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Reviews

The chemistry of 2,3-dihydroisoxazole derivatives

N. V. Chukanov[a,b]**** and V. A. Reznikov***[a,b]

[a]*Novosibirsk State University,*
2 ul. Pirogova, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383) 330 2237. E-mail: decan@fen.nsu.ru
[b]*N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences,*
9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation.
Fax: +7 (383) 330 9752. E-mail: nikita@nioch.nsc.ru

Methods for the synthesis and transformations of 2,3-dihydroisoxazole derivatives are reviewed. Data on reduction and oxidation reactions and intramolecular rearrangements are generalized; their mechanisms are discussed.

Key words: 2,3-dihydroisoxazoles, 4-isoxazolines, rearrangement, aziridines, azomethine ylides, pyrroles.

Introduction

1,3-Dipolar cycloaddition has a considerable synthetic potential: *e.g.*, it provides a good single-step route to complex heterocyclic systems. This reaction is often highly regio- and stereoselective, which allows, in some cases, this synthetic approach to be used in total synthesis of natural compounds.[1—4] In turn, the resulting cycloadducts can serve as precursors for a wide range of polyfunctional acyclic compounds with different topologies and, sometimes, stereochemistry, depending on the cycloaddition conditions.[1] Thus, 1,3-dipolar cycloaddition is the key step in the synthetic strategy affording various classes of polyfunctional (including natural) compounds.

Cycloaddition reactions of alkynes with nitrones as dipoles yield 2,3-dihydroisoxazole derivatives. The properties of these compounds have been systematically examined since the 1960s (see Ref. 5) and the collected data provide evidence for a wide range of their possible transformations.[1,6—10] The relatively weak N—O bond[11] can easily undergo cleavage. In some cases, the resulting 2,3-dihydroisoxazoles are very unstable and, once formed, immediately undergo further transformations with difficult-to-study mechanisms. That is why despite the considerable synthetic material obtained over the last few decades, the study of possible transformations of 2,3-dihydroisoxazoles is promising both for development of novel approaches to the synthesis of various classes of compounds and analysis of their mechanisms. In addition, this can be useful for improvement of the synthetic strategy based on 1,3-dipolar cycloaddition.

The publication of Freeman´s review[6] was a response to the great interest in 2,3-dihydroisoxazole derivatives. It should be noted that more recent reviews[1,7—10] covering

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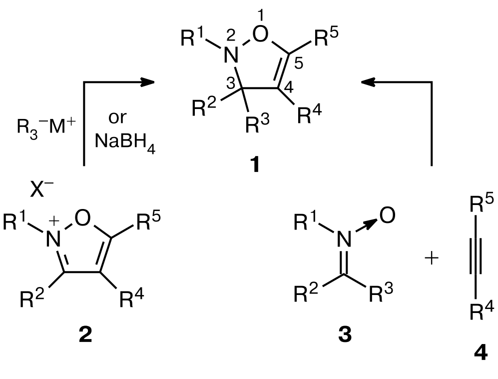
isoxazole derivatives on the whole dwell on the 2,3-dihydroisoxazole system very briefly, without systematic comparison of its various rearrangements. So the topics of the present and aforementioned reviews can be thought to be neatly demarcated. In addition, isoxazol-3-ones, which are formally classified among 2,3-dihydroisoxazoles as well, should be excluded from our analysis because they exhibit quite different chemical properties and can be considered in the isomeric 3-hydroxyisoxazole form. The body of evidence on the properties of 2,3-dihydroisoxazoles has increased substantially in recent years, which necessitates generalization of new data for making well-reasoned conclusions about the mechanisms of the observed transformations.

In this review, we analyzed available experimental data with the aim of finding correlations between the pathways of the transformations of 2,3-dihydroisoxazoles, the reaction conditions, and the character and relative positions of substituents in the heterocycle.

2,3-Dihydroisoxazoles: methods for the synthesis and structures

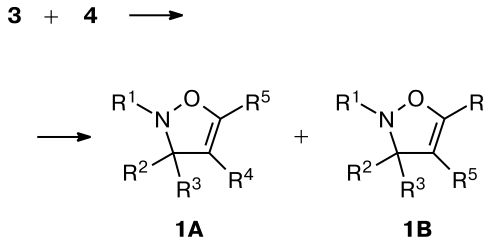
2,3-Dihydroisoxazoles (4-isoxazolines) **1** are five-membered heterocyclic compounds containing two singly bonded heteroatoms (N and O). They can be obtained by nucleophilic addition of organometallic compounds[12,13] or the hydride ion[12,14–16] to isoxazolium salts **2**; however, the most versatile method involves 1,3-dipolar cycloaddition of nitrones **3** to alkynes **4** (Scheme 1).[6,7,17,18]

Scheme 1



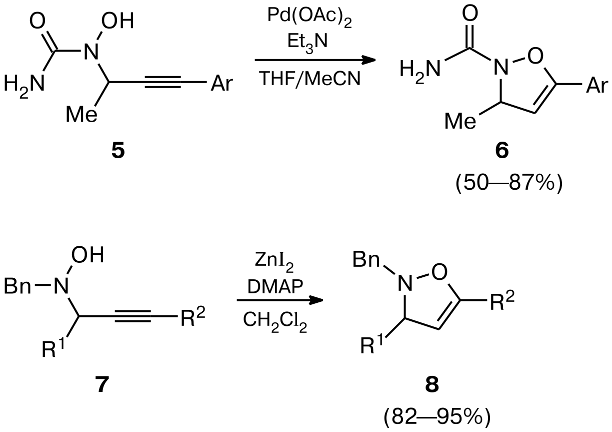
With asymmetrically substituted alkynes as dipolarophiles, the formation of two regioisomers **1A** and **1B** is possible (Scheme 2). However, the reaction is often regioselective and the structure of the major product can be predicted in terms of the frontier orbital theory, particularly when considering the atomic coefficients in the interacting HOMO and LUMO of the dipole and dipolarophile.[19,20]

Scheme 2



Recently, new methods of designing the isoxazoline heterocycle have been developed. In particular, it has been demonstrated that Pd-catalyzed cyclization of *N*-propargyl-*N*-hydroxyurea derivatives **5** gives substituted 2,3-dihydroisoxazoles **6** (Scheme 3).[21] Higher yields of compounds **8** in similar reactions of *N*-propargylhydroxylamines **7** have been achieved with ZnI_2 and DMAP as catalysts (see Scheme 3).[22]

Scheme 3

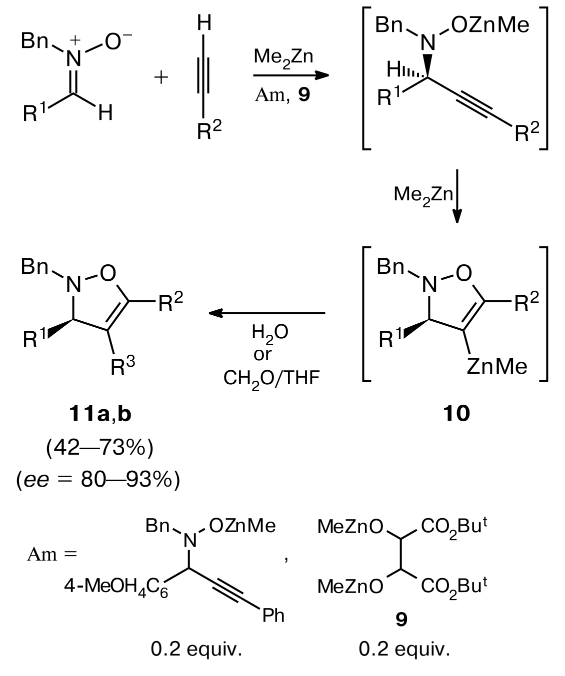


DMAP is 4-dimethylaminopyridine

N-Benzylnitrones react with terminal alkynes in the presence of *N*-propargylhydroxylamines, dimethylzinc, and di(*tert*-butyl) (*R*,*R*)-tartrate **9** as a chirality source to yield chiral *N*-propargylhydroxylamine derivatives, whose cyclization with excess dimethylzinc gives 4-substituted organozinc derivatives of isoxazoline (**10**) (Scheme 4).[23] Subsequent reactions of compounds **10** with water or formaldehyde produce 4-unsubstituted (**11a**, R^3 = H) and 4-hydroxymethylisoxazolines (**11b**, R^3 = CH_2OH), respectively. Reactions of intermediates **10** with DCl in D_2O or with *N*-iodosuccinimide give deuterated or iodo products, respectively.[24] It is worth noting that the enantiomeric purity of products **11** is high (*ee* = 80—93%).

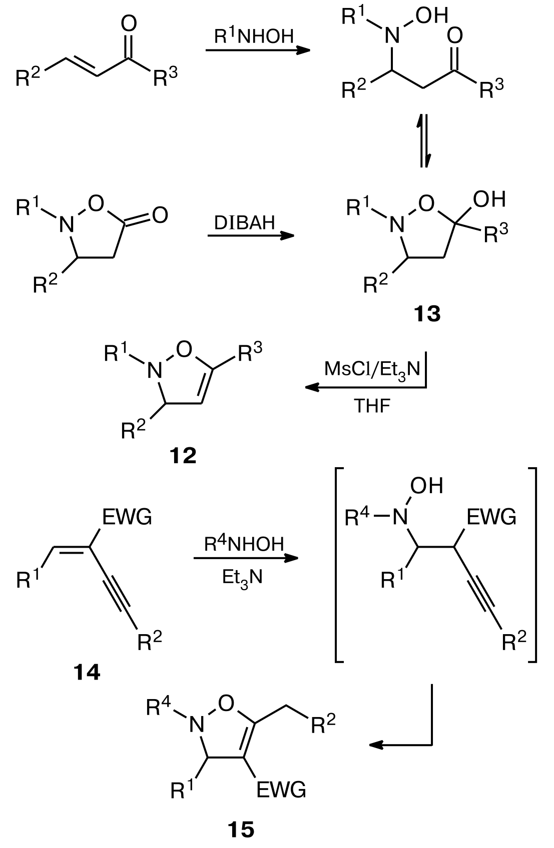
Isoxazolines **12** can be obtained by dehydration of 5-hydroxyisoxazolidines **13**, which are easily accessible through, *e.g.*, reactions of α,β-unsaturated ketones with *N*-substituted hydroxylamines or reduction of isoxazolidinones with diisobutylaluminum hydride (DIBAH) (Scheme 5).[25] Recently,[26] 4-substituted isoxazolines **15**

Scheme 4



R^3 = H (**a**), CH_2OH (**b**)

Scheme 5

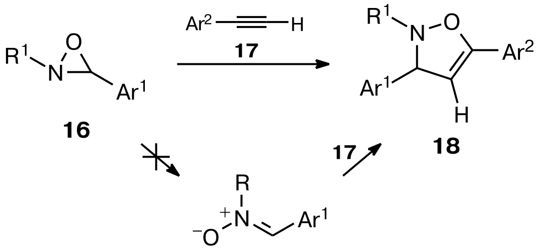


EWG is an electron-withdrawing group

have been obtained from enynes **14** and hydroxylamines. Apparently, the first step of the reaction involves the Michael addition to the double bond followed by intramolecular cyclization through the triple bond (see Scheme 5).

