Oxime radicals: generation, properties and application in organic synthesis

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Abstract

N-Oxyl radicals (compounds with an N–O• fragment) represent one of the richest families of stable and persistent organic radicals with applications ranging from catalysis of selective oxidation processes and mechanistic studies to production of polymers, energy storage, magnetic materials design and spectroscopic studies of biological objects. Compared to other N-oxyl radicals, oxime radicals (or iminoxyl radicals) have been underestimated for a long time as useful intermediates for organic synthesis, despite the fact that their precursors, oximes, are extremely widespread and easily available organic compounds. Furthermore, oxime radicals are structurally exceptional. In these radicals, the N–O• fragment is connected to an organic moiety by a double bond, whereas all other classes of N-oxyl radicals contain an R2N–O• fragment with two single C–N bonds. Although oxime radicals have been known since 1964, their broad synthetic potential was not recognized until the last decade, when numerous selective reactions of oxidative cyclization, functionalization, and coupling mediated by iminoxyl radicals were discovered. This review is focused on the synthetic methods based on iminoxyl radicals developed in the last ten years and also contains some selected data on previous works regarding generation, structure, stability, and spectral properties of these N-oxyl radicals. The reactions of oxime radicals are classified into intermolecular (oxidation by oxime radicals, oxidative C–O coupling) and intramolecular. The majority of works are devoted to intramolecular reactions of oxime radicals. These reactions are classified into cyclizations involving C–H bond cleavage and cyclizations involving a double C=C bond cleavage.

Introduction

Free radicals in which an unpaired electron is localized on the N–O fragment (N-oxyl radicals, Figure 1) occupy a special place in organic chemistry due to the increased stability and ease of generation, the diversity of their structures, properties, and applications. Stable N-oxyl radicals (mainly of the aminoxyl type, Figure 1, I) are used in the development of organic magnetic materials [1], organic batteries [2-4], in the preparation of polymers by living polymerization [5,6], in the studies of biomolecules and living systems by EPR [7] and NMR [8] techniques. Stable
N-oxyl radicals occupy a central place in organic chemistry as scavengers of C-centered radicals [9] and selective oxidation organocatalysts (for example, in the oxidation of alcohols to the corresponding carbonyl compounds [10,11]). Recently, highly reactive imidoxyl radicals (Figure 1, II) have found a wide application in the processes of hydrogen atom abstraction with cleavage of the C–H bond [12-18] and in the processes of functionalization of C=C double bonds [19,20]. Amidoxyl radicals (Figure 1, III) are applied in the functionalization of the double bonds [21-26] and in mild oxidations [27].

In contrast to the mentioned N-oxyl radical classes (Figure 1, I–III) which have two single nitrogen–carbon bonds, the iminoxyl radicals (also known as oxime radicals, Figure 1, IV) have a carbon–nitrogen double bond. This structural feature is responsible for principal differences in the electronic structure, spectral properties, and chemical reactivity between oxime radicals and other types of N-oxyl radicals.

For a long time, the synthetic potential of iminoxyl radicals remained underestimated and their chemistry was mainly represented by fundamental physico-chemical studies. The precursors of imine-N-oxyl radicals are oximes, a widely available and fundamental class of organic compounds. However, oxime radicals almost did not find synthetic use until recently, probably due to the low stability of the majority of representatives of this type of radicals. The applications of oxime radicals in organic synthesis have developed rapidly during the last years, and we believe that this review is essential for the demonstration of a new face of the chemistry of this class of N-oxyl radicals. There are reports on the iminoxyl radical involvement in redox processes occurring in living organisms, for example, in microsomal oxidation of N-hydroxyguanidines and amidoximes [28], oxidation of tyrosine phenolic moiety in the presence of NO [29-33].

This review focuses on the synthetic use of oxime radicals. Most of the works on this topic have been published over the past ten years. In most cases, these are intramolecular reactions of oxidative cyclization. Examples of intermolecular reactions of oxime radicals, a brief description of their structure, stability, and spectral properties are also given. The chemistry of iminoxyl radicals (including their generation, structure, EPR spectroscopy, and reactions) was reviewed in 1978 before the discovery of their substantial synthetic potential [34]. A book chapter was dedicated to the chemistry of stable di-tert-alkyl iminoxyl radicals [35]. Kinetic [36] and EPR data [37] of iminoxyl radicals were previously compiled in tabular form.

**Review**

**General information about iminoxyl radicals: generation, structure, stability, and spectral data**

Iminoxyl radicals were first discovered in 1964 by EPR spectroscopy as short-living intermediates formed from the oximes of both aromatic and aliphatic ketones and aldehydes, as well as from the oximes of quinones under the action of a strong single-electron oxidant, cerium(IV) ammonium nitrate, in methanol [38]. To record EPR spectra, a flow system was used, which allowed observation of radicals with lifetimes of about $10^{-2}$ s [39]. The EPR spectra of iminoxyl radicals are characterized by large values of the hyperfine splitting constants of an unpaired electron with a $^{14}$N nucleus ($a^N \approx 28$–33 G [35-38]), which are very different from those for other N-oxyl radicals, such as imidoxyl ($a^N \approx 4.2$–$4.9$ G [40]), amidoxyl ($a^N \approx 5$–$8$ G [41,42]), and aminoxyl ($a^N \approx 15$ G [43]). The characteristic $^{14}$N hyperfine splitting constant makes EPR spectroscopy a convenient method for the identification of iminoxyl radicals, and for many of them, EPR is the only observation method due to low stability, and therefore low concentration in investigated samples.
systems. For the most stable iminoxyl radicals, sufficiently concentrated solutions were obtained and investigated by IR spectroscopy. The IR spectra show the absence of the line of stretching vibrations of the O–H bond, characteristic of the parent oximes, as well as the appearance of a new intense band corresponding to the asymmetric vibrations of the C=N–O• fragment (1550 cm⁻¹ for the diacetyl)iminoxyl radical [44], 1595 cm⁻¹ for the di(1-adamantyl)iminoxyl, and 1610 cm⁻¹ for the di-tert-butyliminoxyl radical [45]).

Various oxidants were used for the generation of iminoxyl radicals from oximes, including transition metal compounds, such as (NH₄)₂Ce(NO₃)₆ [38,46], Fe(ClO₄)₃ [44,46], CuClO₂ [46], Pb(OAc)₄ [44,46,51], PbO₂ [52], Mn(OAc)₃ [46], KMnO₄ [46], Ag₂O [53], AgO [54], Horseradish peroxidase/H₂O₂ [55], metal-free oxidants PhI(OAc)₂ [46], t-BuOOt-Bu [53] or quinones [56] under UV irradiation. Anodic oxidation was also reported [57].

The establishing of the self-decay pathways of iminoxyl radicals is complicated by the formation of a large number of products, some of the initially formed products are not stable. Moreover, participation of the oxidizing agent not only in the radical generation, but also in its decay also possible [53]. The products formed during the decomposition of iminoxyl radicals 2 generated from oximes 1 under the action of Ag₂O [53] were studied by K. U. Ingold et al. (Figure 2).

In most cases, the reaction was accompanied by the release of N₂ and N₂O, as well as the corresponding carbonyl compounds (3a–c). Dimerization of iminoxyl radicals with the formation of a C–O bond (dimer 4b, oxidation of diisopropyl oxime 1b), an O–N bond (dimer 4c, oxidation of benzophenone oxime 1c), and an N–N bond (dimer 4d, oxidation of benzaldoxime 1d, see also [58]) was observed. As a rule, the initial dimers of iminoxyl radicals are unstable, which makes their analysis difficult. Azine-N-oxides 5a,c were also obtained in significant

![Figure 2: The products of decomposition of iminoxyl radicals generated from oximes by oxidation with Ag₂O.](image-url)
amounts from oximes 1b,c (yields 20–28%). The C–O dimeric product 4b of the diisopropyl iminoxyl radical is unstable at room temperature even in solution. At the same time, it gives a sufficiently strong EPR signal corresponding to the free iminoxyl radical, which indicates the reversibility of dimerization [53]. During the oxidation of pivalic aldoxime 1e by Ag₂O, the formation of nitrile oxide 6e was observed, which then slowly dimerized to the corresponding furoxan 7e.

