 + 3]-cycloreversion is a potentially promising method for the oxidative cleavage of the double bond with simultaneous elongation of the carbon chain at its ends (the so-called method of 'indirect carbolytic cleavage of the double bond').[52, 53]

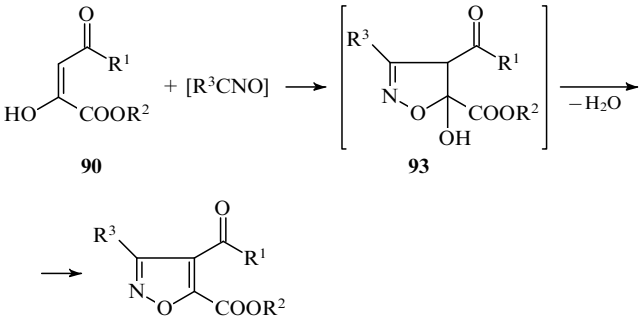




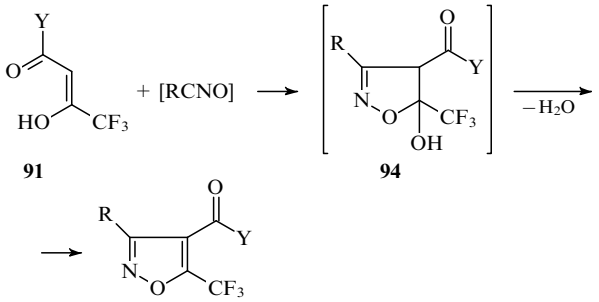
V. Aromatisation of 2-isoxazolines

The tendency toward the formation or elongation of a system of conjugated bonds via the formation of a heteroaromatic ring can be one of the reasons for the conversion of isoxazolines into isoxazoles. Another reason for such conversions is, as a rule, the presence in one of the positions of the carbon skeleton of the isoxazoline heterocycle of a substituent which represents a 'good leaving' group. These substituents can be eliminated spontaneously in the course of isoxazoline formation or under the action of reagents stimulating the elimination process.

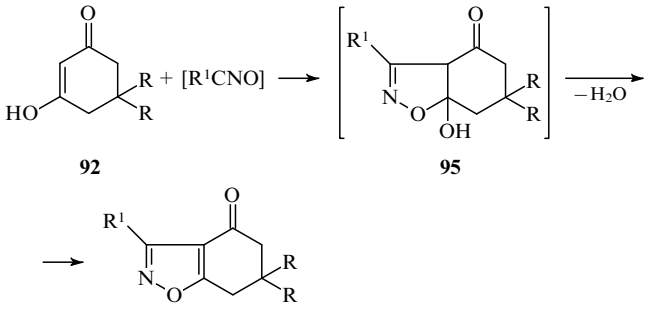
Thus, aromatisation of isoxazolines into the corresponding isoxazoles is often observed in the reaction of 1,3-dipolar cycloaddition of nitrile oxides to enones, 1,3-diones, and their derivatives.[54–59] Aromatisation of the cycloadducts formed as a result of the addition of the nitrile oxide dipole at the double bond of the enolic form of the β-dicarbonyl compounds **90**–**92** occurs via the elimination of the water molecule from the intermediate 5-hydroxy-2-isoxazolines of the **93**–**95** type.



R^1 = Me; R^2 = Me, Et;
R^3 = Ph, $C_6H_4NO_2$, C(O)Me, COOEt, C(O)Ph,[54]