1,3-Dipolar cycloaddition of oxaziridines **16** to alkynes **17** gives 2,3-dihydroisoxazoles **18** (Scheme 6).[27] The reaction is believed[27] to involve no isomerization of oxaziridines into nitrones followed by their 1,3-dipolar cycloaddition. The argument put forward is that cycloaddition of nitrones to alkynes is not regioselective,[28] while the transformation in question yields only a 5-substituted regioisomer of cycloadduct **18**. However, this deduction seems not to be very convincing because many examples have been reported that cycloaddition of acyclic nitrones to phenylacetylene gives a 5-substituted regioisomer as the only product.[25,29—31]

Scheme 6



Reactions of 2,3-dihydroisoxazoles with retention of the isoxazoline ring

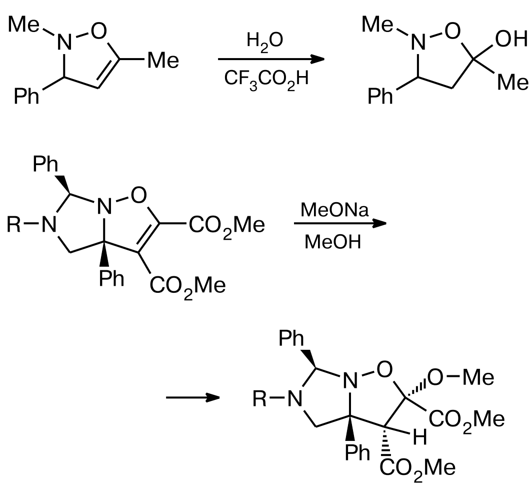
The presence of the double C=C bond in 2,3-dihydroisoxazoles enables electrophilic addition to occur.[32—35] Other characteristic transformations are ring opening reactions usually involving cleavage of the N—O bond.[6]

Below we consider some examples of reactions of 2,3-dihydroisoxazoles with retention of the heterocycle: (1) addition to the double bond leading to isoxazolidine derivatives and (2) elimination reactions giving rise to a new double bond (in this case, isoxazoles are reaction products).

The conjugation between the lone electron pair of the O atom and the double C=C bond in compounds **1** facilitates acid-catalyzed addition reactions.[34] Solvent (alcohol or water) molecules can act as nucleophiles in these processes.[32,33] If the double bond bears electron-withdrawing substituents, base-catalyzed nucleophilic addition is also possible.[35] Examples are shown in Scheme 7.

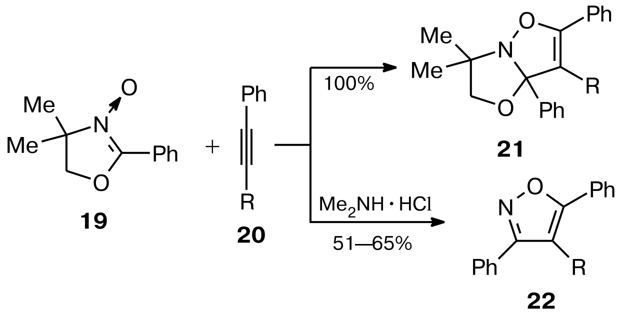
In some cases, 2,3-dihydroisoxazoles undergo elimination to give aromatic isoxazole derivatives. The elimination involves not only the heteroatomic substituent in position 3 but also the C-type substituent at the endocyclic N atom.[36—39] For instance, cycloaddi-

Scheme 7



R = 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 8



R = CO_2Me, CN

tion of nitrone **19** to alkynes **20** in the presence of dimethylammonium chloride yields a mixture of the corresponding cycloadduct **21** and trisubstituted isoxazole **22** (Scheme 8).[36]

Ashburn *et al.*[36] state that isoxazoles **22** are formed *in situ* through a parallel pathway rather than from cycloadducts **21**. The mechanism proposed[36] involves (1) conjugated nucleophilic addition of the nitrone O atom to the triple bond, (2) protonation of intermediate zwitterion **23** to cation **24**, (3) cyclization into intermediate **25** (it is essentially C(4)-protonated cycloadduct **21**), (4) opening of the oxazolidine ring, and (5) elimination of isobutylene oxide **26** (Scheme 9). However, the latter has not been detected experimentally.[36]

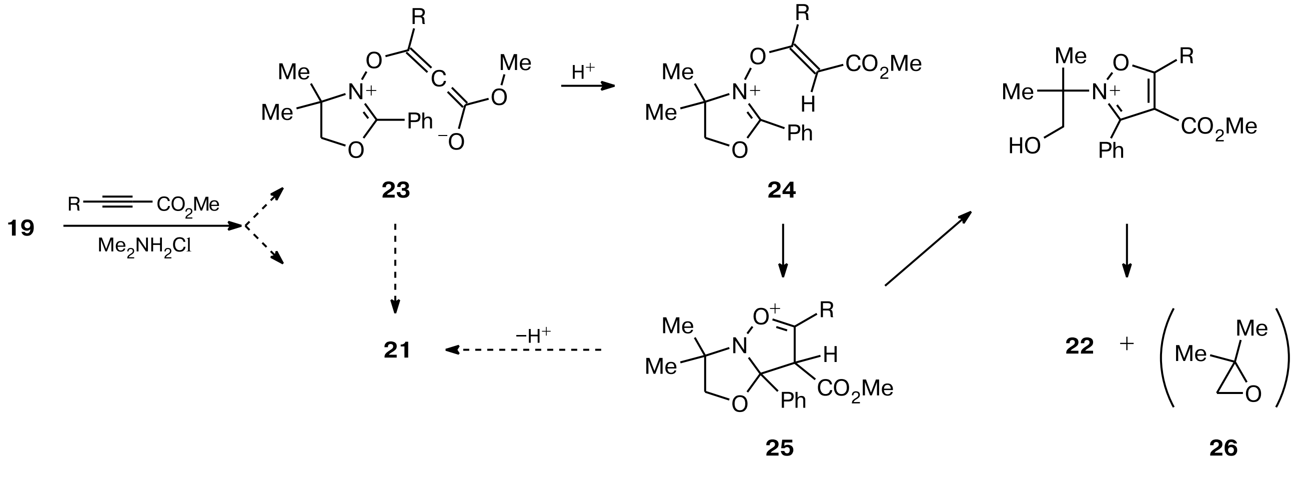
Because intermediate **25** is a protonated form of cycloadduct **21**, the statement that the cycloadduct itself cannot participate in this process seems to be untenable.

A similar transformation of compound **27** in boiling ethanol in the presence of 3 *M* HCl gives benzo[*d*]isoxazole derivatives **28** (Scheme 10).[37]

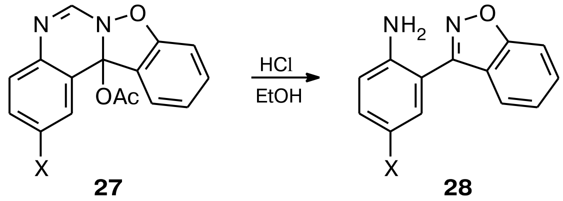
We have found that the cycloadducts obtained from 2-imidazoline (**29a**) and imidazole nitrones (**29b**) and alkynes undergo an acid-catalyzed transformation into the corresponding trisubstituted isoxazoles **30** (Scheme 11).[38,39] The formation of isoxazoles **30** can be explained by initial protonation of the N(1) atom in position 3 of the isoxazoline ring of cycloadducts **31a,b** followed by elimination of the heteroatomic substituent. The process is driven by aromatization of the isoxazoline ring into an isoxazolium cation. The NMR spectra of the reaction mixtures contain signals for the protons of cation **32a**.

Apparently, the presence of the heteroatomic substituent in position 3 of the isoxazoline ring, as well as the presence of a substituent at the isoxazoline N atom that can be eliminated as a stable cation, is a prerequisite for acid-catalyzed formation of isoxazoles.

Scheme 9

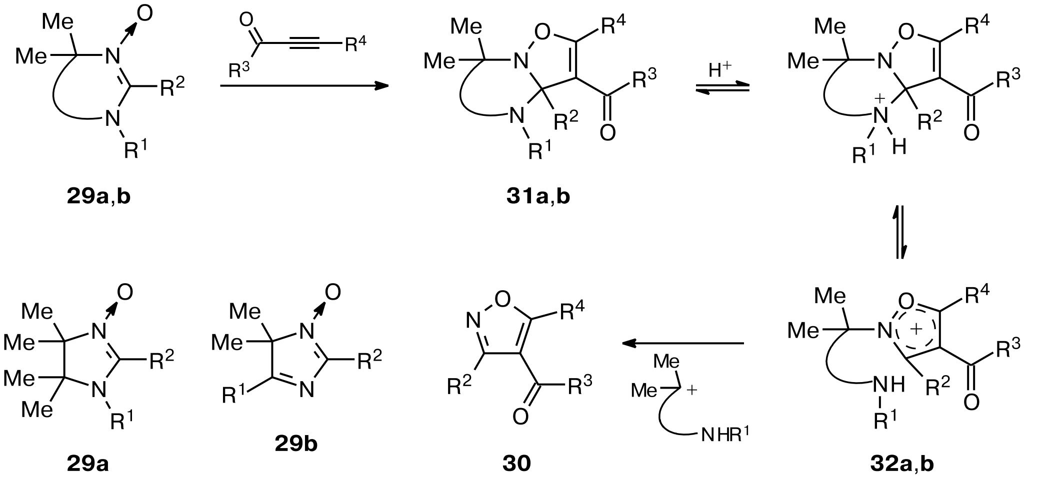


Scheme 10



X = H, Cl

Scheme 11

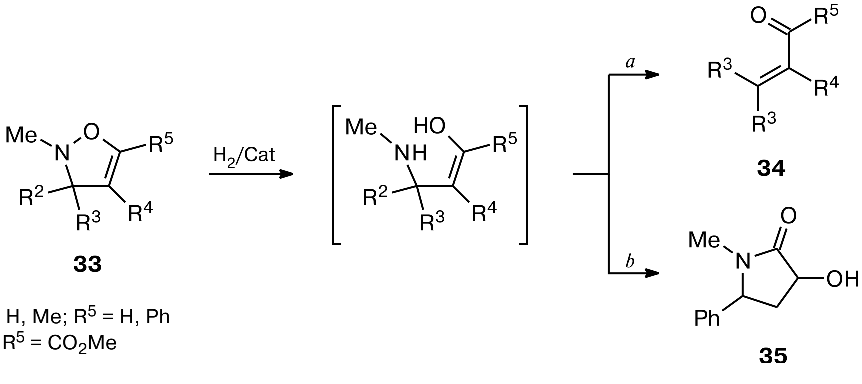


Reactions of 2,3-dihydroisoxazoles with opening of the heterocycle

Transformations of 2,3-dihydroisoxazoles frequently involve cleavage of the N—O bond in the heterocycle. The cleavability of this bond can be enhanced by oxidation at the N atom or its quaternization. Such transformations occur under reduction conditions[6,12,40—42] or under the action of peroxy acids[43] and alkylating reagents.[44,45] Thermolysis[6] and photolysis[46] of 2,3-dihydroisoxazole derivatives usually result in intramolecular rearrangements, also with cleavage of the N—O bond.