The kinetics of the decomposition of dialkyl, arylalkyl, and diaryl oxime radicals was also studied by EPR spectroscopy [53]. Radicals were generated under inert atmosphere directly in the EPR cavity by photolysis of the added di-tert-butyl peroxide (Scheme 1).

The authors pointed out the complexity of the processes of iminoxyl radicals’ decomposition and the difficulties associated with the interpretation of the obtained data [53]. During EPR monitoring of the generation and decomposition of iminoxyl radicals, the formation of several free-radical products of a non-iminoxyl type, probably of the general formula R₁R₂NO•, was observed. It was established that the studied iminoxyl radicals reversibly dimerized in the solution. For sterically unhindered dialkyliminoxyl radicals, the radical–dimer equilibrium was quickly reached, shifted toward the dimer, while a first-order decay kinetics was observed for the iminoxyl radical. For sterically hindered tert-butylmethyliminoxyl and diisopropyliminoxyl radicals, as well as for diaryl and alkyarylhiminoxyl radicals, the radical–dimer equilibrium was reached slowly, it was shifted toward the free radical, and a second-order decay kinetics was observed.

The first synthesized long-lived iminoxyl radical that did not undergo decomposition and dimerization in the solution for a time sufficient to use it as a reagent was the di-tert-butyliminoxyl radical (8) [45,59]. It was obtained by oxidation of di-tert-butyl ketoxime (1f) with silver(I) oxide (Ag₂O) in benzene at 25 °C (Scheme 2). This radical is stable at 25 °C in n-hexane. In pure form it is storable only at −78 °C as a solid. At room temperature, radical 8 is a blue oil. When storing 8 in the dark without solvent at 25 °C for a week, the following decomposition products were identified: di-tert-butyl ketone (9, 42%), di-tert-butyl nitroimine (10, 20%), and pivalonitrile (11, 4%) [45].

The proposed scheme for the decomposition of di-tert-butyliminoxyl radical (8) is presented in Scheme 3 [35,45]. It includes formation of C–O dimer 4f followed by the fragmentation to iminyl radical 12, ketone 9, and nitric oxide. The formation of nitroimine 10 is explained by the interaction of oxime radical 8 with nitric oxide. Pivalonitrile (11) is presumably formed via β-scission of iminyl radical 12 (Scheme 3). During the decomposition of oxime radical 8 an EPR signal typical for a dialkyl aminoxyl radical (type I in Figure 1) was also observed, it was assigned to the di-tert-butyl nitroxyl radical (13).

The proposed pathway of N-nitroimine 10 formation (Scheme 3) was confirmed by additional experiments. It was established that the di-tert-butyliminoxyl radical was not stable in NO atmosphere, the reaction proceeds at room temperature for an hour, and N-nitroimine 10 is formed [45].

Attempts to increase the stability of the iminoxyl radical by replacing the tert-butyl substituent with a bulkier triethylmethyl or other acyclic tert-alkyl substituents were not successful. In the case of Me₃C(Et₃C)C≡NO• radical 14, a monomolecular decomposition process was proposed, associated with an intramolecular hydrogen atom abstraction by an iminoxyl radical leading to the intermediate 15 (Scheme 4) [35,60,61].

In 1974, a di(1-adamantyl)iminoxyl radical 16 was synthesized analogously to di-tert-butyliminoxyl radical (8) from the corre-
Scheme 3: The proposed reaction pathway of the decomposition of di-tert-butyliminoxyl radical (experimentally identified products are highlighted by rectangles).

Scheme 4: Monomolecular decomposition of the tert-butyl(triethylmethyl)oxime radical.

Scheme 5: The synthesis and stability of the most stable dialkyl oxime radicals – di-tert-butyliminoxyl and di-(1-adamantyl)iminoxyl.

Besides the mentioned sterically hindered iminoxyl radicals 8 and 16, iminoxyl radicals with electron-withdrawing substituents at the C=N=O⁻ fragment also demonstrate increased stability compared to ordinary alkyl and aryl iminoxyl radicals. For example, a number of long-lived diacyl iminoxyl radicals 18 were generated by the action of tetrannitromethane [63] or NO₂ [64] on the corresponding β-diketones 17 or barbituric acid. The formation and decay of radicals were studied by EPR spectroscopy [64]. The lifetimes of radicals in the solution ranged from several hours to several days (Scheme 6) [63,64].

Recently, a method for the preparative synthesis of diacetylminoxy radical 20 in high yield via the oxidation of diacetyl oxime 19 by Pb(OAc)₄ was developed [44] (Scheme 7). The resulting radical can be stored for 2–5 days in the solution at room temperature without decomposition according to EPR and IR

Scheme 6: The preparation and stability of diacyl oxime radicals: di-tert-butyliminoxyl and di-(1-adamantyl)iminoxyl.

Scheme 7: Preparative synthesis of diacetyl iminoxyl radical 20.
spectroscopy. Compound 20 represents a very rare example of sterically unhindered, but nonetheless extremely persistent oxime radical.

Other long-living oxime radicals with electron-withdrawing substituents are also known, for example, based on N-containing heterocycles (isoxazolones, pyrazolones, pyrazolidin-3,5-diones, and 1,2,3-triazolones [52]), sulfones [65], and phosphonates [54] (Scheme 8).

Based on the data of EPR spectroscopy [35,38,49,50,66] and quantum chemical calculations [67], the maximum spin density in iminoxyl radicals is located on oxygen and on nitrogen. A lone electron pair of sp\(^2\) hybridized nitrogen located in the plane of the C=N–O fragment serves for the delocalization of an unpaired electron. Thus the unpaired electron is localized on the orbital that is orthogonal to the C=N π-bond, and therefore, the oxime radicals are considered as σ-radicals [35]. The electronic structure of the iminoxyl radical can be represented by two
main resonance forms presented below. The calculated and experimental data indicate that the localization of an unpaired electron on the NO fragment is also valid for the case of arylalkyl and diaryl oximes – conjugation of the radical center with π-systems of aryl rings is not observed [47,49,50,67].

It is known that the angular structure is characteristic for the CNO fragment of oxime radicals, and in the case of different substituents at the carbon atom, two isomers (E and Z) exist. The isomerization of oxime radicals proceeds much easier than for the corresponding oximes; the observation of individual isomers is generally possible only at low temperatures [68,69] (about 190 K). According to quantum chemical calculations, the oxime radicals have an increased C=N–O angle and a shortened N–O bond compared to the corresponding oximes (Figure 3) [44,52,70].

One of the important quantitative values that determine the reactivity of O radicals is the O–H bond dissociation enthalpy (BDE) in the parent OH compound (Figure 4). This value affects both the ease of the generation of radicals from the corresponding OH compounds and the oxidative properties of the O radicals. The O–H BDE values were determined for a number of oximes by the computational [67,70,71] and experimental [70,72] methods. It was established that the BDE decreased with an increase in the volume of substituents at the C=NOH fragment, which was consistent with the spatial structure of the oxime radicals – an increase in the C=N–O angle in the radical compared to the oxime led to a decrease in steric repulsion between the substituents at the carbon atom and the oxygen atom. It should also be noted that there is no noticeable decrease in the O–H BDE in diaryl oximes compared to dialkyl oximes (some examples are shown in Figure 4 [71]), which is consistent with

![Figure 3](image-url)  
**Figure 3:** The electronic structure iminoxyl radicals and their geometry compared to the corresponding oximes.

![Figure 4](image-url)  
**Figure 4:** Bond dissociation enthalpies (kcal/mol) of oximes and N,N-disubstituted hydroxylamines calculated on UB3LYP/6-311+G(d,p) level using an isodesmic reaction referencing the experiment BDE of phenol.
the idea that an unpaired electron is delocalized by the conjugation with a lone pair of the nitrogen atom, but not by the conjugation with the π-system of the molecule.

Figure 4 also shows examples of the calculated values of the O–H BDE of non-oxime compounds with a NOH fragment [71]. The O–H bond in oximes is stronger than in hydroxylamines with a similar structure, except for hydroxylamines with strong electron-withdrawing groups (such as carbonyl and CF$_3$).