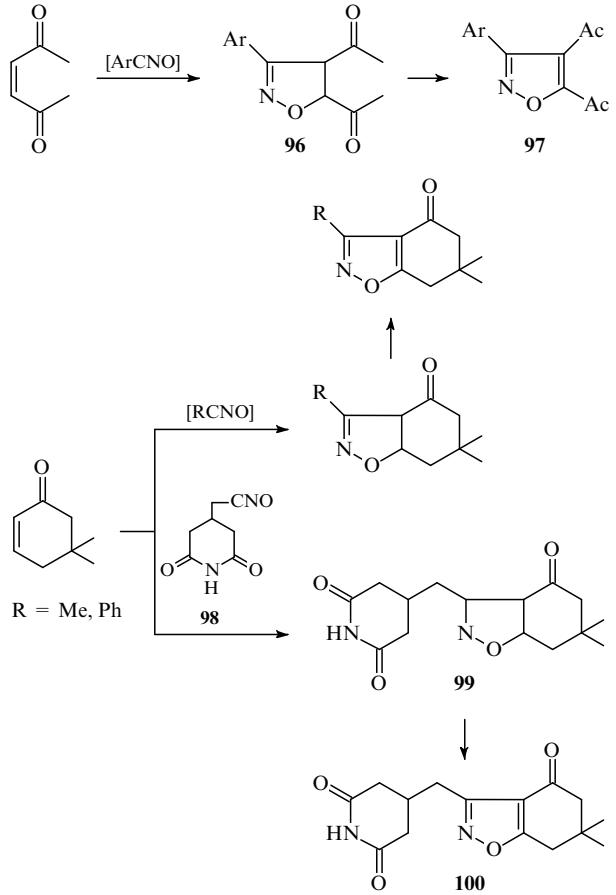


Y = OAlk, Ar, thienyl-2; R = Alk, Ar,[55]

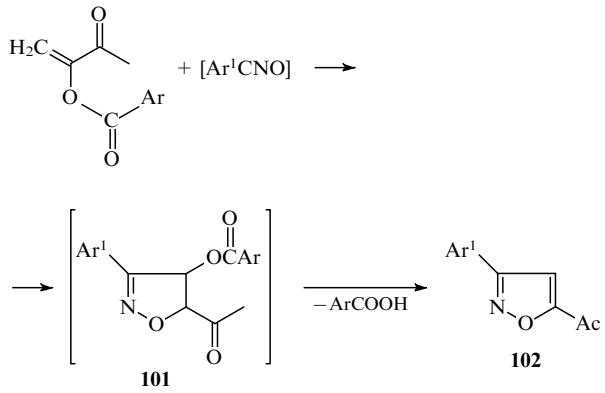


R = H, Me; R^1 = Alk, Ar.[56, 57]

Aromatisation of cycloadducts with enones is a result of an oxidative transformation.[58, 59] One can assume that the aromatisation of 4,5-diacetyl-2-isoxazoline **96** into 4,5-diacetylisoxazole **97** occurs via an identical mechanism.[60] The reaction of the nitrile oxide **98** with 5,5-dimethylcyclohex-2-enone gives the isoxazoline **99**; however, it is readily converted into the corresponding isoxazole **100** during purification on a column or on boiling in *tert*-butyl alcohol in the presence of chloranil.[61, 62]

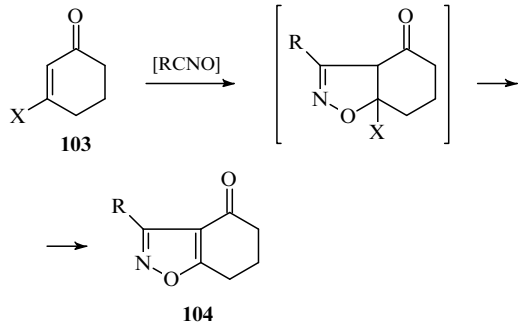


The ease of elimination of the substituent at C(5) of isoxazoline is not only due to the effect of the reaction medium, but also due to the presence of such good leaving groups as acyloxy, alkoxy, and amino groups. Thus, an attempt to synthesise the isoxazoline **101** from the corresponding enone and nitrile oxide has led to the 5-acylisoxazole **102**.[63]



101 **102**

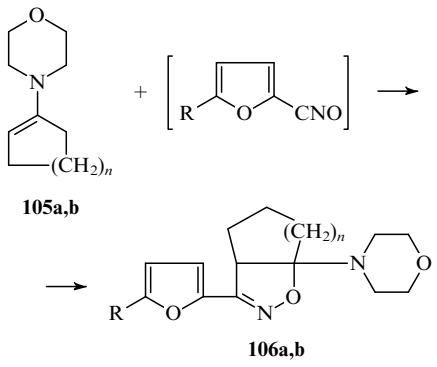
The secondary amino group, first of all, belongs to those, which are easily eliminated from the isoxazoline molecule. Spontaneous aromatisation of the heterocycle was observed in the reaction of 1,3-dipolar cycloaddition of the nitrile oxide to derivatives of the cyclic enone **103**, the highest yields of the isoxazoles **104** being observed in the case of cycloaddition to the enamino ketones **103**.[57]