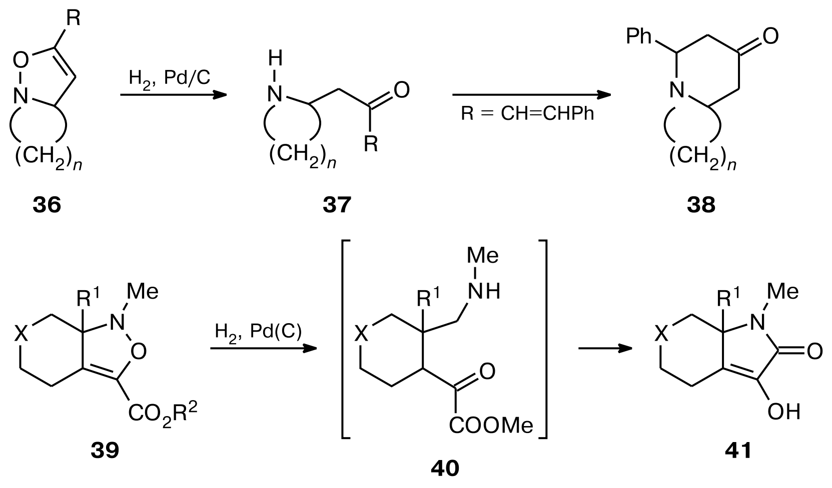
Reduction. Opening of the isoxazoline ring can be effected by its catalytic hydrogenation or by using various reducing agents.[6] The initial step is hydrogenolysis of the N—O bond followed by either elimination of the amine (Scheme 12, pathway *a*) leading to α,β-unsaturated ketones **34** or intramolecular cyclization (see Scheme 12, pathway *b*) leading to lactams **35**.[12,33,40]

Scheme 12



a: R^2 = Me, Ph; R^3, R^4 = H, Me; R^5 = H, Ph
b: R^2 = Ph; R^3 = R^4 = H, R^5 = CO_2Me
Cat stands for catalyst

Схема 13



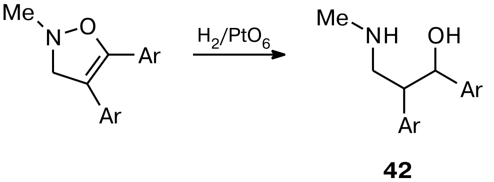
n	R	Yield (%)
3	Ph	60
3	CH=CHPh	52
4	Ph	86
4	C_5H_{11}	71
4	Me	50
4	CH=CHPh	35

X	R^1	R^2	Yield (%)
CH_2	H	Me	94
CH_2	Me	Me	89
O	H	Me	86
CH_2	H	Bn	82
CH_2	H	$4-NO_2Bn$	72

Hydrogenation of fused 4-isoxazolines **36** at a less active catalyst yields the corresponding β-amino ketones **37** (see Refs 41 and 47) or products of their intramolecular cyclization (**38**) (Scheme 13).[41] Amino ketones **40** obtained by reduction of 4-isoxazolines **39** with molecular hydrogen on Pt also undergo intramolecular cyclization into compounds **41** (see Scheme 13).[42]

In some cases, the reduction with hydrogen on platinum gives amino alcohols **42** (Scheme 14).[15]

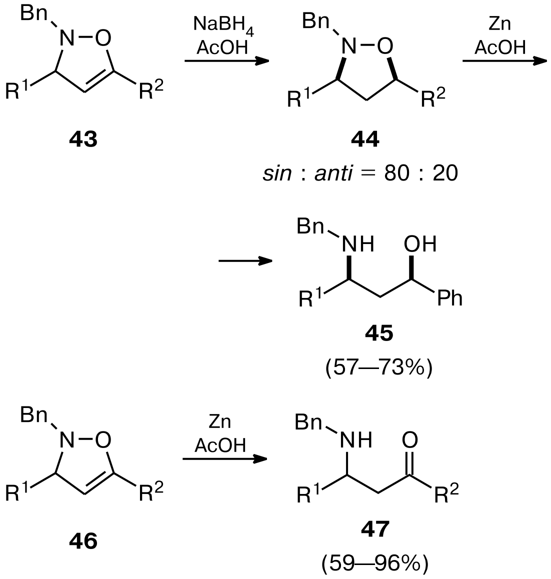
Scheme 14



42

Ar = Ph, 3,4-$(MeO)_2C_6H_3$

Scheme 15



47: R^2 = Bu^n, Bu^t

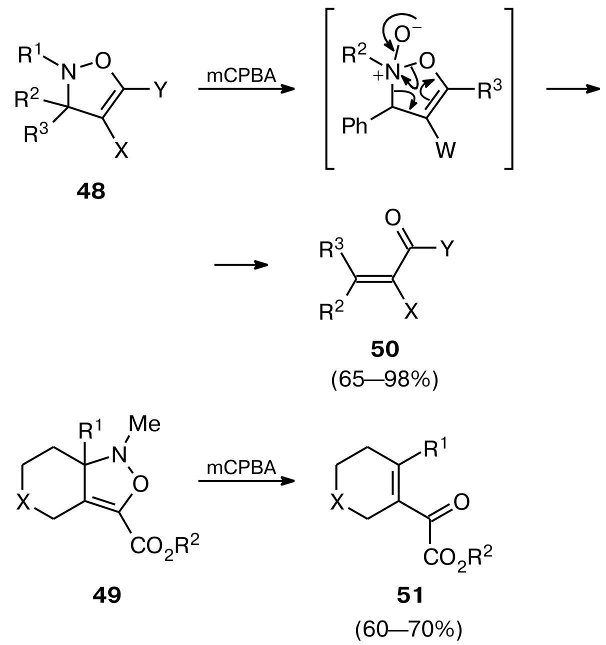
According to recent data,[48] reduction of isoxazolines **43** with mild reducing agents can afford isoxazolidine derivatives **44** (Scheme 15). This highly stereoselective reaction gives the *syn*-isomer as the major product, which can further be reduced to the corresponding *syn*-β-amino alcohol **45** in good yield (the absolute configurations of the asymmetric centers in **45** are determined by their configurations in **44**). Reduction of compounds **46** with zinc in acetic acid produces β-amino ketones **47** (see Scheme 15).

Oxidation. Oxidation of 2,3-dihydroisoxazoles with peroxy acids usually occurs at the N atom, which makes it more electron-deficient and facilitates opening of the heterocycle. Oxidation of 4-isoxazolines **48** and **49** with *m*-chloroperoxybenzoic acid (mCPBA) gives α,β-unsaturated carbonyl compounds **50** and **51** in excellent yields (Scheme 16).[42,43,49] The advantage of the synthesis of compounds **50** and **51** by cycloaddition of nitrones followed by oxidative opening of cycloadducts **48** and **49** is that both the reactions occur in neutral media.

Oxidation of bicyclic 4-isoxazolines **52** under the same reaction conditions gives either tricyclic adducts **53** (see Ref. 49) or, as with compound **54**, dimeric nitroso compounds **55** (Scheme 17).[17]

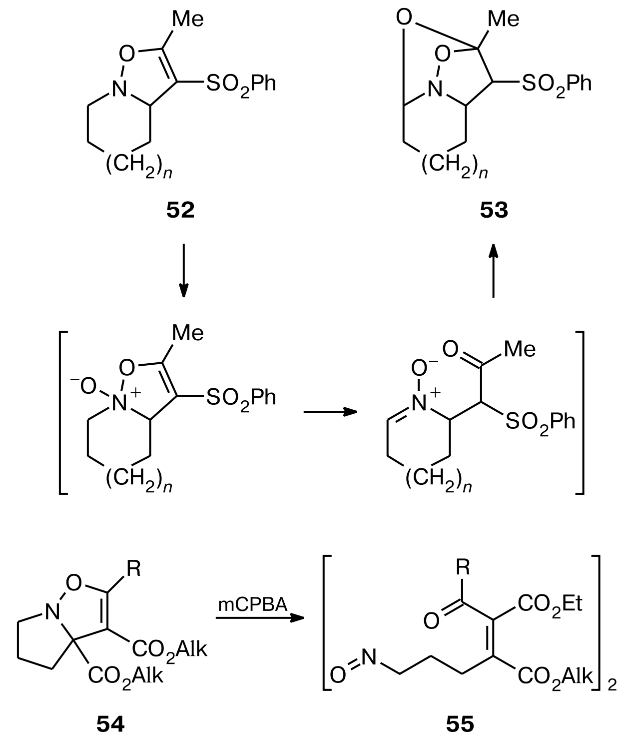
Very recently,[50] the oxidation reaction has been successfully applied to the synthesis of ketones **56**, which are the starting materials for the Nazarov cyclization (Scheme 18).

Scheme 16



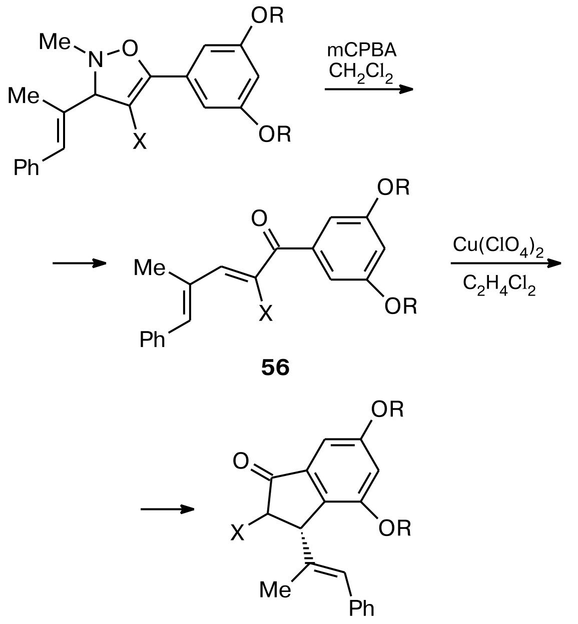
50: R^1 = Me, Bu^t; R^2 = H, Me, Pr; R^3 = Ph, Me, H
X = SO_2Ph, CO_2Me, CN, *p*-Ts, H
Y = Me, Me_3Si, Pr, CH_2CH_2CCH, CO_2Me, H, CHCHPh
51: R^1 = H, Me; R^2 = Me, CH_2Ph, CH_2-4-$C_6H_4NO_2$
X = CH_2, O

Scheme 17



n = 0, 1

Scheme 18



Quantum-chemical computations have provided convincing evidence for the stepwise biradical mechanism of the oxidation reaction.[51,52]

The same approach has been successfully employed in the final steps of the synthesis of a precursor of biologically active (±)-Roseophilin.[53]

Alkylation. In some cases, the ring opening can be initiated by alkylating reagents.[44,45] A wide range of isoxazolines **1** and **57** react with, *e.g.*, methyl iodide to yield α,β-unsaturated carbonyl compounds **58** and **59** (Scheme 19).

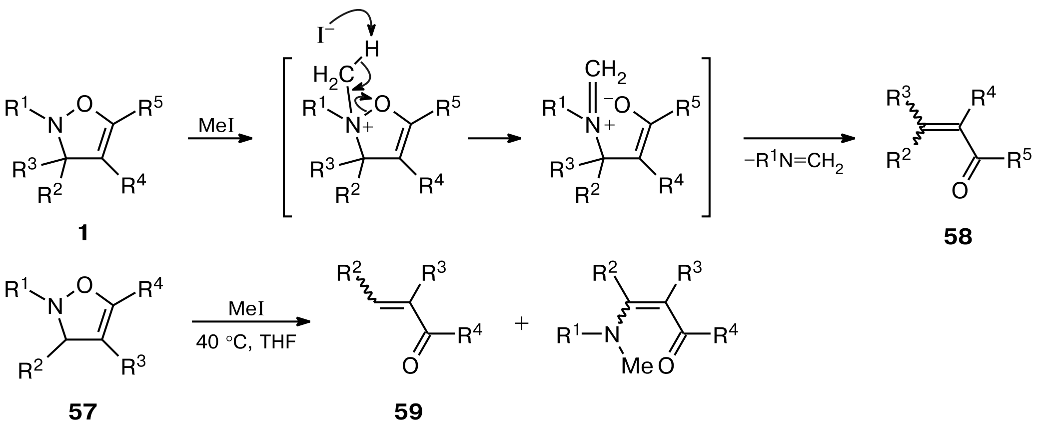
Reactions of 2,3-dihydroisoxazoles **60** with methyl trifluoromethanesulfonate (TfOMe) give alkylation products **61**, which undergo an unusual transformation in hot methanol into α,β-unsaturated amides **62** (Scheme 20).[54]

Opening of the isoxazoline ring can also be initiated thermally or photochemically in the absence of any other reagents. As a rule, such processes are accompanied by skeletal rearrangements.

Thermally initiated ring-opening reactions passing through acylaziridine intermediates. According to the reviewed data,[6] the general pathway of thermal rearrangements of 2,3-dihydroisoxazoles **1** involves their transformation into aziridines **63**, which then undergo ring opening to ylides **64** capable of yielding 4-oxazoline (**65**), pyrrole (**66**), and other products (P) (Scheme 21).