Oxime radicals did not find wide application in organic synthesis and were mainly the subject of fundamental physicochemical studies for a long time since their discovery in 1964. The possible reason is the low stability of the majority of iminoxyl radicals. Only the relatively stable di-tert-butyliminoxyl radical was studied as a reagent in oxidative transformations of various substrates, such as unsaturated hydrocarbons, phenols, amines, and organometallic compounds. A breakthrough in the synthetic use of iminoxyl radicals has occurred in recent years when they found a wide application in intramolecular processes of oxidative cyclization with functionalization of C–H and C=C fragments.

In the majority of works related to synthetic use of oxime radicals, intramolecular reactions are reported. Perhaps this is due to the low stability of oxime radicals. The main preparative reactions involving oxime radicals include the addition of the oxime radical to the C=O double bond or hydrogen atom abstraction. Due to the delocalization of the unpaired electron between the oxygen and nitrogen atoms in the oxime radicals, they can form both C–O and C–N bonds. As a rule, a C–O bond is formed in intramolecular reactions, intramolecular cyclization generally occurs with the formation of a five-membered cycle of isoxazoline (C–O bond formation) or nitrone (C–N bond formation).

Application of the oxime radicals in organic synthesis: intermolecular reactions

Selective intermolecular reactions involving oxime radicals are relatively rare compared with intramolecular ones. Many of these reactions involve a stable di-tert-butyliminoxyl radical. Violuric acid and $N,N'$-dimethylvioluric acid, precursors of the corresponding persistent iminoxyl radicals, were studied as mediators for the electrochemical oxidation of lignin [73] and enzymatic oxidations [74-76] but have not been widely used in organic synthesis.

The di-tert-butyliminoxyl radical proved to be quite unreactive with respect to a C=C double bond containing substrates that are considered as effective scavengers of free radicals (Scheme 9). It remains unchanged [45] when dissolved in styrene (2 hours, 25 °C) or vinyl acetate (20 minutes, 60 °C; conversion of the oxime radical was less than 10% after 3 days at 25 °C). The inertness of the di-tert-butyliminoxyl radical with respect to the mentioned substrates with a C=C double bond was explained by the steric hindrance of the iminoxyl radical.

On the other hand, di-tert-butyliminoxyl radical (8) can react with unsaturated hydrocarbons by abstracting the hydrogen atom from the allyl or benzyl position (Scheme 10) [35,45,60,61]. The C-centered radicals formed after hydrogen atom abstraction from the allyl or benzyl position couple with the di-tert-butyliminoxyl radical forming the oxime ethers 21 and 22. 1,4-Cyclohexadiene is dehydrogenated to benzene instantly and exothermally at room temperature [45]. The solvent-free reaction of oxime radical 8 and cyclohexene takes 1 h at 25 °C [61]. The benzyl hydrogen atoms are abstracted at higher temperatures [35,45].

Reactions of di-tert-butyliminoxyl radical (8) with allylic moieties can theoretically occur by two pathways that give the same final product – the O-allyl derivative of the oxime [35,77]. In the first pathway (Scheme 11A), the initial addition of the di-tert-butyliminoxyl radical to the double bond is followed by hydrogen atom abstraction from the resulting alkyl radical 24. The second pathway (Scheme 11B) begins with the abstraction of an allylic hydrogen atom, then the di-tert-butyliminoxyl radical adds to either end of the resulting allylic radical 25. However, the results of pathways A and B are different for selectively deuterated cyclohexene 23 in Scheme 11. The addition–abstraction pathway (A) results in a single deuterated product 26a, whereas the abstraction–addition pathway (B) gives two products: the product obtained by pathway A (26a) and a product 26b unique to pathway B. The abstraction–addition process (B) is dominant for three alkenes studied, namely, cyclohexene, cyclooctene, and 3-hexene, with 90–92% of the overall reaction occurring by this mechanism [77].

The reactions of the di-tert-butyliminoxyl radical with phenol and its derivatives are faster than with alkenes. The highest reaction rates are observed in the case of electron-donating substituents (Y) in 4-YC$_6$H$_4$OH [35,78]. The hydrogen atom

Scheme 9: Examples demonstrating the low reactivity of the di-tert-butyliminoxyl radical towards the substrates with double C=C bonds – styrene and vinyl acetate.
abstraction rate accelerating effect of electron-donating substituents was explained by the decrease of the O–H bond dissociation energy by the electron-donating substituent Y [35,79-84].

The result of these reactions depends on the phenol structure. 4-Methylphenol (27a) and 2,6-di-tert-butyl-4-methylphenol (BHT, 27b) gave 4-methyl-4-iminooxycyclohexadienones 28a,b (Scheme 12). Phenol (29) and 1-naphthol (30) were transformed into 4,4-bisoximes 31 and 32, respectively (Scheme 12) [35,78].

Imines 37–40 were obtained with good yields by the reaction of di-tert-butyliminoxyl radicals with primary and secondary amines 33–36 for several hours at room temperature in pentane or hexane (Scheme 13) [85]. Due to the low stability of most imines, they were not isolated in pure form but were transformed into 2,4-dinitrophenylhydrazones. For example, the yields of 2,4-dinitrophenylhydrazones from 37, 38 and 39 were

Scheme 10: The reactions of di-tert-butyliminoxyl radical with unsaturated hydrocarbons involving hydrogen atom abstraction.

Scheme 11: Possible mechanisms of reaction of di-tert-butyliminoxyl radical with alkenes.

Scheme 12: Products of the reaction between di-tert-butyliminoxyl radical and phenol derivatives.
79, 68 and 78%, respectively [85]. The example of N-benzylidenedenemethylamine (40), shows the dependence of the imine yield on reaction time and temperature (Scheme 13). Higher yields of 40 were achieved at lower temperatures but longer reaction times were necessary in this case [85].

Di-tert-butyliminoxyl radicals react with Grignard reagents and organolithium reagents 41 at 0 °C in Et₂O forming mainly di-tert-butyl oxime 1f and the products of C–O coupling [86]. The reactions were performed by addition of the solution of the organometallic compound 41 in Et₂O to the solution of di-tert-butyliminoxyl radical in Et₂O. The product yields obtained employing organolithium reagents are presented below (Scheme 14). The Grignard reagents demonstrated very similar results that are omitted.

Among the major C–O coupling product (oxime ether 42) small amounts of C–N coupling products (nitrones 43) were detected in the case of sterically unhindered organolithium reagents. Presumably, the reaction proceeds via SET from the organometallic compound and iminoxyl radical with the formation of an oxime anion and an intermediate C-centered radical. In the case of MeLi and PhLi, which correspond to the most reactive methyl and phenyl radicals, products 44 of hydrogen atom abstraction from Et₂O followed by C–O coupling of the resultant C-centered radical with the iminoxyl radical was observed.

Recently, examples of selective intermolecular C–O coupling between oxime radicals generated in situ from oximes and different types of CH-reagents have been reported. 1,3-Diketones and 1,3-ketoesters 45 undergo cross-dehydrogenative C–O coupling with oximes under the action of oxidizing agents [46], such as KMnO₄, Mn(OAc)₃ or the KMnO₄/Mn(OAc)₃ system (Scheme 15). A radical mechanism is suggested for the formation of the C–O coupling products 46 in which the oxidizing agent serves to generate oxime radicals from oximes and perform one-electron oxidation of 1,3-dicarbonyl compounds 45. The formation of oxime radicals under the reaction conditions was confirmed by EPR spectroscopy [46].

1,3-Diketones and 1,3-ketoesters with easily oxidizable groups, such as allyl and benzyl, were tolerated (46i and 46j). The yield of the C–O cross-coupling products 46 increases with the rise in the stability of the corresponding oxime radicals. For example, in the row 46f–h the yield becomes higher with the increase of the steric effect of the alkyl substituents attached to the oxime group. The lowest yield was obtained with an aromatic oxime (product 46e, yield 27%).

Later, the Cu(BF₄)₂ (cat.)/t-BuOOH oxidative system [87] was proposed as an alternative to stoichiometric metal-containing oxidants, such as KMnO₄, Mn(OAc)₃, and KMnO₄/Mn(OAc)₃ (Scheme 16).