103 **104**

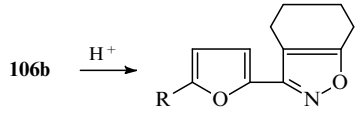
R = Me, Ar, 3-O_2NAr; X = NH_2, —N⟨ ⟩, —N⟨ ⟩O, −OCOMe, Cl, OMe.

Synthesis of fused 4,5-cycloalkanoisoxazolines from the enamines derived from cyclic ketones was accompanied by aromatisation in the case of cyclohexanoisoxazolines (**106b**) prepared from cyclohexanone enamine (**105b**), which served as a dipole. The corresponding isoxazolines **106a** were obtained in the reaction with the cyclopentanone enamine **105a**. Obviously, the main obstacle to the aromatisation of derivatives of isoxazolines **106a** is the increase in the strain of the bicyclic system formed.[64]



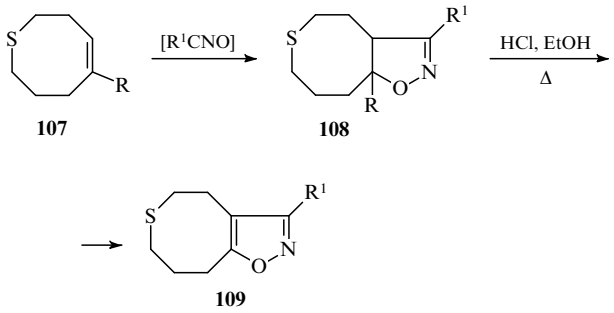
105a,b **106a,b**

n = 1 (**a**), 2 (**b**),



106b

Derivatives of 5-amino-2-isoxazolines readily aromatise under the action of acidic reagents. Thus, the 1,3-dipolar cycloadducts **108** of aromatic nitrile oxides and eight-membered heterocyclic ketone enamines **107** were converted into the isoxazoles **109** under the action of HCl by elimination of the substituent at C(5) of the isoxazoline ring:[65]



107 **108** **109**

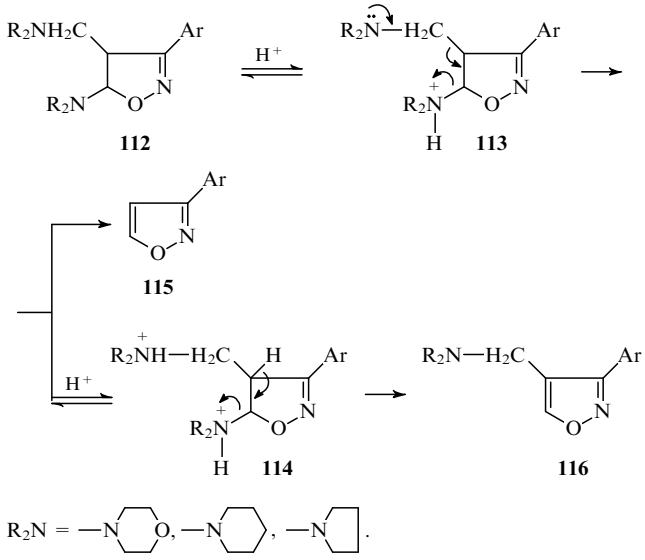
R = NMe_2, —N⟨ ⟩, —N⟨ ⟩O; R^1 = 4-ClC_6H_4, 3-FC_6H_4.