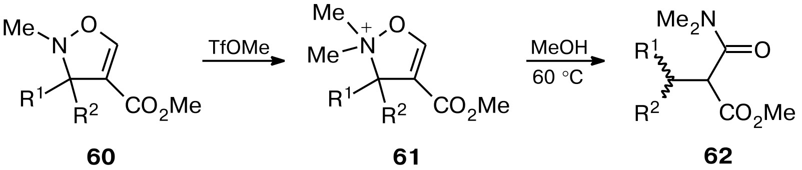
4-Isoxazolines are not always stable even at room temperature; that is why their formation with subsequent ring opening in such cases is of partly declarative character.[66] However, a large body of evidence suggests that an acylaziridine derivative is the key intermediate for most rearrangements. The sequence of transformations 4-isoxazolines→aziridines→4-oxazolines has been confirmed with various nitrones and alkynes as examples.[55]

Scheme 19

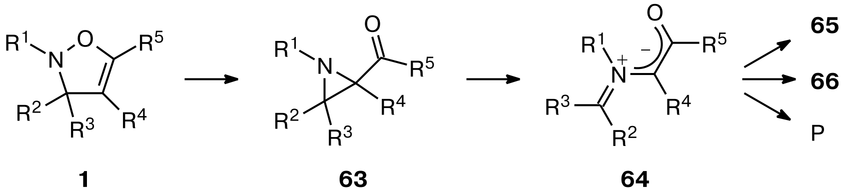


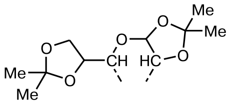
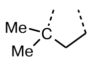
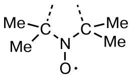
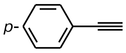
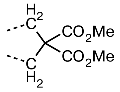
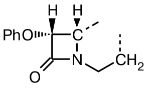
R^1 = Me, *cyclo*-C_6H_{13}
R^2 = Ph, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$, CO_2Et
R^3 = H, CO_2Et
R^4 = H, CO_2Et, Ph

Scheme 20

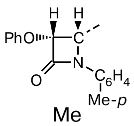
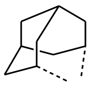


Scheme 21



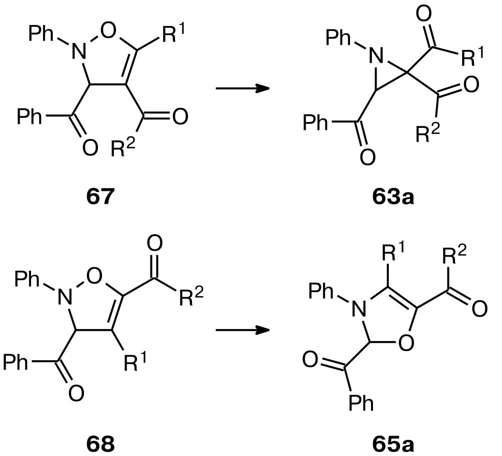
R^1	R^2	R^3	R^4	R^5	Product	Reference
Mesityl	H	H	CO_2Me	CO_2Me	**63**, **65**	55
Bu^t	H	H	H	CMe_2OH	**63**	55
Me	H	H	H	Ph	**63**	40
Bu^t	H	H	H	Ph	**63**	40
Ph	H	H	Me	Ph	**63**	40
Me			H	Ph	**63**	30
Ph	H	COPh	CO_2Et	Ph	**63**	56
Ph	H	COPh	COMe	Ph	**63**	56
		Me	H	Ph	**63**, **66**	57, 58
		H	H		**63***	59
Me	H			CH_2OMe	**63**	60
PhCH$_2$	H			CH_2OMe	**63**	60
Me	H			H	**63**	61
PhCH$_2$	CHMe$_2$	H	H	Ph	**63**	25

* Migration also takes place.

R^1	R^2	R^3	R^4	R^5	Product	Reference
PhCH$_2$	Ph	H	H	Ph	**63**	25
	4-$MeOC_6H_4$	H	H	Ph	**63**	25
	C_6H_{11}	H	H	Ph	**63**	25
	Me	Me	H	Ph	**63**	25
	Ph	H	H	Me	**63**	25
	Ph	H	$SiMe_3$	$SiMe_3$	**63**	25
	CHMe$_2$	H	$SiMe_3$	$SiMe_3$	**63**	25
	CHMe$_2$	H	H	Bu	**63**	25
	CHMe$_2$	H	H	H	**63**	25
		H	H	CO_2Me	**63**	62
Me		H	H	CO_2Me	**63**	62
Bu^t	Me	H	H	Ph	**63**, **67**	63
OMe	CN	H	H	COPh	**63**	64
	CN	H	H	COMe	**63**	64
	CO_2Me	H	H	COPh	**63**	64
	CO_2Me	H	H	COMe	**63**	64
	CO_2Me	H	H	CO_2Me	**63**	64
Me	CF_3	H	H	Ph,	**63**	29
				4-MeC_6H_4,	**63**	29
				C_6H_{13}	**63**	29
Me			CO_2Me	CO_2Me	**63**	65

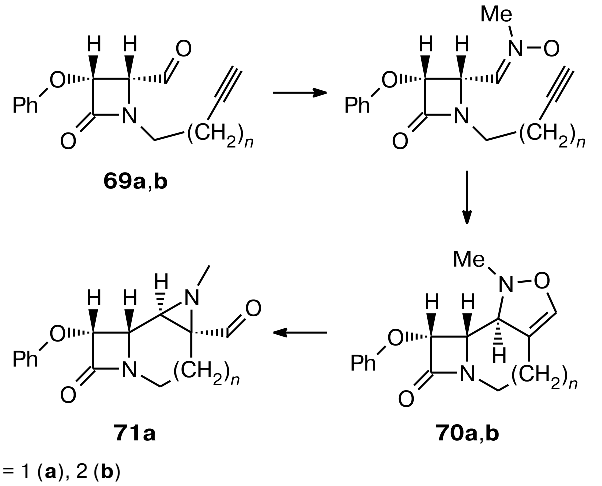
The thermal stability of intermediate acylaziridines depends on the substituents in the starting isoxazoline. For instance, heating of 3,4-diacylated compounds **67** gives stable acylaziridines **63a**, while their 3,5-diacylated isomers **68** further change into 4-oxazoles **65a** under the same conditions (Scheme 22).[56]

Scheme 22



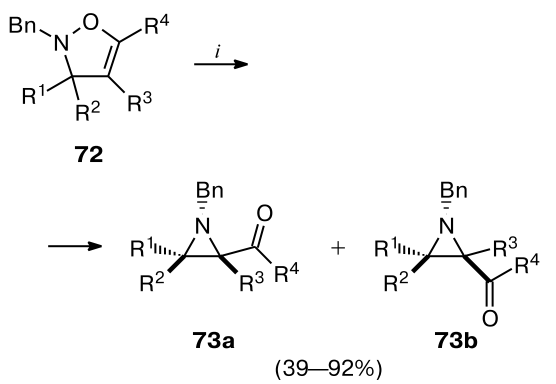
The size of the ring annulated with the 4-isoxazoline ring seems to be crucial as well. For instance, reactions of aldehydes **69** with methylhydroxylamine in hot toluene yield 4-isoxazoline **70b** ($n = 2$) or acylaziridine **71a** ($n = 1$) (Scheme 23).[61]

Scheme 23



Recently, it has been found[25] that $Co_2(CO)_8$-catalyzed rearrangement of 2,3-dihydroisoxazoles **72** into acylaziridines **73a,b** occurs even at 75 °C (Scheme 24); in the absence of cobalt carbonyl, isoxazolines **72** are stable at this temperature.

Scheme 24



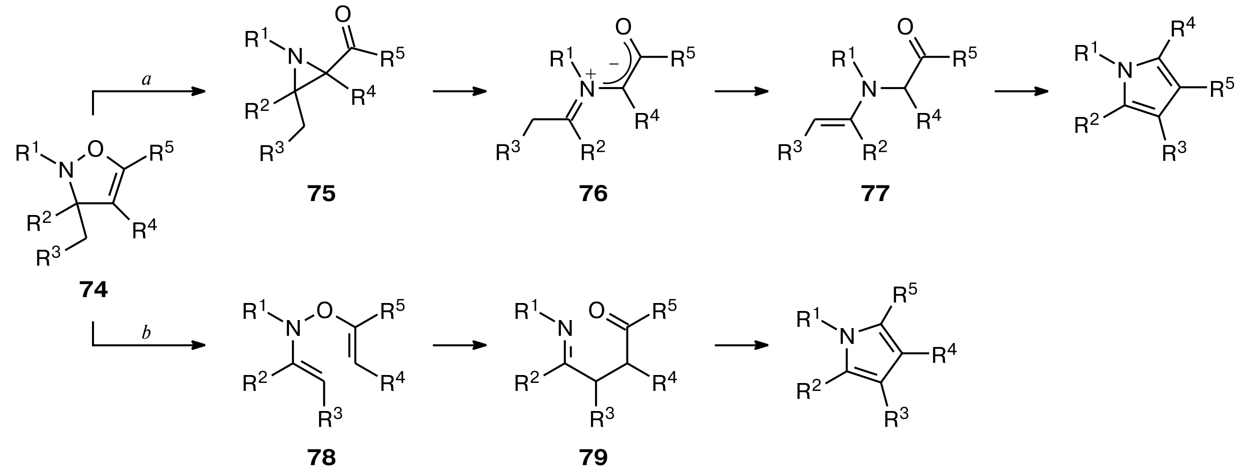
i. $Co_2(CO)_8$ (50 mol.%), MeCN/75 °C, 0.5—1.0 h.

Another pathway of rearrangements of 2,3-dihydroisoxazoles **74** leads to pyrroles; at least, two fundamentally different schemes of this reaction are disputed. One scheme involves intermediate formation of acylaziridine **75**, its transformation into ylide **76**, proton transfer giving rise to enamine **77**, and its cyclization into a pyrrole derivative (Scheme 25, pathway *a*). The assumption that the reaction can follow the other scheme is based on the controversial statement of the initial cleavage of the C(3)—C(4) bond leading to enamine **78**. The next steps are the hetero-Cope rearrangement into compound **79** and cyclization (see Scheme 25, pathway *b*).

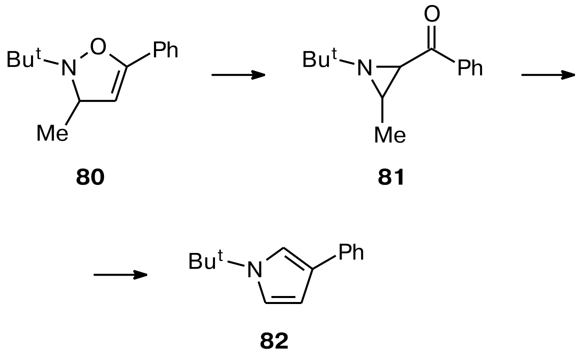
Note that when substituents R^4 and R^5 are identical, either scheme will lead to the same products, which precludes experimental distinction between the above pathways.[67—70] For $R^4 \neq R^5$, alternative schemes should yield regioisomeric products. The formation of both regioisomeric pyrroles in this reaction has been documented.[71] The formation of amino ketone **79** as the sole product from isoxazoline **74** with R^1 = Me and $R^2 = R^3 = R^4 = R^5 =$ = CO_2Me suggests that the reaction follows pathway *b*.[72] However, the structures of the pyrroles obtained in most of the relevant studies correspond to the pathway passing through intermediate acylaziridine.[12,57,58,73—75] Moreover, according to NMR data,[63] thermolysis of 4-isoxazoline **80** initially leads to aziridine **81**, which is transformed into pyrrole **82** (Scheme 26).

Researchers often seem to be unfamiliar with the long-accepted (and confirmed) concepts of the reaction schemes and sometimes propose their own sufficiently speculative and ill-substantiated reaction pathways. An example is the assumption that the formation of *p*-cyclophanylpyrrole **83** results from nucleophilic addition of nitrone **84** as an ene hydroxylamine tautomer to dimethyl acetylenedicarboxylate (DMAD) followed by cyclization of zwitterion **85** (Scheme 27).[70] This scheme is doubtful because nitrones can be enolized only under certain conditions and an electrophilic attack in this case occurs at the enamine C atom or the O atom.[10] A reaction of nitrone **84** with methyl propiolate "surprisingly" gives a normal cycloadduct.