1,3-Ketoesters (products 46a,b, 46m,n), 1,3-diketones (product 46r), as well as lactones (products 46o–q) were used in the oxidative C–O coupling reaction. The coupling of oximes with 1,3-diketones proceeded in lower yields than with 1,3-ketoesters (products 46a and 46r). Despite the presence of t-BuOOH in the system, a Kharash peroxidation of 1,3-dicarbonyl compounds [88-93] did not occur, and a selective formation of the C–O product with oximes was observed.
Scheme 15: Cross-dehydrogenative C–O coupling of 1,3-dicarbonyl compounds with oximes under the action of manganese-based oxidants.

Scheme 16: Cross-dehydrogenative C–O coupling of 1,3-dicarbonyl compounds with oximes under the action of Cu(BF$_4$)$_2$ (cat.)/t-BuOOH system.
Benzylmalononitrile (47) was introduced into the oxidative C–O coupling with diacetyl oxime (19) analogously to 1,3-dicarbonyl compounds [46], but Cu(ClO$_4$)$_2$ afforded a better yield of the C–O coupling product 48 than the manganese-based oxidants in this case (Scheme 17) [94].

A radical mechanism was suggested. The copper(II) ion reacts with oxime 19 to generate iminoxyl radical 20 and also forms complex 49 with dinitrile 47. Interaction of radical 20 and complex 49 results in the coupling product 48 (Scheme 18). The formation of radical 20 from the oxime 19 under the action of Cu(ClO$_4$)$_2$ in acetonitrile was proved by EPR spectroscopy [46].

Free-radical oxidative C–O coupling of pyrazolones 50 with different classes of N-hydroxy compounds, including oximes, was demonstrated [44]. In contrast to the cross-dehydrogenative coupling of oximes with 1,3-dicarbonyl compounds, both one-electron oxidants (Fe(ClO$_4$)$_3$, (NH$_4$)$_2$Ce(NO$_3$)$_6$) and two-electron oxidants (PhI(OAc)$_2$, Pb(OAc)$_4$), that vary greatly in properties, are applicable for this process. After optimization of the reaction conditions Fe(ClO$_4$)$_3$ was chosen as the optimal oxidant for the synthesis of C–O cross-dehydrogenative coupling products 51 (Scheme 19).

The extremely persistent diacetyliminoxyl radical (20) [44] was directly introduced into the reaction with pyrazolones 50 with the formation of the corresponding C–O coupling products 51 (Scheme 20). The yields were close to that obtained with in situ generated of iminoxyl radicals (Scheme 19).

Recently, the oxidative C–O coupling of oximes with acetonitrile, esters 52, and ketones 53 was realized [95] (Scheme 21). The authors suggested a radical mechanism in which the iminoxyl radical is generated from the oxime anion under the action of perfluorobutyl iodide through the formation of an EDA complex (electron donor–acceptor complex, which is also called charge-transfer complex). The perfluorobutyl radical formed at this step served for the hydrogen atom abstraction from the CH-reagent (MeCN, 52 or 53).

Ketone oximes of both aromatic (products 54a–c) and aliphatic structures (54d,e) were successfully used in coupling with acetonitrile. The C–O coupling product 54f of acetonitrile with benzaldoxime was obtained in a lower yield. The aromatic oximes reacted with esters and ketones to give oxidative coupling products in moderate to good yields (products 55a–e and 56a–e, respectively). In the case of asymmetric ketones, the C–H bond at the more substituted carbon was cleaved (products 56d,e).

Recently, the copper-catalyzed addition of oximes to the C=C double bond of maleimides was reported [96]. The iminoxyl radicals were detected by EPR spectroscopy, but the non-radical
Application of the oxime radicals in organic synthesis: intramolecular reactions

There are two main types of intramolecular reactions involving oxime radicals (Scheme 22). In the first type, an initial hydrogen atom abstraction is followed by a cyclization (transformation of 57 to 58). In the second type, an addition of oxime radicals to a C=C double bond takes place (transformation of 59 to 60 or 61). As a result of the reaction, a 5-membered cycle is formed via the formation of C–O (products 58 and 60) or C–N bond (product 61) in accordance with the ability of oxime radicals to act as O- or N-radicals.

The formation of the heterocycles, mainly isoxazolines/isoxazoles, from unsaturated oximes can be achieved through different ways including addition of electrophiles to the C=C double bond of the unsaturated oxime followed by intramolecular nucleophilic attack of the oxime group [97-100], metal-catalyzed cyclization [98,101-108], cyclization under the action of photocatalysts [109,110], cyclization of nitroso intermediate [111], etc. [112,113]. At least some of these reactions do not involve oxime radicals as intermediates. It should be noted that free-radical cyclizations mediated by iminoxyl radicals frequently afford products that are hardly achievable or not achievable by non-radical methods. In this review only works in which the participation of iminoxyl radicals was confirmed or assumed are discussed.

Oxidative cyclization with the cleavage of the C–H bond

In one of the first works in this area oximes with activated C–H bond in the β-position were transformed into isoxazolines or isoxazoles by oxidative cyclization [114] under the action of TEMPO and K₂CO₃ (Scheme 23).

The presence of aryl substituents at the β-position of the oxime contributed to high yields of the desired products (63a–c, 55–87%), in the presence of only methyl substituents moderate yields were observed (63d, 34%). The reaction proceeds exclusively with the closure of the five-membered cycle and participation of the C–H bond located exclusively in the β-position with respect to the oxime group. This regularity is maintained even when the activated benzylic C–H bond is present in the
Scheme 21: Oxidative C–O coupling of oximes with acetonitrile, ketones, and esters.

γ-position with respect to the oxime group (example 63e, yield 14%). Almost in all examples, an aryl substituent (R^1 = Ph or substituted phenyl) was located at the oxime group; the product 63f with R^1 = Et was obtained in a moderate yield of 40%. In the presence of only one aryl group in the β-position (R^2 = H, R^3 = Ar) and further processing of the reaction mixture with atmospheric oxygen, an aromatization occurs with the formation of isoxazoles (64a,b 55–95%).

Scheme 22: Intramolecular cyclizations of oxime radicals to form substituted isoxazolines or cyclic nitrones.
Scheme 23: TEMPO-mediated oxidative cyclization of oximes with C–H bond cleavage.

Presumably, the reaction of TEMPO with oxime 62 affords the iminoxyl radical 65 (Scheme 24). 1,5-HAT in the radical 65 gives a C-centered radical 66, which is captured by TEMPO to form intermediate 67. Elimination of TEMPOH leads to a β-unsaturated oxime 68, which could undergo cyclization by ionic or radical mechanisms to give isoxazoline 63 [114,115].

A similar cyclization with the formation of isoxazolines 70 was realized [116] by the oxidation of oximes 69 by the Selectfluor/Bu₄NI system (Scheme 25). A radical mechanism was proposed in which the hypoiodite formed from the oxime undergoes a homolytic cleavage of the O–I bond with the formation of the iminoxyl radical.

As a rule, R¹ is an aromatic ring, and the yield of the target product weakly depends on the electronic effects of substituents in this ring (products 70a–d). Good yields were obtained even with substrates having inert non-benzyl C(sp³)–H bonds (products 70f–h). It is important to note that products with two substituents in the α-position to the oxime group (70i,j) were obtained with good yields. The formation of 70i and 70j is impossible through an intermediate similar to intermediate 68 in Scheme 24.

Oxidative cyclization of N-benzyl amidoximes 71 was realized [117] under the action of molecular oxygen with the formation of either 1,2,4-oxadiazoles 72 or quinazolinones 73.
Scheme 25: Selectfluor/Bu$_4$NI-mediated C–H oxidative cyclization of oximes.

(Scheme 26), depending on the reaction conditions. The 1,2,4-oxadiazole ring was selectively obtained in DMF at 60 °C under oxygen atmosphere (1 atm) in the presence of an excess of K$_3$PO$_4$, whereas in DMSO at 100 °C under air and in the presence of Cs$_2$CO$_3$ quinazolinones 73 were selectively synthesized.