Aromatisaton of the isoxazoline ring was observed in the course of 1,3-dipolar cycloaddition of the nitrile oxide to the enamine **110**:[66]



110 **111**

Elimination of the azaheterocycle from the 4-aminomethyl-3-aryl-5-azahetaryl-2-isoxazolines **112** upon boiling with hydrochloric acid results in 4-aminomethyl-3-arylisoxazole **116** and 3-arylisoxazole **115**.[67] The mechanism of the acid-catalysed aromatisation involves the intermediate formation of protonated intermediates **113** and **114**, the formation of the 3-arylisoxazole **115** being represented as the result of the Mannich retroreaction.[67]



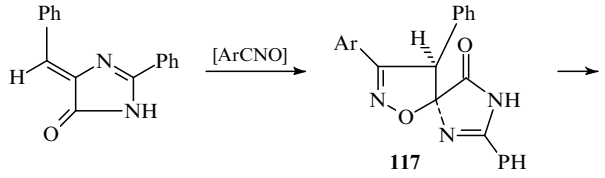
112 **113** **115** **114** **116**

R_2N = —N⟨ ⟩O, —N⟨ ⟩, —N⟨ ⟩.

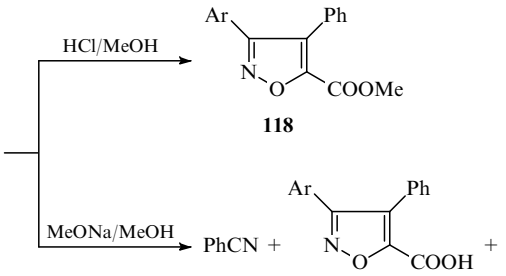
It should be noted that when the isoxazolines **112** were boiled with methanolic sodium hydroxide, the reaction stopped at the stage of formation of the isoxazoles **116**, while prolonged heating with sodium methoxide gives the products of the heterocycle cleavage at the N—O bond.

It was of interest to discuss the aromatisation of the isoxazolines **117** obtained by 1,3-dipolar cycloaddition. These compounds were stable during chromatoghraphic purification on

silica gel, did not react with nucleophilic reagents, but readily converted into the isoxazoles **118**–**120** upon acid or alkaline hydrolysis. In this particular case, the aromatisation of the isoxazoline **117** occurs through the elimination of the lactam ring fragments formed upon the hydrolytic cleavage of the azlactone substituent at C(5).[68]



117



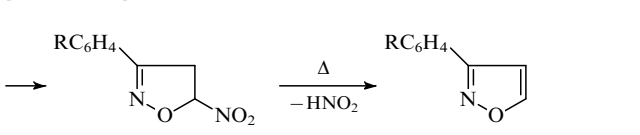
118

119

120

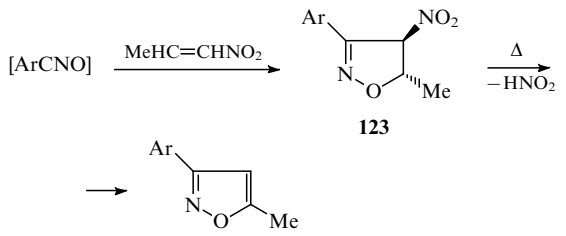
Ar = 2,4,6-$Me_3C_6H_2$.

The instability of 4- and 5-nitro-2-isoxazolines was repeatedly observed in their synthesis from nitrile oxides and nitroalkenes, when the primary product of the cycloaddition, the corresponding 2-isoxazoline, converted into the isoxazole with elimination of nitrous acid.[46] Some nitroisoxazolines formed in this reaction are rather stable under reaction conditions; however, they undergo rapid aromatisation on heating. Thus, the interaction of aromatic nitrile oxides with nitroethylene resulted in the 5-nitro-2-isoxazolines **121**, which on boiling in toluene gave high yields of the isoxazoles **122**.[43, 44]

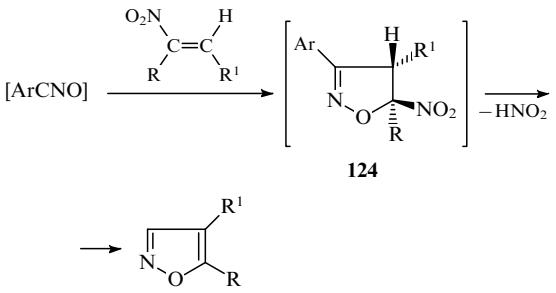


121 **122** (86%–92%)

The ability to eliminate nitrous acid differs for various substituted 4- and 5-nitroisoxazolines. Thus, 4-nitro-5-methylisoxazolines **123** aromatise upon prolonged heating, whereas the derivatives of 5-nitro-2-isoxazoline **124** aromatise spontaneously under reaction conditions.[45, 46]