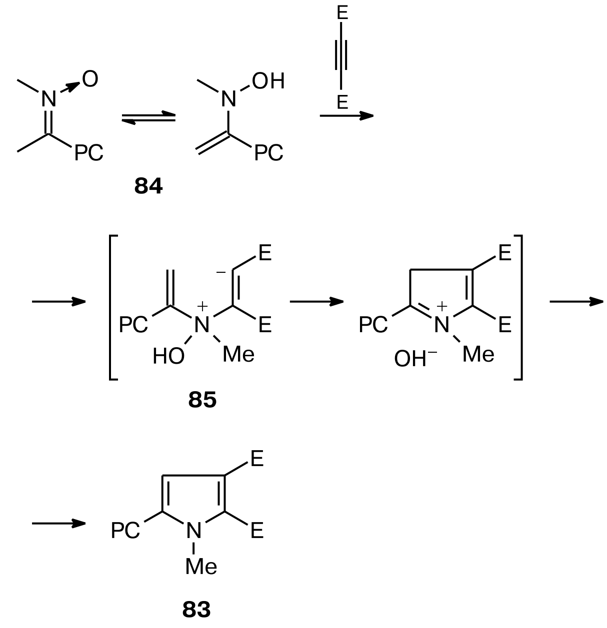
Scheme 25



Scheme 26



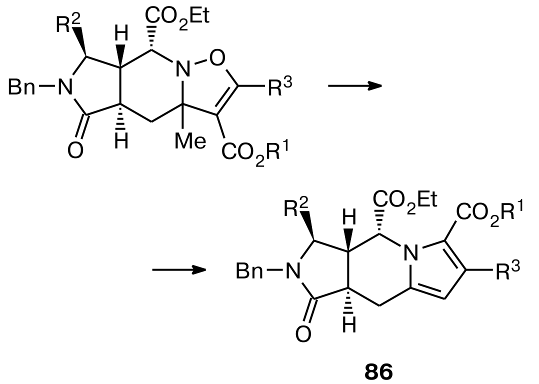
Scheme 27



E = CO_2Me, PC is 4-[2.2]*n*-cyclophanyl

The formation of pyrrole derivatives is a fairly general pathway of thermal transformations of isoxazolines. For instance, this transformation has been proposed[74] for the synthesis of alkaloid-like heterocycles **86** (Scheme 28).

Scheme 28

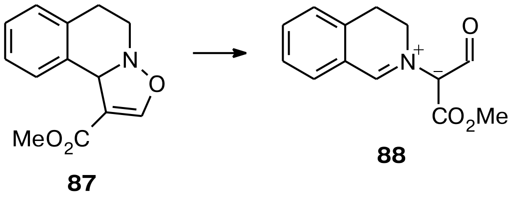


(58—72%)

An analysis of the literature data allows the following conclusions to be drawn. Acylaziridines are formed from sterically unhindered 4-isoxazolines with at least one (or better two or three) H atoms in positions 3 and 4 of the heterocycle[25,29,30,40,55—64] (see Scheme 21). Apparently, the only exception is the formation of an adamantyl derivative of aziridine.[65] If a substituent in position 4 is a strong electron acceptor and a substituent in position 3 can make an efficient π-conjugation, the most probable product is an ylide,[33,67,76—80] which can further undergo 1,3-dipolar cycloaddition,[81] dimerization,[82] hydrolysis,[83] or a combination of several reactions.[75] In some cases, ylides can be transformed into oxazolines[55,66,84,85] or (for ylides containing an α-methylene fragment) pyrroles.[12,57,58,63,67—75,86—92]

Mechanism of formation of acylaziridines. As a rule, the rearrangement of isoxazolines into acylaziridines is considered to follow three possible pathways: (1) heterolytic cleavage of the N—O bond at the rate-limiting reaction step, (2) homolytic cleavage of the N—O bond at the rate-limiting reaction step, and (3) a concerted process. The first pathway seems to be very unlikely because the reaction rate depends only slightly on the solvent polarity, which has been demonstrated with several examples.[82,93] The biradical mechanism is preferred by some researchers. In particular, it has been found[82] that the rearrangement of compound **87** into ylide **88** (Scheme 29) is a first-order reaction and that its rate depends only slightly on the solvent polarity (the half-conversion times in benzene and acetonitrile at 60 °C are 52 and 70 min, respectively). At the same time, the data obtained,[82] though being consistent with the single-step sigmatropic mechanism too, rule it out because the concerted process $[{}_{\sigma}2_{s} + {}_{\pi}2_{s}]$ is forbidden; the possibility of this reaction following the allowed process $[{}_{\sigma}2_{s} + {}_{\pi}2_{a}]$ is passed over.

Scheme 29



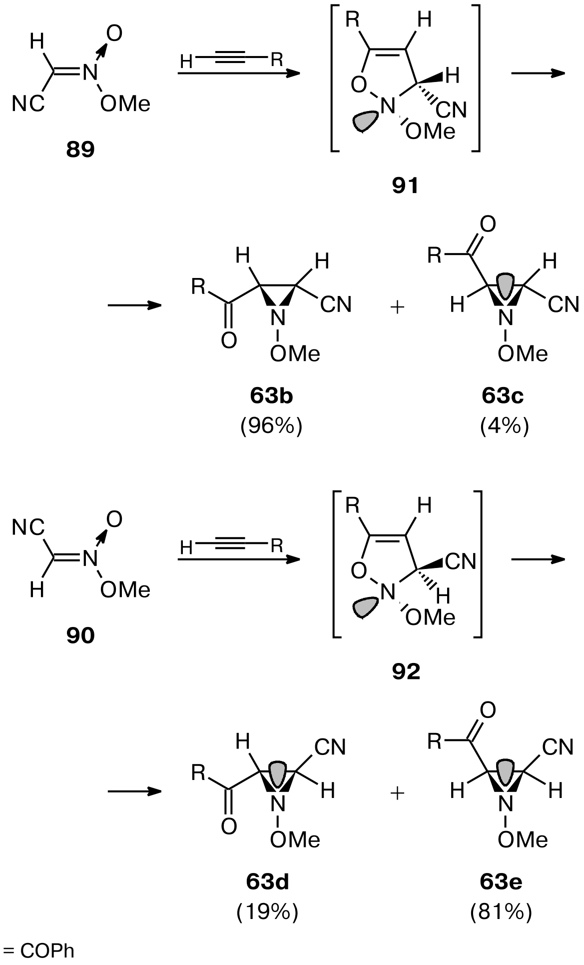
Later,[88] the biradical mechanism has been also postulated from the previous data.[55,73] However, it has been noticed[55,73] that the rearrangement rate does not depend on oxygen, radical inhibitors, or small amounts of acids or bases. These facts, in contrast, provide evidence against the radical mechanism.

To compare the biradical and concerted pathways to acylaziridines, let us consider the stereoselectivity of this rearrangement. Concerted processes obey the Woodward—Hoffman rules of orbital symmetry and give definite stereoisomers, while biradical processes are usually not stereoselective.

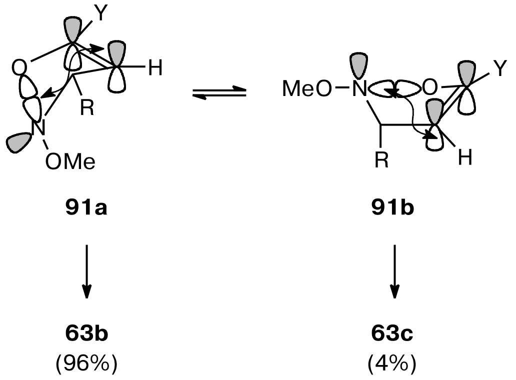
Earlier,[6] it has been noted that alkynes undergo stereospecific cycloaddition to *N*-alkoxy nitrones **89** and **90** to yield isoxazolines **91** and **92**; their subsequent rearrangements into acylaziridines are also highly stereoselective[64] (Scheme 30).

Gree *et al.*[64] have reasonably noted that the biradical mechanism excludes such a high stereoselectivity and that the experimental facts are best described by the concerted process $[{}_{\sigma}2_{s} + {}_{\pi}2_{a}]$. Since isoxazoline can exist as two conformers **91a** and **91b**, the rearrangement should give a mixture of isomeric products **63b** and **63c** (Scheme 31). With consideration that the preferred isoxazolidine conformation contains a pseudoaxial methoxy group,[94,95] it has been suggested[64] that major isomer **63b** is formed from more stable conformer **91a**.

Scheme 30



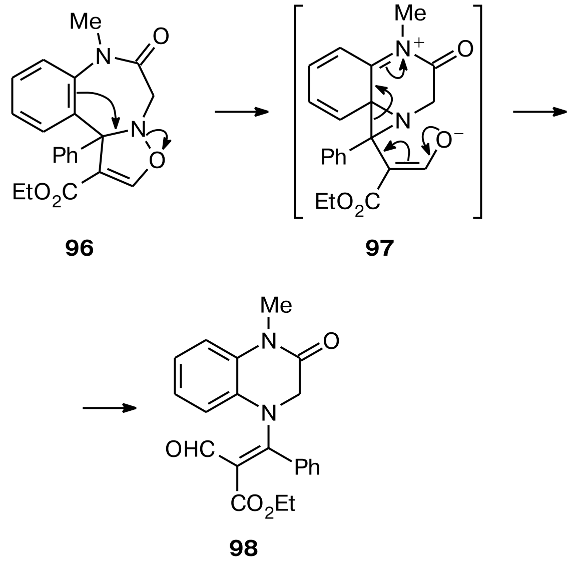
Scheme 31



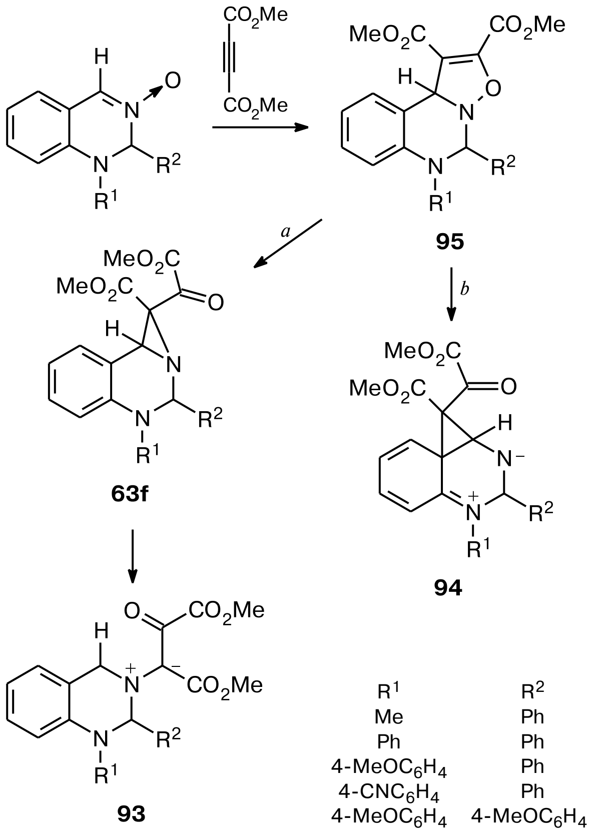
Likewise, the rearrangement of 2,3-dihydroisoxazole **70a** is also stereoselective (see Scheme 23).[61]

The formation of azomethine ylides **93** (Scheme 32) has been attributed[79] to an alternative pathway passing through intermediate **94** rather than directly through acylaziridine **63f** (pathway *a*). The reason for this mechanism to be proposed is that *N*-aryl derivatives **95** are more stable than the *N*-methyl analog. We find it incorrect to make an analogy[79] between the proposed mechanism and the rearrangement mechanism of isoxazolobenzodiazepines[96] because these transformations are fundamentally different (Scheme 33).

Scheme 33



Scheme 32



R^1	R^2
Me	Ph
Ph	Ph
4-$MeOC_6H_4$	Ph
4-CNC_6H_4	Ph
4-$MeOC_6H_4$	4-$MeOC_6H_4$

Still more intricate schemes of formation of acylaziridines **63** are discussed for the rearrangements of isoxazolines **99** (Scheme 34).[80] Apparently, the first step involves heterolysis of the C(3)—C(4) bond rather than cleavage of the N—O bond. 1,3-Sigmatropic shift in the resulting zwitterion leads to azomethine ylide **100**. The formation of these ylides through acylaziridines **101** is denied because the π-donating substituents in Ar favor the declared scheme (see Scheme 34). However, this fact is contradictory to the formation of acylaziridine *via* homolysis of the N—O bond (Ar should not influence the stability of a biradical); possible formation of compound **101** according to a concerted mechanism has been left out.