Scheme 26: Oxidative cyclization of N-benzyl amidoximes to 1,2,4-oxadiazoles.
The authors proposed that 1,2,4-oxadiazoles were formed by a mechanism [117], analogous to the mechanism of the TEMPO-mediated oxidative oxime cyclization (Scheme 23 [114]). Apparently, both 1,2,4-oxadiazoles 72 and quinazolinones 73 are produced via the common intermediate, 4,5-dihydro-1,2,4-oxadiazole. An example of such intermediate 74 is shown in Scheme 27. Oxidative aromatization of 74 leads to 1,2,4-oxadiazole 72a (Scheme 26). The second pathway, hydrogen abstraction followed by β-scission presumably leads to iminyl radical, which forms the observed quinazolinone 73a (Scheme 27) [118].

A radical mechanism was proposed in which the oxime moiety is oxidized by DDQ to the iminoxyl radical 77, which undergoes 1,5-HAT to give a C-centered radical 78 stabilized by a sulfur atom. 78 is oxidized by DDQ to a carbocation 79, followed by the closure of the oxathiazole ring (Scheme 29). Later, DDQ-mediated oxidative cyclization of amidoximes with the formation of 1,2,4-oxadiazoles (analogous transformation with K3PO4/O2 system was shown above in Scheme 26) was realized without the addition of TsOH [120].

Isoxazolines 82 were synthesized by a one-pot sequence, which included the substitution of a halogen atom in α-halogenated oxime 80 by dicarbonyl compound 81 and oxidative cyclization (Scheme 30) [121].

The method for oxidative cyclization of thiohydroximic acids 75 under the action of DDQ and p-TsOH with the formation of the corresponding 1,4,2-oxathiazoles 76 was developed (Scheme 28) [119]. The authors noted that reaction in the absence of p-TsOH proceeded with lower yield of 76.

The introduction of electron-donating substituents into the benzene ring of the oxime increases the yield of the reaction product (example 82d, 90%), and the introduction of the electron-withdrawing substituents decreases it (example 82e, 64%). Non-aromatic oximes of chloro- or bromoacetone are not suitable for this method; product 82f was observed in trace amounts. According to the proposed reaction pathway, the nucleophilic substitution of the halogen atom with the formation of intermediate 83 proceeds in the presence of a base (Scheme 31). Oxidation of 83 with silver(I) affords the iminoxyl radical 84, which undergoes cyclization to form 85. Subsequent oxidation leads to intermediate 86, which is deprotonated to form the final product 82.

![Scheme 27: The formation of quinazolinone 73a from 5-phenyl-4,5-dihydro-1,2,4-oxadiazole 74 under air.](image-url)

![Scheme 28: DDQ-mediated oxidative cyclization of thiohydroximic acids.](image-url)
A convenient method for the synthesis of 1,2,4-oxadiazolines 88 by oxidative cyclization of amidoximes 87 under the action of molecular oxygen and visible light in the presence of catalytic amounts of 2,4,6-tris(4-fluorophenyl)pyrillium tetrafluoroborate (T(p-F)PPT) was proposed (Scheme 32) [122].

Pyrrolidinyl oxime derivatives having both aromatic (products 88a–d) and aliphatic (products 88e,f) substituents are applicable. Oximes with an isoindoline or tetrahydroisoquinoline fragment also undergo this transformation to give substituted oxadiazolines (products 88g,h). The authors note that T(p-F)PPT plays the role of a photocatalyst that promotes the formation of an oxime radical that undergoes 1,5-HAT to form the target product.

**Oxidative cyclization with the cleavage of π-bond C=C**

Early examples of oxidative cyclization of iminoxyl radicals with an attack on π-bonds were reported in the 1980s [123]. However, the structure of the products was not exactly proved, the scope of application and preparative potential of these reactions was not studied (Scheme 33).
Scheme 32: T(p-F)PPT-catalyzed oxidative cyclization of oximes with the formation of 1,2,4-oxadiazolines.

Scheme 33: Intramolecular cyclization of iminoxyl radicals involving multiple C=C and N=N bonds.
When the oxime 89 with an azo fragment was treated by lead(IV) acetate at −60 °C, an EPR signal with the HFS constant $a_N = 31$ G was observed which indicated the formation of the iminoxyl radical 90. Presumably, the radical 90 underwent cyclization involving the azo group to form indazole 91.

During the photolysis of a mixture of di-tert-butyl peroxide with oxime 92 containing an alkenyl fragment at temperatures from −30 to −10 °C, two signals were observed in the EPR spectrum with a constant HFC $a_N = 30$ G and 32 G, corresponding to iminoxyl radicals 93. At higher temperature (+10 °C), only one signal was observed with $a_N = 19.75$ G. This HFS value is characteristic of bicyclic nitroxyl radicals [123]. The authors suggested that the formed iminoxyl radical underwent cyclization with the formation of alkyl radical 94. The latter attacked the nitrone moiety to form the bicyclic nitroxyl radical 95. When oxime 96 was oxidized with lead(IV) acetate, products 98 and 99 were observed. This result can be explained by the intramolecular attack of iminoxyl radical 97 on the phenyl π-system. According to EPR data, the authors suggested that iminoxyl radicals 101 generated from oximes 100 by photolysis with the addition of the di-tert-butyl peroxide gave nitroxides 102 [123].

The widespread use of iminoxyl radicals in organic synthesis involving a radical addition to a C=C bond started to develop extensively only after 2010. The oxidation of β,γ- and γ,δ-unsaturated oximes (103 and 104, respectively) using the TEMPO/DEAD system or only DEAD (diethyl azodicarboxylate) afforded 5-exo-trig radical cyclization [124] with the formation of the corresponding isoxazolines 105 and 106 or cyclic nitrones 107 and 108 (Scheme 34).

Scheme 34: Oxidative cyclization of β,γ- and γ,δ-unsaturated oximes employing the DEAD or TEMPO/DEAD system with the formation of C–O and C–N bonds.
A variety of β,γ-unsaturated oximes 103 with an aromatic substituent at the C=NOH group reacted with the formation of isoxazolines (products 105a–d, 106a–c, yields 88–93%). Product 105e containing a non-aromatic tert-butyl R1 group was synthesized in good yield (77%). When γ,δ-unsaturated oximes were applied the formation of cyclic nitrones was observed (products 107a,b, 108a.b). In this case, the intermediate oxime radicals reacted as N-centered radicals, which was consistent with the calculations [124]. If the double bond of the starting oxime was endocyclic, high stereoselectivity was observed with the formation of trans-products (examples 106c and 108b).

The oxidative cyclization of β,γ-unsaturated oximes 109 under the action of molecular oxygen and catalytic amounts of bis(5,5-dimethyl-1-(4-methylpiperazin-1-yl)hexane-1,2,4-trione)cobalt(II) (Co(nmp)2) resulted in isoxazolines 110 with a hydroxymethyl group or methylisoxazolines 111 (Scheme 35) [125].

The reaction in iPrOH under an oxygen atmosphere with the addition of 10 mol % of t-BuOOH (conditions A) produced hydroxymethylisoxazolines 110, and the reaction in toluene under air with the addition of 20 equivalents of cyclohexa-1,4-diene (CHD) as hydrogen atom donor (conditions B) led to methylisoxazolines 111. Both aromatic (examples 110a–c.f, 111a,b,f) and aliphatic (examples 110d,e and 111c–e) β,γ-unsaturated oximes undergo this cyclization. The conditions A were also applied for the oxidation of α,β-unsaturated oxime 109‘. As a result, 5-endo-trig cyclization affording hydroxyisoxazoline 110‘ in good yield was observed.

Another approach to the synthesis of hydroxy-substituted isoxazolines 113 is the manganese(III) acetylacetonate catalyzed reaction of β,γ-unsaturated oximes 112 with oxygen of air (Scheme 36) [126].

The peroxide initially formed in the reaction was reduced by treatment with a saturated Na2S2O4 solution. The formation of peroxide was confirmed by a control experiment in which the hydroperoxide 113b’ was isolated when the treatment of the reaction mixture with sodium dithionite was omitted. High yields were reached for both monosubstituted (products 113a,d,f,h) and disubstituted C=C bonds (products 113b,c,e,g). Aliphatic oximes also undergo this transformation in high yields (products 113c,g,h).