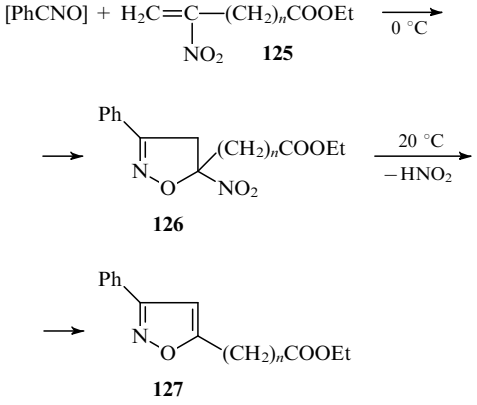


123



124

The 1,3-dipolar cycloaddition of benzonitrile oxide to α-substituted nitroethylenes of the type **125** at 0 °C gives the isoxazolines **126**, which spontaneously convert at 20 °C into the isoxazoles **127** with the elimination of the nitro group:[69]

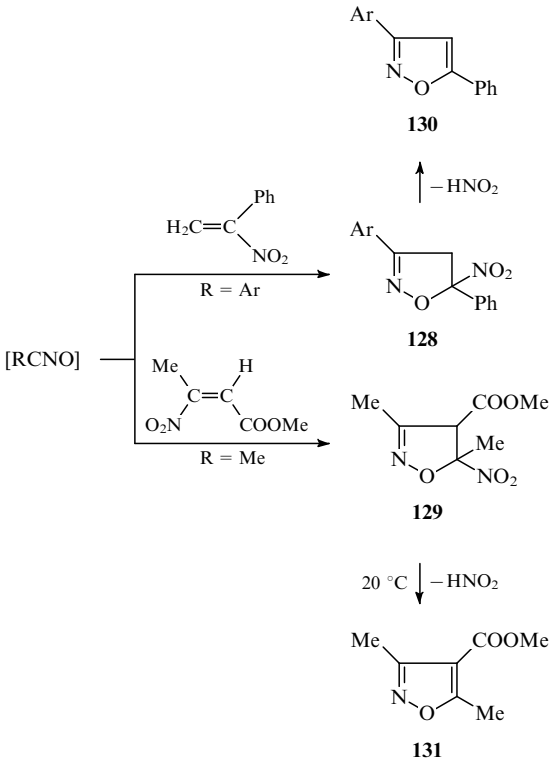


125

126

127

The nitro group can be eliminated more readily from isoxazolines than the cyano and carboxy groups.[70, 71] Thus, the nitro group eliminates preferentially from C(5) of the 5-nitro-5-alkyl(aryl)isoxazolines **128** and **129** to give the corresponding 3,5-diaryl- (**130**)[72] or 3,5-dialkylisoxazoles (**131**).[72, 73]



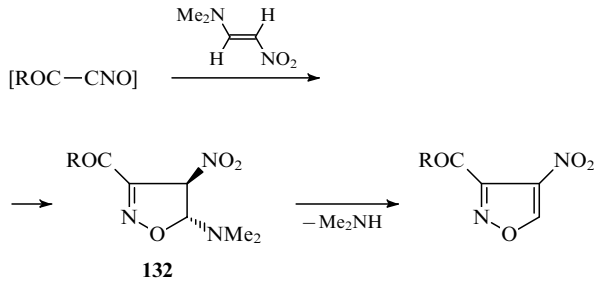
130

128

129

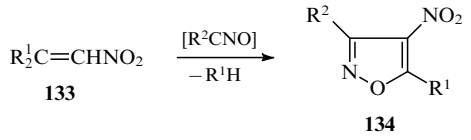
131

However, if the isoxazoline contains an amino group as in the case of 4-nitro-5-dimethylaminoisoxazoline **132**, it is this group that is eliminated during aromatisation.[74, 75]