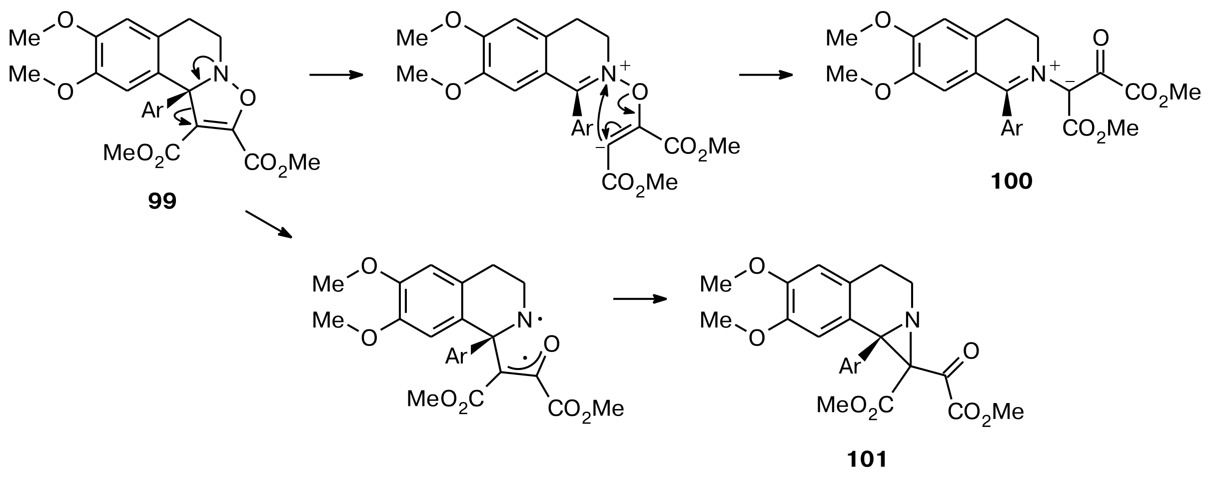
Later,[97] the same concepts have been used to propose the following scheme for the rearrangement of 4-isoxazolines **102** (Scheme 35). The final products were always the corresponding aldehyde R^2CHO and dihydroisoquinoline derivative **103**. The latter was identified only from the NMR spectrum of the reaction mixture and the data collected by an MS detector of a gas-liquid chromatograph (column temperature 200 °C) for its molecular ion fragment. According to the scheme put forward, the aldehyde and imino carbene **104** are products of an electrocyclic ring-opening reaction of dihydrooxazole **105**. The very complicated scheme proposed to explain the formation of dihydroisoquinoline **103** from imino carbene **104** is omitted here.

The assumption of possible formation of an acylaziridine intermediate is refused again,[97] although this scheme seems to be simpler and more plausible since it is consistent with the main route of isoxazoline transformations observed by many independent researchers. Apparently, 4-isoxazoline **102** is initially rearranged into acylaziridine **106**, which undergoes ring opening to ylide **107** (Scheme 36). Subsequent hydrolysis of the ylide produces an aldehyde and intermediate **108**, whose *in situ* intramolecular cyclization leads to dihydroisoquinoline derivative **109**. A similar sequence of transformations has been observed earlier.[83]

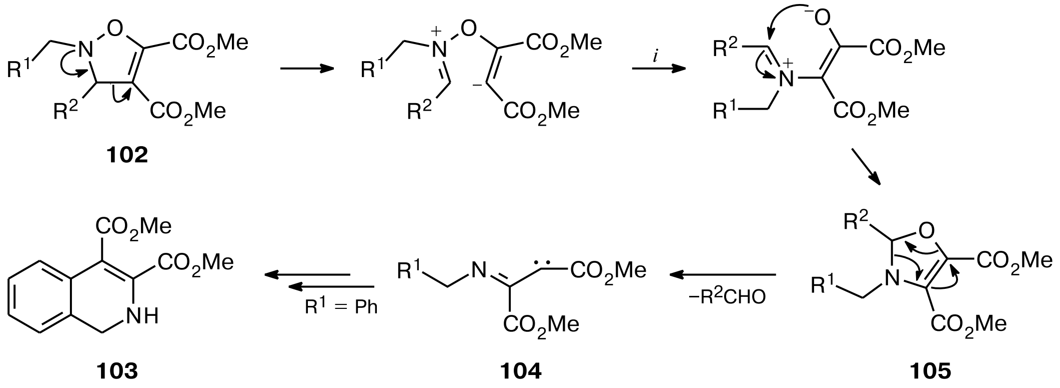
Thus, the number of the mechanisms proposed in the literature for the rearrangement of 2,3-dihydroisoxazoles is more than one or two. Considering single facts and not going into the kinetics of the process, some researchers discuss fairly speculative schemes. In some cases, more confusion arises from neglect of the simplest reaction pathways.

Rearrangements with migration of the hydrogen atom. Opening of the isoxazoline ring can be accompanied by hydrogen migration from the C(3) atom to the N(2) atom. Ease of this process precludes some intermediate isoxazolines from being isolated. Note that hydrogen migration almost always occurs in annulated 4-isoxazolines of the type **110** (Scheme 37).[5,59,60,92,98,99] However, pro-

Scheme 34

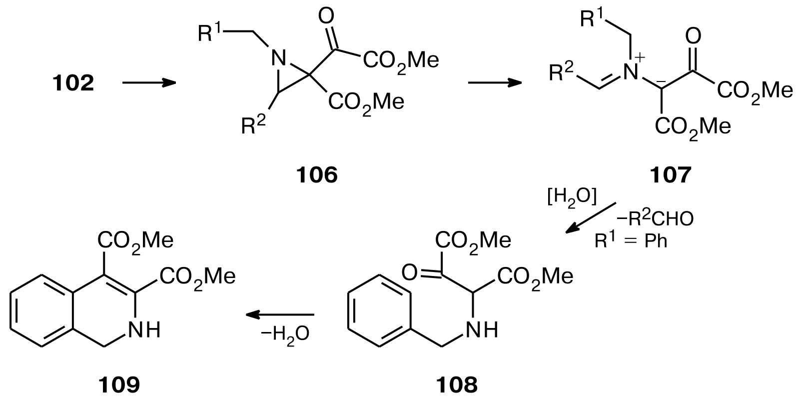


Scheme 35



i. 1,3-Sigmatropic shift.

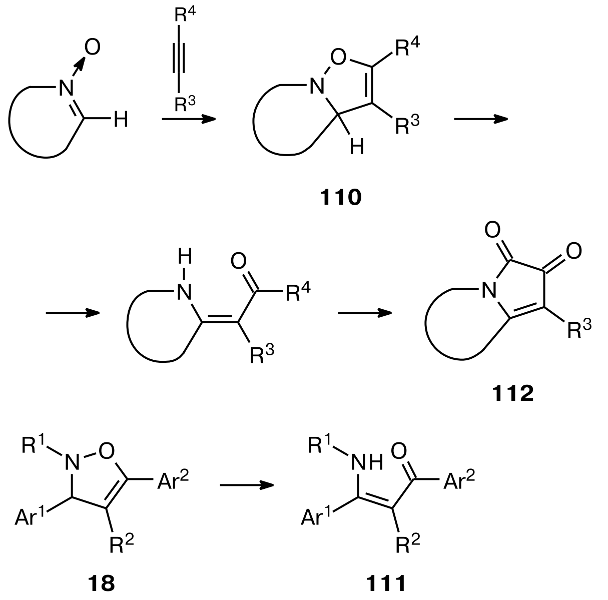
Scheme 36



longed heating of monocyclic derivatives **18** at 110 °C also gives the corresponding enamino ketones **111** (Scheme 37).[27]

Enamino ketones **111** can further undergo *in situ* intramolecular cyclization into 1*H*-pyrrole-2,3-diones **112** (see Scheme 37).[78,100]

Scheme 37



$R^3 = R^4 = CO_2Alk$

Two mechanisms suggested[100] for the formation of compound **113** include 1,2-hydride shift in compound **114** (pathway *a*) and proton elimination—addition (pathway *b*) (Scheme 38); however, preference has been given to neither.

A reaction of nitrone **115** with dehydrobenzene as a dipolarophile gives phenol **116** (Scheme 39).[101] The formation of this product can be explained by a similar scheme involving proton migration to the N atom followed by aromatization of the resulting quinonoid structure **117**.

Recently,[17] it has been demonstrated that hydrogen migration from position 3 of the isoxazoline ring is catalyzed by palladium triphenylphosphine complexes in the presence of triethyl- or triphenylsilane. This reaction leads to the corresponding enamino ketones **118** in moderate yields (Scheme 40). In contrast to the reduction with hydrogen on Pd/C,[41] the C=C bond remains intact. The reaction is catalyzed by neither Pd/C nor palladium black in the presence of a silane.[17] In addition, the use of a silane alone (without a palladium catalyst) or addition of triethylamine as a base is also ineffective.

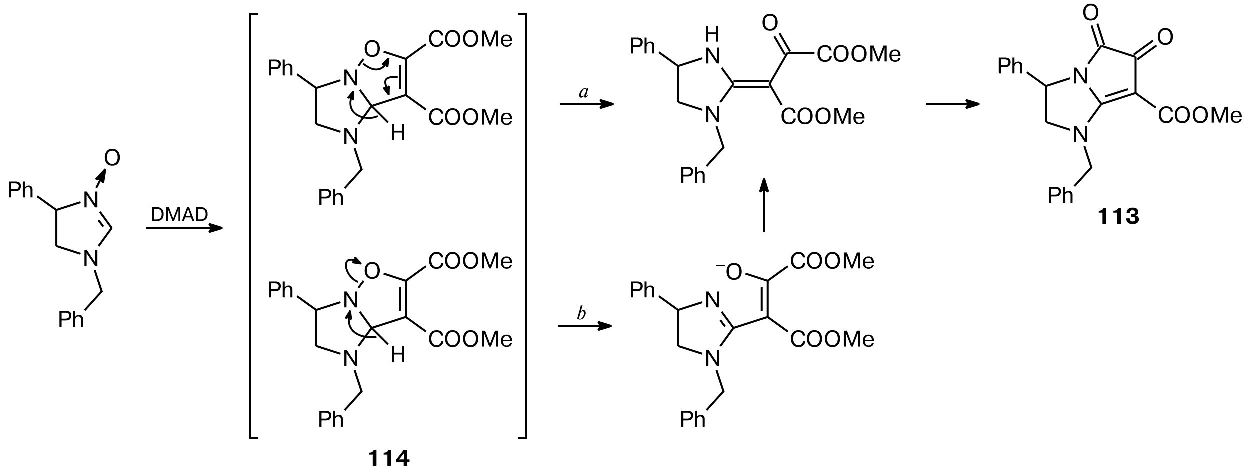
Rearrangements with migration of a non-hydrogen substituent. In some cases, it is a non-hydrogen substituent that migrates from position 3 to the N atom of the isoxazoline ring. Examples of such rearrangements are much more infrequent and usually fewer, which precludes one from making definite conclusions about their mechanisms.

Freeman *et al.*[96] have shown that cycloadduct **96** at 80 °C is transformed into quinoxaline derivative **98**, probably through zwitterionic aziridine intermediate **97** (see Scheme 33). Note that out of two aromatic substituents in position 3 of the isoxazoline ring, it is the stronger π-donor that migrates. Other examples (see below) also display a similar substituent effect, which agrees with the concept of a σ-complex transition state in this rearrangement.