The photocatalytic oxidative cyclization of β,γ-unsaturated oximes 114 was carried out under the action of a PC-I/TEMPO
Scheme 36: Manganese-catalyzed aerobic oxidative cyclization of $\beta,\gamma$-unsaturated oximes.

Catalytic system and the irradiation of blue LEDs (Scheme 37) [127].

A variety of electronically rich and electronically poor aryl or heteroaryl groups at the oxime group ($R_1$) are well-tolerated (products 115a–e). Oximes with disubstituted double C=C bond also successfully undergo this cyclization (products 115f–h).

C-centered radicals generated in a radical 5-exo-trig cyclization of $\beta,\gamma$-unsaturated oximes 116 upon oxidation by the TBAI/TBHP system were trapped by an isonitrile group of 2-arylphenyl isonitriles 117 to synthesize substituted phenanthridines 118 (Scheme 38) [128].

Both aliphatic (example 118c) and aromatic (examples 118a,b,d–h) $\beta,\gamma$-unsaturated oximes enter this cascade cycliza-
Scheme 38: TBAI/TBHP-mediated radical cascade cyclization of the $\beta,\gamma$-unsaturated oximes.

Scheme 39: TBAI/TBHP-mediated radical cascade cyclization of vinyl isocyanides with $\beta,\gamma$-unsaturated oximes.

Another example of a cascade oxidative cyclization involving an isonitrile group is the reaction of $\beta,\gamma$-unsaturated oximes with vinyl isocyanides to form substituted isoquinolines (Scheme 39) [129].

Both $\alpha,\alpha$-disubstituted aromatic oximes (products 121a,b,e–h) and unsubstituted ($R_2 = R_3 = H$, products 121c,d) undergo the
reaction successfully. The authors noted the effect of substitu-
ents in the phenyl fragment attached to the oxime group (R1): high yields were obtained with para- and meta-substituted sub-
strates; however, when ortho-substituents were present, the product 121 was not observed. Two aryl groups at the vinyl 
fragment of the isocyanide are important for a successful syn-
thesis of products 121. In the case of R5 = H or alkyl the forma-
tion of the oxidative cyclization product 121 was not observed
[129].

The oxidative cyclization of unsaturated oximes 122 under the action of i-BuONO (TBN), followed by treatment with NEt3 
leads to isoxazolines 123 or cyclic nitrones 124 with an addi-
tional oxime group (Scheme 40) [130].

The authors showed that the initial product of the oxidative cyclization of oxime 122a under the action of TBN was the dimer 127 of the nitroso compound 126, which was formed, presumably, as a result of nitrosation of the C-centered radical 125 by TBN [130]. Intermediate 127 was isolated in 96% yield 
and its structure was confirmed by a single-crystal X-ray 
diffraction. Under the action of Et3N, the dimeric nitroso com-
pound 127 was converted into the more stable oxime tautomeric 

![Scheme 40](image1)

**Scheme 40**: tert-Butylnitrite-mediated oxidative cyclization of unsaturated oximes with the introduction of an additional oxime group.

![Scheme 41](image2)

**Scheme 41**: Transformation of unsaturated oxime to oxyiminomethylisoxazoline via the confirmed dimeric nitroso intermediate.
Another reaction pathway of a TBN-mediated oxidative cyclization of β,γ-unsaturated oximes 128 was achieved by switching from the argon atmosphere to air or oxygen atmosphere and by lowering the reaction temperature to −10 °C [131]. Oximes 128 undergo cyclization to form nitrooxymethyl-substituted isoxazolines 129 (Scheme 42). THF was found to be the optimal solvent.

Aliphatic (examples 129b,f,g) and aromatic (examples 129a,c,d,e,h) unsaturated oximes undergo this cyclization. Oximes containing disubstituted double bonds also give the corresponding isoxazolines 129c,h. The authors proposed a mechanism involving a 5-exo-trig cyclization of the oxime radical followed by the addition of molecular oxygen to the formed C-centered radical with a formation of a peroxyl radical. The interaction of the latter with NO leads to the final oxynitro compound [131].

Cyano-substituted oxazolines 131 were synthesized from unsaturated oximes 130 using a combination of t-BuONO and a ruthenium catalyst (Scheme 43) [132]. The authors proposed that the interaction of unsaturated oxime with TBN produced a hydroxyiminomethylisoxazoline (Scheme 40) [130] that was transformed into the cyano-substituted oxazoline in the pres-
ence of a ruthenium catalyst. This possible reaction pathway was confirmed by a control experiment in which the hydroxyiminomethylisoxazoline was transformed to a nitrile in the presence of [RuCl₂(p-cymene)]₂.

Aromatic oximes with various substituents, as well as heteroaromatic oximes, give cyano-substituted oxazolines in good yields (products 131a–e). Aliphatic oximes also enter this transformation, including an oxime containing a TBDPS protecting group (products 131f–h).

The combination of AgSCF₃ and catalytic amounts of Cu(OAc)₂ was used for the synthesis of trifluoromethylthiolated isoxazolines 133 from unsaturated oximes 132 (Scheme 44) [133]. Substrates with both aryl (products 133a,d–h) and alkyl substituents (product 133b) at the oxime fragment (R¹ in 132) were successfully used for the oxidative cyclization. The proposed reaction mechanism involves the formation of an oxime radical and its 5-exo-trig cyclization to form a C-centered radical, which undergoes a trifluoromethylthiolation by •SCF₃-radical generated from AgSCF₃ [133]. The iminoxyl radical 5-exo-trig cyclization step was confirmed in experiments with the capture of a C-centered radical by TEMPO. It should be noted that in the case of γ,δ-unsaturated oxime an unusual six-membered oxazine 133h was reported as the major product [133].

A similar cyclization of oximes 134 with the introduction of an azido group was carried out using TMSN₃ as an azide source (Scheme 45) [134].
The reaction is applicable for β,γ-unsaturated oximes having both aryl (products 135a,d–h) and alkyl substituents (products 135b,c) at the oxime fragment (R¹). An oxime with a disubstituted double bond (R² = Me) also reacts with the formation of isoxazoline 135g having a quaternary carbon atom.

Under the action of t-BuOOH (TBHP), β,γ-unsaturated oximes 136 undergo a cascade cyclization with N-aryl-N-methylmethacrylamides 137 affording substituted oxindoles 138 (Scheme 46) [135].

In the majority of examples, aromatic β,γ-unsaturated oximes (examples 138a–c, e–h) were used. Oximes having a disubstituted double bond also successfully entered this reaction (example 138c). The relatively low yield of product 138f was explained by the steric effect of the ortho-methyl substituent in amide 137. In most cases, N-aryl-N-methylmethacrylamides were used for this cyclization to obtain oxindoles (products 138a–g) except for one example where a homologous amide was used to obtain six-membered lactam 138h.

The catalytic system Cu(OAc)²/bipyridine (bpy) was applied to perform the oxidative cyclization of unsaturated oximes 139 accompanied by the introduction of an amino group with the formation of isoxazolines 141 and cyclic nitrones 142 (Scheme 47) [136].

The best results were obtained using DTBP or aerial oxygen as an oxidant. Aliphatic, aromatic, and heteroaromatic amines 140, both primary and secondary, are applicable for this reaction.

The reaction of TEMPO with β,γ- and γ,δ-unsaturated oximes 143 leads to substituted unsaturated isoxazolines 144 and cyclic nitrones 145, respectively (Scheme 48) [137]. Presumably, the C-centered radical formed after 5-exo-trig cyclization of the oxime radical recombines with TEMPO. The resulting adduct undergoes β-elimination of TEMPOH with the formation of final unsaturated compounds. The intermediate coupling product of the C-centered radical and TEMPO was observed when the reaction was carried out at lower temperature (80 °C).

Isoxazolines 144 were synthesized from β,γ-unsaturated aryl oximes (R¹ = Ar) with electron-donating (examples 144a–c) and moderately electron-withdrawing substituents (example 144d). The reaction of γ,δ-unsaturated aliphatic and aryl oximes with TEMPO yielded cyclic nitrones (products 145a–j). The majority of the synthesized cyclic nitrones were disubstituted in α-position to the C=NO group (145a–l,b–j), the unsubstituted nitrone 145g was synthesized in the lowest yield. In the case of 145j–145j’ the dehydrogenation of the side chain attached to C=NO fragment was observed.