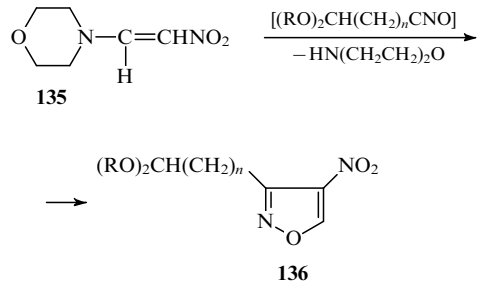
132

The reactions of the β,β-diaminonitroethylenes **133** with nitrile oxides give the 5-amino-4-nitro-3-R-isoxazoles **134**, the products of elimination of one of amine molecules.[76] In the case of the 1,3-dipolar cycloaddition of the nitrile oxide to the nitroalkene **135**, the isoxazole **136** is also formed as a result of preferential elimination of morpholine.[74]



133 **134**

R^1 = NHMe, N⟨ ⟩; R^2 = Bu^t, Ph, 4-ClC_6H_4,

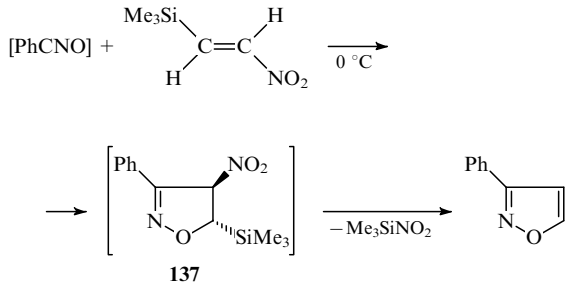


135

136

The adducts of benzonitrile oxide with halonitroethylenes aromatise to give 4- and 5-nitroisoxazoles which can be explained by the ability of intermediate isoxazolines to eliminate the hydrogen halide molecule more readily than HNO_2.[46] It should be noted that spontaneous elimination of hydrogen halide under conditions of nitrile oxide synthesis was often observed when halogenoalkenes were used as dipolarophiles.[57,77] Hence, in some cases unstable 4- and 5-nitroisoxazoles can be obtained by cycloaddition to nitroalkenes containing a substituent group, which eliminates more readily than the nitro group.[46]

The nitro group can be split off, not as nitrous acid, but as a stable compound with another substituent in the isoxazoline ring. Such an ability for elimination is useful in the synthesis of some isoxazoles. For example, in the synthesis of 3-phenylisoxazole by the nitrile oxide method, the substituents at C(4) and C(5) eliminate simultaneously from the isoxazoline **137** formed in the first stage of the reaction:[78]



137

According to their ability for cleavage, the 2-isoxazoline substituents can be arranged in the following order: NR_2 > Hal, OR > NO_2 > CN, COOR.

Aromatisation of isoxazolines was observed either under conditions of nitrile oxide synthesis or under the action of reagents (predominantly acidic). Spontaneous aromatisation of isoxazolines formed as intermediate adducts of the nitrile oxide synthesis occurs with the participation of bases and if C(5) contains hydrogen, which is readily cleaved by bases. Aromatisation of amino-substituted isoxazolines occurs, as a rule, under conditions of proton catalysis.

As noted above, aromatisation of some 5-substituted isoxazolines is a very likely reason for the formation of unusual degradation products upon interaction with metal polycarbonyls (see Section III). Thus, the formation of enamino ketones upon treatment of isoxazolines with iron or molybdenum polycarbonyls [34,39] apparently involves elimination of 5-acyloxy-, 5-ethoxy-groups, or 5-pyrrolidinyl substituents, since the corresponding hydroxy ketones must be the normal products of cleavage of the N—O bonds of isoxazolines.

The competing process of aromatisation is the reason for the conversion of 5-aminoisoxazolines into enamino ketones, the aromatisation being the major pathway in the interaction of isoxazolines with molybdenum hexacarbonyl. The tendency to aromatisation is also realised for 4,5-diacylisoxazolines. Their reactions with bases give isoxazoles in addition to 1,3-cyclodegradation products (see Section IV). In this case, aromatisation is the result of hydride shifts occurring with the participation of acyl substituents or it is analogous to the oxidative transformations of the adducts of the nitrile oxide synthesis.

The examples considered above provide evidence for the competition of the aromatisation of the isoxazolines with the reactions of 1,4- or 1,3-cyclodegradation, which is particularly true for the isoxazoline derivatives carrying good leaving groups as substituents.

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