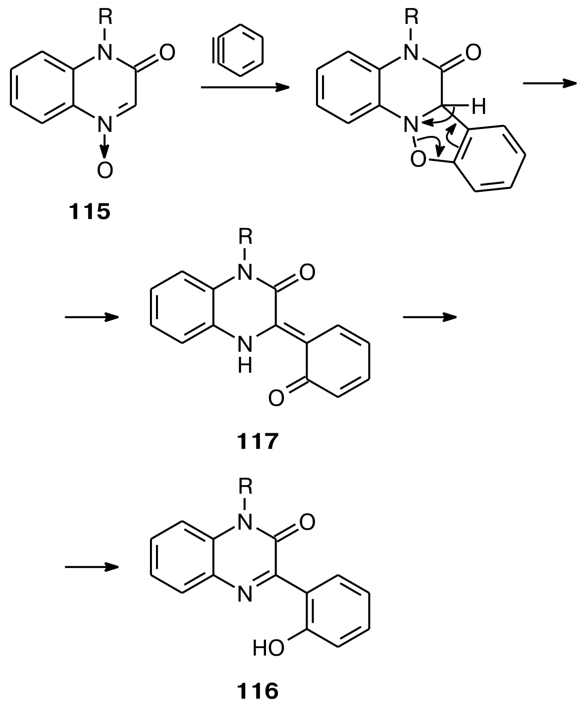
In 4-isoxazoline **119d**, migration of the dimethylaminophenyl group takes place (Scheme 41).[66] At the same time, related compounds **119a—c** undergo a different rearrangement leading to the corresponding 4-oxazolines **120a—c**.

The migration of aromatic substituents and the styryl group has been revealed for a number of tetrahydroimidazo[1,2-*b*]isoxazoles **122**.[93,102] When heated, they either undergo ring opening into ylides **123** or yield products **124** and **125**, depending on substituents R^1 and R^2 (Scheme 42).

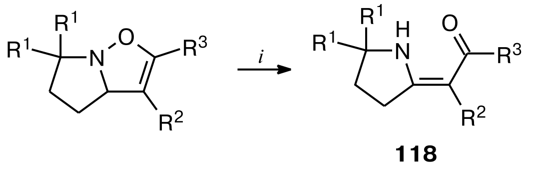
Scheme 38



Scheme 39



Scheme 40

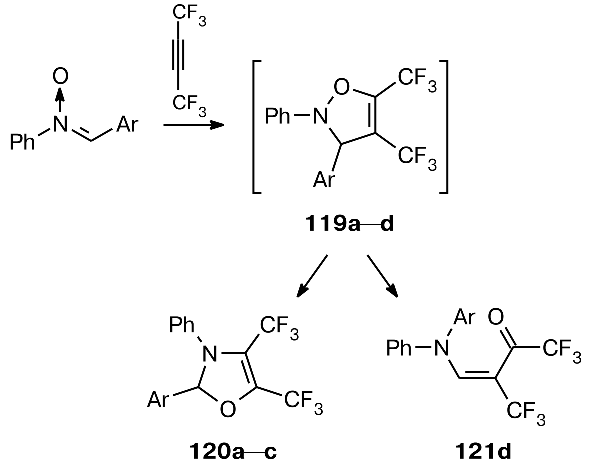


R^1	R^2	R^3	R^4	Yield (%)
H	CO_2Et	Ph	Et	10
Me	CO_2Et	Ph	Et	56
Me	CO_2Et	Me	Et	35
Me	H	Ph	Et	69
H	CO_2Et	Ph	Ph	70
Me	CO_2Et	Me	Ph	53

i. 20% $Pd(PPh_3)_4$, $HSiR_3$ (4—10 equiv.), CH_2Cl_2.

The rearrangement rate in polar solvents (*e.g.*, DMSO) is appreciably higher than that in nonpolar solvents, which suggests a polar transition state. The migratory ability of an aromatic substituent is enhanced by π-donating substituents (this is also evident from the preceding example of the rearrangement of compounds **119a—d**).[66] DFT quantum chemical calculations allow plotting the reaction energy (Fig. 1) versus the length of the cleaving N—O bond (r) and the bond angle R^2—C(7a)—N(4) (L). The bond length r(N—O) and the bond angle L(R^2—C—N) in the starting compound have been taken as zeros in the diagram. The absence of local minima on the potential energy surface shows that the concerted pathway is thermodynamically most favorable in the gas phase. According to experimental data and DFT calculations, the rearrangement may be envisioned as a concerted process passing through polar transition state **126** (Scheme 43).[93]

Scheme 41



Ar = 4-$NO_2C_6H_4$ (**a**), Ph (**b**), 4-$OMeC_6H_4$ (**c**), 4-$NMe_2C_6H_4$ (**d**)

For the rearrangement to occur as a concerted process, the migrant and the lone electron pair on nitrogen, to which the migrant moves, must be *syn* to each other. This becomes evident from the rearrangements of compounds

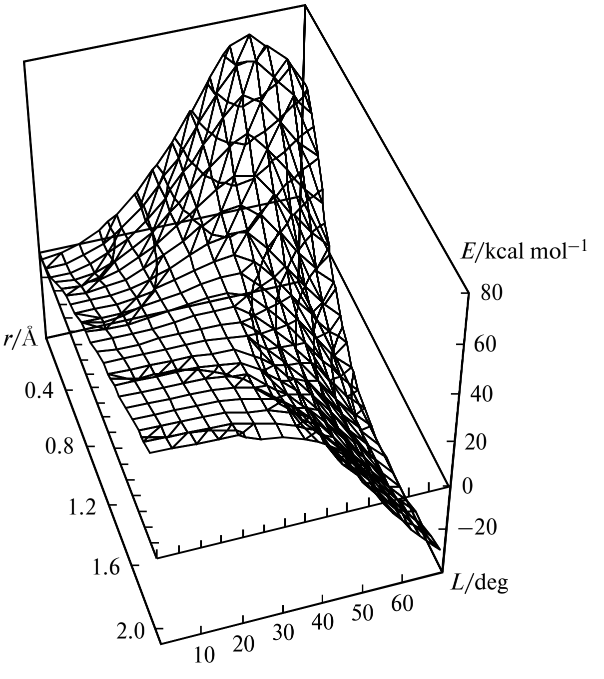
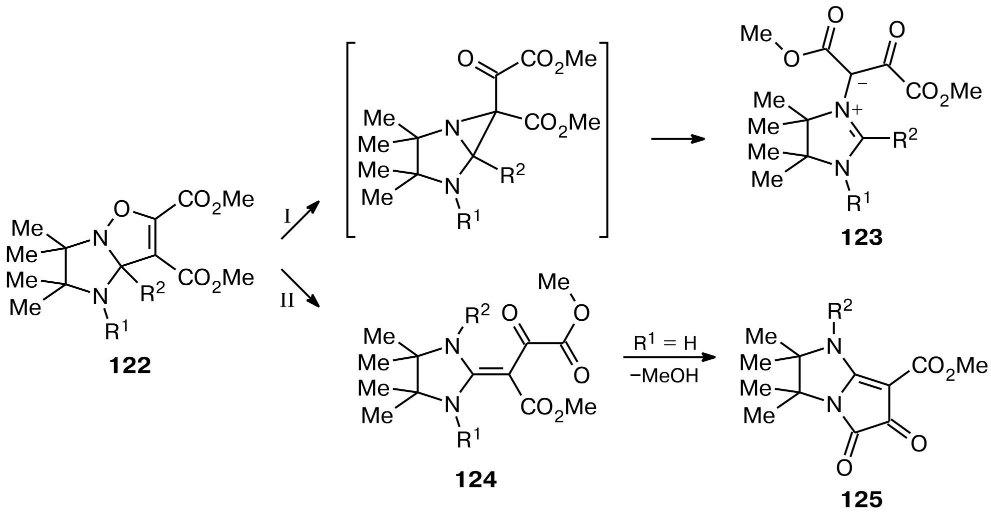
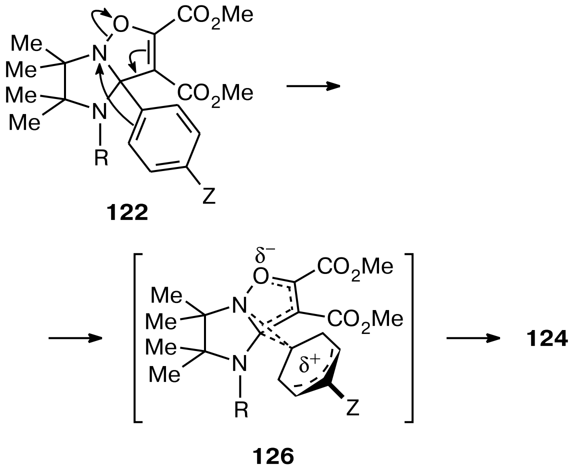


Fig. 1. Reaction energy surface of the rearrangement of compounds **122** into **124** in the coordinates of the N—O bond length r and the R^2—C—N bond angle L.

Scheme 42



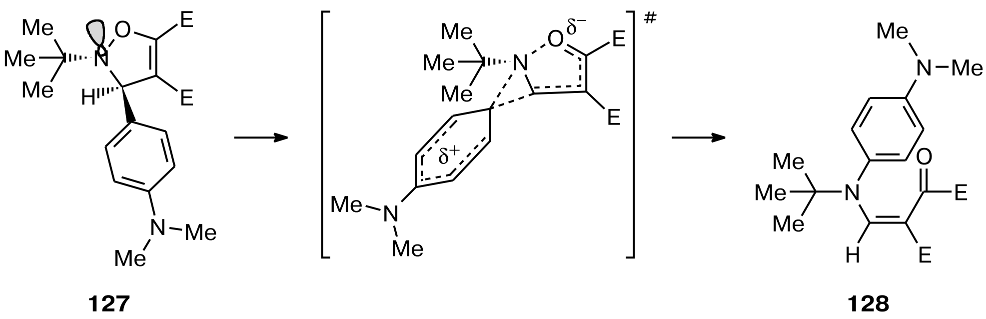
Scheme 43



127 (Scheme 44)[102] and **119d** (see Scheme 41).[66] The *trans*-arranged bulky substituents at the adjacent N(2) and C(3) atoms prevent the migration of the H atom even at 100 °C. In contrast, the *p*-dimethylaminophenyl group (as mentioned above, it is a good migrant) is *syn* to the lone electron pair of the N(2) atom in these compounds, so it is this group that migrates to form compounds **128** and **121d**, respectively. At the same time, thermolysis of 2,3-dihydroisoxazole **18** is accompanied by hydrogen migration (see Scheme 37); however, much more drastic conditions are required for this rearrangement because the fittest conformation for migration is thermodynamically unfavorable.

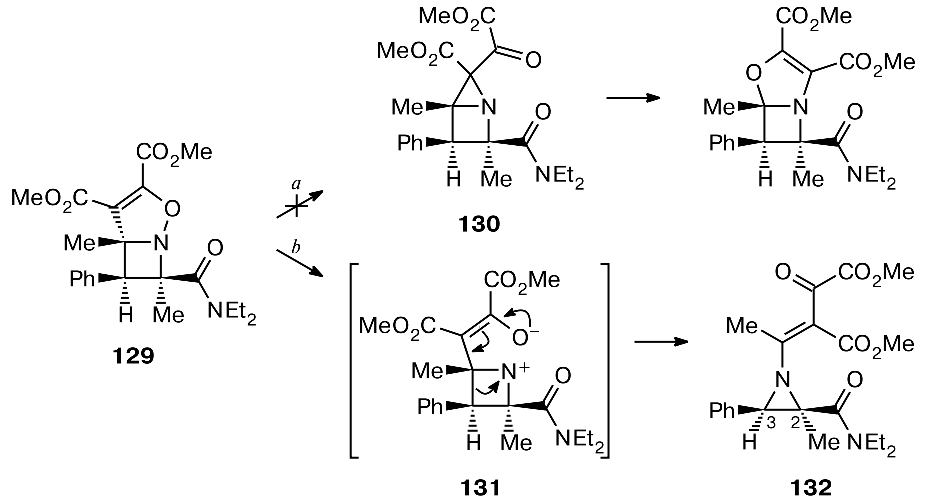
Migration of an alkyl substituent can result in contraction of an annulated four-membered ring to a three-membered one[103] (Scheme 45). It should be noted that the rearrangement of isoxazoline **129** into aziridine **132** does not change the configurations of the C(2) and C(3) atoms. Pathway *a* leading to acylaziridine **130** is unfeasible, which can be attributed[103] to unfavorable formation of a strained bicyclic system. The rearrangement is believed[103] to be a nonconcerted process passing through biradical or zwitterionic intermediate **131**. In our opinion, the retention of the configurations of the chiral centers provides unambiguous evidence for a concerted mechanism.