![Scheme 46: TBHP-mediated oxidative cascade cyclization of β,γ-unsaturated oximes and unsaturated N-arylamides.](image-url)
Scheme 47: Copper-catalyzed oxidative cyclization of unsaturated oximes with the introduction of an amino group.

Scheme 48: TEMPO-mediated oxidative cyclization of unsaturated oximes followed by elimination.
Under the action of the TMSCF$_3$/trichloroisocyanuric acid/TCCA/CuOAc/CsF system $\beta,\gamma$-unsaturated oximes $146$ undergo oxidative cyclization to form substituted isoxazolines $147$ with a trifluoromethyl group (Scheme 49) [138]. The authors note that the presence of 1,10-phenanthroline is necessary to stabilize the intermediate CuCF$_3$.

Aromatic oximes with various electron-donating and electron-withdrawing substituents afford cyclization products in high yields (products $147a$–$d$). In addition to aryl oximes, benzyl and tert-butyl substituted oximes (products $147e,f$) were successfully used.

Oxidative cyclization of unsaturated oximes with the formation of isoxazolines or cyclic nitrones and the introduction of a nitrile group was achieved using the CuCN/NNNN'-pentamethyldiethylenetriamine (PMDETA)/TBHP system (Scheme 50) [139]. Other aliphatic amine ligands (NNNN'-tetramethylethlenediamine and 1,1,4,7,10,10-hexamethyltriethylenetetramine) showed moderate results and aromatic
nitrogen-containing ligands (2,2’-bipyridine and phenanthroline) were even less efficient for the synthesis of target the isoxazolines.

Both aromatic (products 149a,b,e) and aliphatic oximes (products 149c,d) undergo this transformation with the formation of isoxazolines. Oximes with a disubstituted double bond also enter this reaction (product 149e). The 5-exo-trig cyclization of γ,δ-unsaturated oximes under these conditions leads to substituted cyclic nitrones (products 150a–d).

A similar cyanation reaction was realized using TMSCN as a cyanide source and the oxidative system Cu(NO$_3$)$_2$/K$_2$S$_2$O$_8$ (Scheme 51) [140].

Both aromatic (products 152a–c) and aliphatic (products 152d–f) β,γ-unsaturated oximes undergo this transformation. Oximes substituted at the α-position (R$_1$, R$_2$ = Me), as well as oximes having a disubstituted double bond, also give cyclization products with good yields (products 152b,c).

The interaction of β,γ-unsaturated oximes 153 with sodium sulfinitates in the presence of copper(II) acetate leads to substituted isoxazolines 154 with the sulfonyl group (Scheme 52) [141].

Oximes, mainly aromatic ones, cyclize effectively (products 154a–d,f–h). Examples 154b–d demonstrate the effect of substituents in the phenyl ring of oxime (R$^1$) on the product yield. When a substituent is present in the ortho-position of the benzene ring, the yield decreases compared to para- and meta-substituted substrates. In addition to sodium aryl sulfinites, sodium methane sulfinate was used for the synthesis of product 154h in good yield. The presence of an electron-withdrawing group in the aromatic ring of sulfinate decreases the yield (product 154f compared to product 154a), and the presence of an electron-donating group increases the yield of isoxazoline (product 154g compared to product 154a).

Another approach to the synthesis of isoxazolines with a sulfonyl moiety is the reaction of unsaturated oximes 155 with sulfonyl hydrazides 156 under the action of TBHP and a catalytic amount of iodine (Scheme 53) [142].

Aromatic β,γ-unsaturated oximes containing both electron-donating and electron-withdrawing substituents in the phenyl ring give cyclization products in good yields (products 157a–c). Aliphatic oximes also enter this reaction effectively (products...
157d,e). Under the same reaction conditions aromatic γ,δ-unsaturated oximes give sulfonyl-substituted cyclic nitrones (products 158a–d).

Another example of the oxidative cyclization of oximes with the formation of an isoxazoline ring and C–S bond is the reaction of aromatic β,γ-unsaturated oximes 159 with the FeCl₃/KSCN/K₂S₂O₈ system that affords thiocyanates 160 (Scheme 54) [143].

Under the action of PIDA (PhI(OAc)₂), β,γ-unsaturated oximes 161 react with diselenides and disulfides 162 to form isoxazolines 163 (Scheme 55) [144].

Various disulfides of both aromatic (products 163a,b,d–f) and aliphatic nature (product 163c) were used. The presence of electron-donating substituents in the para-position of the phenyl ring of disulfide increases the yield of the isoxazoline (example 163b), compared to electron-withdrawing substituents (exam-
Like disulfides, diselenides lead to the corresponding Se-containing isoxazolines 163g, h in high yields. β,γ-Unsaturated tosyl hydrazones react with disulfides and diselenides analogously to oximes [144].

Under the action of the PIDA/NaOAc/HOAlkyl system, β,γ-unsaturated aryl oximes 164 undergo oxidative cyclization with the formation of substituted isoxazolines 165 containing an ether group (Scheme 56) [145]. The alcohol acts both as a solvent and as a reagent in this transformation.

Most of the tested oximes contained a tetrasubstituted C=C double bond (examples 165a–i) but the product of cyclization involving a disubstituted C=C double bond was also reported (example 165j). The ionic pathway was proposed for the formation of the products 165 as the most plausible but free radical pathway involving iminoxyl radicals was not ruled out [145]. In both considered reaction pathways the final stage was the formation of ether C–O bond by a nucleophilic attack of the intermediate carbocation by the alcohol.

Under the action of the related oxidative system PhI(OAc)$_2$/DABCO in THF, cyclization of allyl-substituted oximes 166 without the introduction of a functional group at the terminal carbon atom was realized (Scheme 57) [146].

The authors proposed a mechanism in which a 5-exo-trig cyclization of the iminoxyl radical formed from oxime 166 under the
action of the PhI(OAc)$_2$/DABCO system produced the primary C-centered radical. Presumably, the final product 167 is formed via hydrogen atom transfer from THF to the intermediate C-centered radical [146]. This process is similar to the cobalt-catalyzed cyclization in the presence of 1,4-cyclohexadiene as hydrogen atom donor discussed above (Scheme 35) [125].

The reaction of unsaturated oximes 168 with ethynylbenziodoxolone (EBX) reagents 169 in the presence of copper(II) triflate leads to substituted isoxazolines 170 and cyclic nitrones 171 with an alkyne group (Scheme 58) [147].

Various aromatic and some aliphatic oximes were tested as substrates (products 170a–l). The yield of the reaction product is weakly dependent on the substituent in the benzene ring (examples 170a,b,c). Oximes unsubstituted in α-position (R$_2$ = R$_3$ = H) also undergo this transformation (example 170d). Both various aromatic substituents (products 170e–g) and alkyl substituents (example 170h) may be present in the EBX reagent at R$_6$. Under the same reaction conditions, γ,δ-unsaturated oximes give substituted cyclic nitrones (products 171a–e).

The oxidative cyclization of C-glycoside ketoximes 172 was carried out under the action of catalytic amounts of TEMPO under oxygen (1 atm) with the formation of substituted isoxazoles 173 (Scheme 59) [148].

The proposed mechanism includes the oxidation of starting oxime to iminoxyl radical by TEMPO, 5-endo-trig cyclization and oxidative aromatization with the formation of the final isoxazole 173 [148].

Under the action of the Selectfluor/AgOAc system, β,γ-unsaturated oximes 174 undergo oxidative cyclization with the formation of fluoroalkyl isoxazolines 175 (Scheme 60) [149].

The majority of products were fluoromethyl isoxazolines (examples 175a–g). The exception was the product 175h, which was synthesized from oxime with an endocyclic C=C double bond. The proposed mechanism includes the 5-exo-trig cyclization of the intermediate iminoxyl radical followed by fluorination of the formed C-centered radical. The 5-exo-trig radical cyclization was confirmed by a control experiment with the addition of TEMPO as a trapping reagent for the C-centered radical. The TEMPO-adduct was obtained in 75% yield [149].

The formation of haloalkyl isoxazolines 177 was achieved upon the interaction of β,γ-unsaturated oximes 176 with t-BuONO and selected halogenating agents (Scheme 61) [150].

Both aromatic (products 177a–e,g) and aliphatic oximes (products 177f,g) successfully participate in this transformation. The yield of the reaction product weakly depends on the substituents in the aromatic ring of oxime (products 177a,b,c). Oximes with a disubstituted double bond (R$_4$ = Me, product 177d), as well as α-unsubstituted or α-disubstituted oximes (R$_2$ = R$_3$ = H or Me) also produce isoxazolines with high yields (products 177a–d and 177e–h). Bromination and iodination of some substrates using CBr$_4$ and CHI$_3$ instead of AlCl$_3$ were carried out (products 177i–l). The radical mechanism including 5-exo-trig cyclization of the intermediate iminoxyl radical was supported by a radical trapping control experiment with TEMPO and a radical clock experiment with cyclopropane ring opening [150].
**Scheme 58:** Oxidative cyclization-alkynylation of unsaturated oximes.

**Scheme 59:** TEMPO-mediated oxidative cyclization of C-glycoside ketoximes to C-glycosymethylisoxazoles.
A similar transformation of \( \beta,\gamma \)-unsaturated oximes 178 into haloalkylisoxazolines 179 was realized employing the catalytic system halogenating reagent/Cu(OTf)\(_2\)/phenanthroline/Na\(_2\)CO\(_3\) (Scheme 62) [151]. The authors proposed an analogous mechanism involving 5-exo-trig cyclization of intermediate iminoxyl radical.

Under the action of the PhI(OAc)\(_2\)/TEMPO system on halogen-substituted unsaturated oximes 180, halomethyl isoxazoles 181 and cyclic nitrones 182 are formed (Scheme 63) [152]. The authors note that the reaction proceeds through the 5-exo-trig cyclization of iminoxyl radical followed by a 1,2-halogen radical shift.
Scheme 62: Cyclization of $\beta,\gamma$-unsaturated oximes into haloalkyl isoxazolines under the action of the halogenating reagent/Cu(OTf)$_2$/phenantroline/Na$_2$CO$_3$ system.

Scheme 63: Synthesis of haloalkyl isoxazoles and cyclic nitrones via oxidative cyclization and 1,2-halogen shift.

Chloro-, bromo-, and iodosubstituted $\beta,\gamma$-unsaturated oximes enter the reaction effectively (products 181a–e). When $\gamma,\delta$-unsaturated oximes were used instead of $\beta,\gamma$-unsaturated oximes, the formation of cyclic nitrones with a TEMPO fragment (products 182a–e) was observed. Chloro- and bromo-substituted $\gamma,\delta$-unsaturated oximes were applicable for this transformation, but iodo-substituted $\gamma,\delta$-oximes gave target products 182 only in trace amounts.

The TEMPO-mediated electrochemical cyclization of biaryl oximes 183 leads to $N$-heteroaromatic $N$-oxides 184 or $N$-heteroaromatic compounds 185 depending on a cathode ma-
The proposed mechanism includes the formation of an iminoxyl radical followed by its cyclization onto the phenyl ring and oxidative rearomatization to N-heteroaromatic N-oxide 184. In the case of Pt-cathode it is the final product, and in the case of Pb-cathode it is reduced to the N-heteroaromatic compound 185 [153].

The rare example of the intramolecular cyclization of iminoxyl radicals involving a triple bond is shown in Scheme 65 [154]. In the presence of catalytic amounts of copper(II) salt and molecular oxygen (1 atm) 5-exo-dig cyclization of unsaturated oximes 186 occurs.

Various β,γ-unsaturated oximes 186 react with the formation of substituted isoxazoline α-ketols 187a–d. Using an oxime with a terminal triple bond, isoxazolone 187e was obtained. Under analogous conditions γ,δ-unsaturated oximes afford cyclic nitrones 188a–e in moderate yields.

Under irradiation of blue LED (450-455 nm) of the mixture of oximes 189, sulfonyl hydrazides 190, silver(I) oxide and disodium salt of eosin Y in an inert atmosphere sulfones 191 are formed [155] (Scheme 66). In this case, hydrosulfonfyllation of the C=C double bond takes place instead of typical cyclization of β,γ-unsaturated oximes 189 to isoxazolines.

Both aromatic (examples 191a–c, e–h) and aliphatic (example 191d) sulfonyl hydrazides undergo this reaction successfully. Good yields were obtained with both electron-donating (example 191b) and electron-withdrawing substituents (example 191e) in the aromatic ring of sulfonyl hydrazide. The introduction of a methyl group in the β-position relative to the oxime group leads to a decrease in yield (example 191h).

The authors proposed a radical mechanism in which the addition of the sulfonyl radical to the double C=C bond, is followed by 1,5-HAT from the oxime hydroxy group to the carbon radical. An experiment with a deuterium label on the hydroxy group of oxime confirmed this hypothesis: the deuterium was found at the β-carbon atom of the product [155].

Examples of synthesized compounds, yields:

- **184a**, 97% (moderate)
- **184b**, 73% (>20:1)
- **184c**, 66% (>20:1)
- **184d**, 75%
- **185a**, 85%
- **185b**, 92% (>20:1)
- **185c**, 82%
- **185d**, 54%

Scheme 64: Electrochemical oxidative cyclization of diaryl oximes.
The combination of Koser’s reagent 193 and Fe(acac)2 as catalyst was used for the synthesis of sulfonates 194 from unsaturated oximes 192 [156] (Scheme 67).

In the presence of a substituent in the ortho-position of the benzene ring, the yield of the product decreases remarkably, probably due to steric hindrances during the reaction (example 194d). Aliphatic oximes (example 194e) and oximes with a disubstituted C=C bond (example 194f) undergo this transformation with moderate yields. Free-radical mechanism involving the cyclization of the iminoxyl radical was confirmed by trapping of a C-centered radical, TEMPO-adduct 194a’ was iso-
lated in 92% yield instead of \(194a\) when TEMPO was added to the reaction mixture. The authors also showed that the presence of water in the system can lead to the formation of alcohol instead of sulfonate [156].

Under ultrasound irradiation \(\beta,\gamma\)-unsaturated oximes \(195\) react with \(\text{KHSO}_3\cdot0.5\text{KHSO}_4\cdot0.5\text{K}_2\text{SO}_4\) and diselenides \(196\) to form isoxazolines \(197\) [157] (Scheme 68).

The introduction of electron-withdrawing substituents (example \(197b\)) into the benzene ring of diselenide leads to an increase in yield compared to the case of electron-donating substituents (example \(197c\)). Dialkyl diselenides also undergo this transformation (example \(197d\)). Similar yields of the target product \(197a\) were obtained when the reaction mixture was heated by microwave irradiation or an oil bath instead of sonication. However, control experiments allowed to suggest that...
the reaction can proceed by both radical and ionic mechanisms. The authors proposed that under ultrasonic stimulation the mechanism is predominantly radical, while under microwave conditions the ionic mechanism becomes significant [157].

**Conclusion**

An unprecedented renaissance in the chemistry of oxime radicals has been observed during the last years. Over the past decade, a diverse pattern of methods for oxidative cyclization involving oxime radicals was developed. 5-Exo-trig cyclization of oxime radicals generated from unsaturated oximes can now be considered as a robust and general approach to the synthesis of functionalized isoxazolines, isoxazoles, and cyclic nitrones. Moreover, iminoxyl radicals were demonstrated to be promising intermediates for cyclizations involving C(sp^3)–H bonds, C≡C triple bonds and aromatic π-systems.

The majority of iminoxyl-radical-mediated synthetic transformations are intramolecular reactions, presumably due to the lack of stability of the oxime radicals. Nevertheless, examples of intermolecular cross-dehydrogenative C–O couplings employing oxime radicals as the key intermediates emerged recently.

The areas of the future development of the chemistry of iminoxyl radicals include: (1) the development of selective intermolecular reactions with oxime radicals; (2) the development of new oxidative systems for the generation of oxime radicals, including electrochemical and photochemical approaches; (3) the search for new stable oxime radicals which can be used as reagents for organic synthesis and other applications.

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