Scheme 44



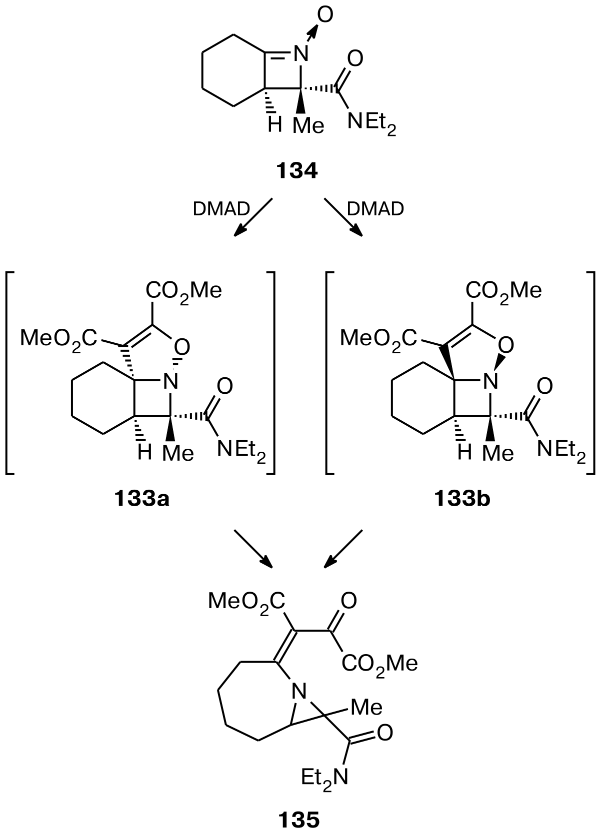
E = CO_2Me

Scheme 45



Cycloadduct **133** obtained from DMAD and nitrone **134** cannot be isolated because of its spontaneous isomerization into compound **135** (Scheme 46).[103]

Scheme 46



The instability of this cycloadduct has been attributed[103] to mutual repulsion between the O atoms of the amide group and the isoxazoline ring in structure **133a** (they are on the same side of the azetidine ring), which should substantially weaken the N—O bond. However, this explanation seems not to be very convincing: due to the steric hindrances presented by the amide group, the cycloaddition reaction will rather give stereoisomer **133b**, in which the aforementioned "repulsion between the O atoms" is absent.

Isoxazolines with a spiro C(3) atom (as in spirobicyclic system **136**) undergo an interesting ring-expansion (rather than ring-contraction) rearrangement[104] of the four-membered ring into a five-membered, giving product **137** (Scheme 47).

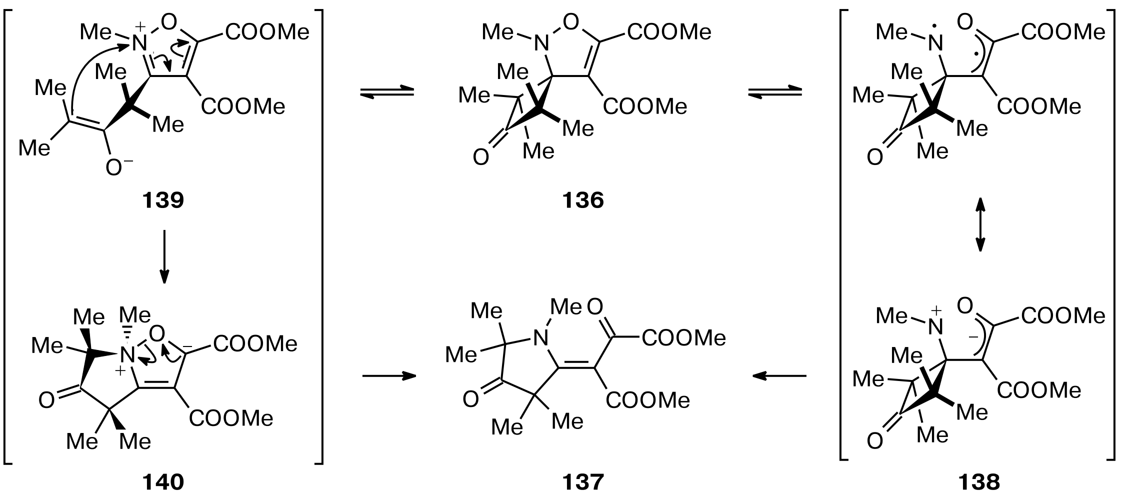
The rearrangement may begin[104] with either reversible formation of biradical or zwitterionic intermediate **138** or heterolysis of one cyclobutane C—C bond to zwitterion **139**. A subsequent intramolecular attack of the enolate anion on the N atom leads to compound **140**, which undergoes opening of the isoxazoline ring. The nucleophilic attack on the iminium N atom seems to be very unlikely since nucleophilic addition to the N atom has never been observed before in iminium salts: they always react with nucleophiles at the C atom.

Thus, the migration of a substituent is among the most uncommon rearrangements of 2,3-dihydroisoxazoles that involves nontrivial structures and often gives "unexpected" products. However, a study of trends in such reactions would be useful for development of original routes to novel compounds.

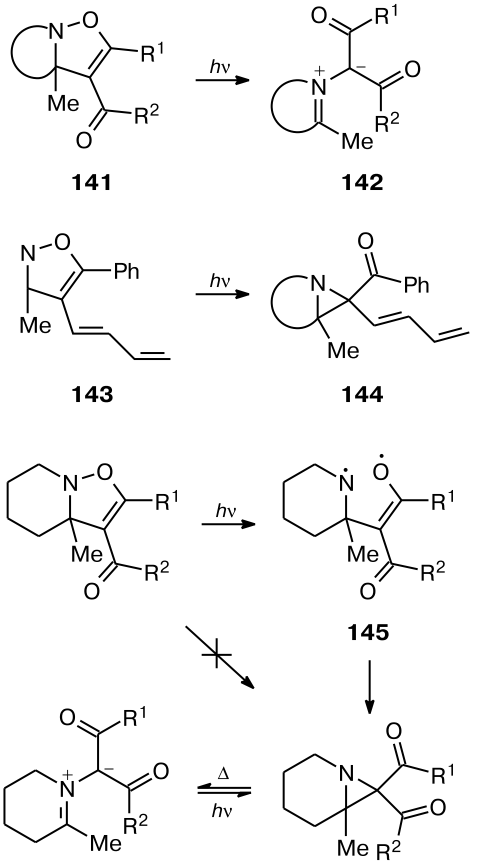
Photochemical rearrangements. According to recent data,[105,106] the aforesaid rearrangements can be induced photochemically. For example, 2,3-dihydroisoxazoles **141** and **143** undergo isomerization into ylides **142** and acylaziridine **144**, respectively (Scheme 48).

When interpreting experimental data, Lopez-Calle *et al.*[46] have excluded the symmetry-allowed 1,3-shift of

Scheme 47

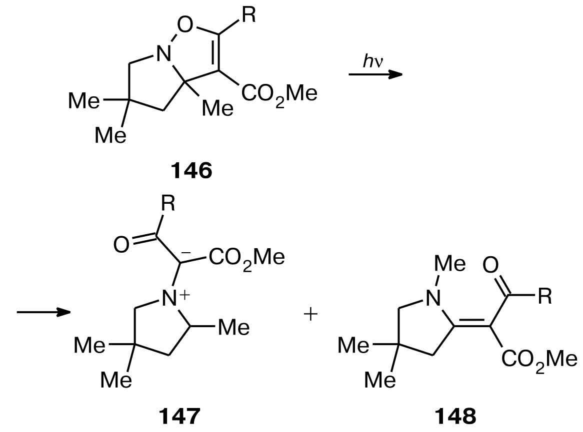


Scheme 48



nitrogen (see Scheme 48) because they detected the formation of intermediate biradical **145**. In addition, photoinduced migration of the methyl group has been found to be possible (Scheme 49).[46]

Scheme 49



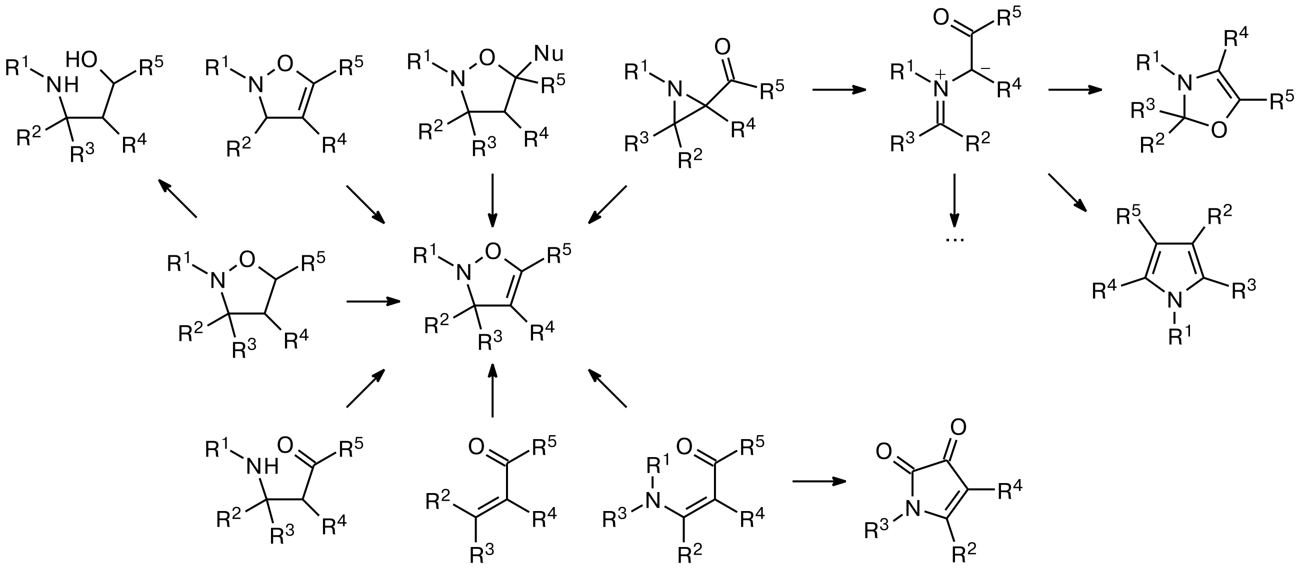
R = H, CO_2Me

The rearrangement of 4-isoxazoline **146** into ylide **147** and enamino ketone **148** probably involves, as in the preceding case, the formation of a biradical intermediate.[46]

Conclusion

To sum up, 2,3-dihydroisoxazoles can be transformed into various products, depending on the reaction conditions and their substituents. Based on available data, one can state that 2,3-dihydroisoxazoles can serve as precursors of many classes of organic compounds. For instance, addition of nucleophiles to the double bond gives tetrahydro derivatives, while elimination of a good leaving group from position 3 of the heterocycle and from the N(2) atom leads to isoxazoles. However, most reactions are accompanied by opening of the heterocycle. Reduction gives β-amino alcohols, β-amino ketones, α,β-unsaturated ke-

Схема 50



tones, or their intramolecular cyclization products, depending on the reaction conditions. Oxidation also yields α,β-unsaturated ketones, which allows one to dispense with acid or basic catalysts while synthesizing these compounds. α,β-Unsaturated ketones can also be obtained by alkylation of 2,3-dihydroisoxazole derivatives; however, the reaction products may be enamino ketones as well. Intramolecular rearrangements afford an especially copious variety of the resulting structures. 2,3-Dihydroisoxazoles can serve as precursors for substituted aziridines, azomethine ylides, 4-oxazoles, and pyrroles; of course, the above list of products is far from being exhaustive (Scheme 50).

For the moment, it seems to be still difficult to gain a deep understanding of these transformations. Analysis of their mechanisms is complicated by the instability of 2,3-dihydroisoxazoles themselves and key intermediates. This gives rise to different, often conflicting, opinions of the pathways followed by one or another process. That is the reason why much effort should now be focused on the study of both the synthetic scope of the transformations of 2,3-dihydroisoxazoles and the mechanisms of these transformations.

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