Review of the synthesis of acyclic and cyclic oxime ethers

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and S. Morteza F. Farniad

Oxime ethers have attracted much attention due to their potential biological activities and wide variety of synthetic applications. Developing more efficient methods for the synthesis of oxime ethers has been the subject of numerous of papers in recent years. This review surveys literature methods for the synthesis of acyclic and cyclic oxime ethers.

1. Introduction

The name oxime ether is an abbreviation of oxy-imine ether. As one of the prominent medicinal motifs, the oxime ether group is featured in a large number of pharmaceutically important compounds and is widely applied in a variety of pesticides. 1,2 For example, oxiconazole 1 (Fig. 1), with the brand name oxistat, is an antifungal drug marketed worldwide for the treatment of skin infections. 3–5 Fluvoxamine maleate 2 is used for treating obsessive compulsive disorder. 6–9 A series of novel thioaryl naphthylmethanone oxime ether analogs 3 exhibit excellent anticancer activities towards various cancer cells. 10 Roxithromycin 4 is a semi-synthetic macrolide antibiotic which was introduced in the 1980s, and is used to treat infections caused by bacteria. 11–14 Fenpyroximate 5 is a pesticide with oxime ether motif, this compound is very active against acaricide and widely used around the world. 15–17 Wang’s group showed that a series of benzyolphenylureas 6 have excellent larvicidal activities against oriental armyworm. 18 These representative examples show that the oxime ether group offers very attractive options for drug design of various pharmacological agents, due to their relative ease of synthesis and their impressive medicinal chemistry applications.

Oxime ethers are important and versatile intermediates in organic synthesis. These compounds were successfully transformed into amines, 19–24 1,2-aminoalcohols, 25 α- and β-amino acids, 26,27 hydroxylamines, 28–41 nitriles, 42–44 pyridines, 45–50 benzo furanes, 51–53 indoles, 54,55 pyroles, 56,57 pyrazines, 58 isoquinolines, 59,60 isoazoles, 61–64 8-hydroxytetrahydroquinolines, 65

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Morteza Abdoli was born in Miyandoab, Iran, in 1987. He received his B.Sc. from the Payame Noor University in 2010. He pursued his postgraduate study at the same university under the supervision of Dr H. Saeidian and obtained his M.Sc. (1st class honor) degree in 2013. Currently he is doing his doctoral research on synthesis and reactions of sulfur-containing compounds under the supervision of Prof. Dr A. Kakanejadifard and Dr H. Saeidian, at Lorestan University.
aminocyclopentitols, aziridines, fluorenones, diarylmethylidenefluorenone and phenanthrene. Furthermore, oxime ether is an elegant directing-group for activation of aromatic or vinylic C–H bonds for construction of new C–O, C–X and C–N bonds by metal-catalyzed cross-coupling reactions. Considering the widespread synthetic applications and biological activities of oxime ethers and extensive attention on these compounds in recent years, especially in the field of metal-catalyzed cross-coupling reactions, there is an urgent need for a review article on the synthesis of titled compounds. In this review, we describe variety of methods for the synthesis of oxime ethers. We have classified these synthetic reactions based on the type (acyclic and cyclic), the starting materials (e.g. synthesis from oxime and alkyl halides, oxime and aryl halides, and oxime and epoxides) and the reactions type (e.g. cross-coupling reactions between oxime and arylboronic acids, and oxime and epoxides) and the reactions type (e.g. cross-coupling reactions between oxime and aryloboronic acids, and 1,3-dipolar cycloaddition of nitrile oxides to carbon–carbon double bonds). The most detailed discussion is focused on the synthesis of acyclic oxime ethers. It should be noted that we have not discussed synthesis of six membered cyclic oxime ethers, since it has recently been described in another publication. To summarize, the main methods for the synthesis of acyclic and cyclic (four and five membered cycles) oxime ethers is depicted in Fig. 2.

2. Synthesis of acyclic oxime ethers

2.1. From oximes and alkyl halides

The best-known method for synthesis of acyclic oxime ethers is the reaction of oximes with alkyl- and aryl halides (Scheme 1). A safe method for the preparation of oximes involves reaction of carbonyl compounds (aldehydes and ketones) with hydroxyl amines (Scheme 2). This type of reaction was introduced by Schiff in 1864 and nowadays is the best choice for the synthesis of titled compounds.

The alkylation of the oxygen atom of oxime moiety with alkyl halides has been performed using various base, such as sodium hydride, sodium hydroxide, potassium hydroxide, and potassium carbonate. As well as, the system Na/ketone alcohol has also been utilized. Using potassium carbonate as base and acetonitrile as solvent clearly accelerated the alkylation of the oxime moiety compared to other bases/solvents, and the desired products were synthesized in good yields (Table 1).

Recently, an excellent method for generation of oxime ethers from oximes and epichlorohydrin have been reported by Cerra and co-workers using acetone/water/K2CO3 system.

Synthesis of oxime ethers from oximes and halides in the presence of phase transfer catalysis has been the subject of a number of papers. However, preparation of oxime ethers using this method resulted in poor to moderate yields of desired products. In 2009, Li and co-workers reported the benzoylation of oximes by combination of phase transfer catalysis and ultrasound irradiation. They tested several catalysts and solvents, and the system NaOH/benzyltrimethylammonium chloride/H2O was found to be superior. Under optimized conditions, the reaction tolerates both electron-donating and electron-withdrawing groups in the phenyl ring of oxime and gave corresponding products in good to excellent yields (Table 2). To compare the yields of product 3a (78%) to the same reaction which was...
reported under toluene/H₂O/NaOH/TBAB by Wang et al. (76.6%), it can be concluded that the latter system is superior, due to the former method which was carried out under ultrasound irradiation.

The attempts to synthesis of O-propargylated oximes 16a,b with treatment of oximes 14 with propargyl bromide 15 in the presence of KOH in DMSO/H₂O 9 : 1 resulted in products with higher than 86% yield (Scheme 4).

2.2. From oximes and aryl halides
In 2007, the successful metal catalyzed cross-coupling of aryl halides with oximes have been reported by Maitra et al. Oximes 17a,b were found to undergo O–H arylation with various iodo- and bromoarenes 18 in the presence of CuI as catalyst,
Cs₂CO₃ as base, Na- or K-tartrate as chelating agent, and 1,10-phenanthroline as a ligand in toluene or DMSO and gave corresponding O-aryl oximes 19a,b in moderate to good yields (Scheme 5). Some important information of the reactions are listed below: (1) the reactions will not work with 1-iodo-4-methoxybenzene; (2) aldoximes compare to ketoximes gave lower yield of desired products; (3) the protocol is efficient for intramolecular cross-coupling reactions but not for intermolecular version; and (4) haloarenes bearing electron-withdrawing substituents gave higher yield of products than haloarenes with electron-donating substituents.

Following this work, Buchwald research team in 2010, has investigated the O-arylation of ethyl acetohydroximate 20 with aryl chlorides, bromides, and iodides using (allylPdCl)₂ as catalyst, t-BuBrettPhos 22 or t-BuXPhos 23 as ligand in toluene at 65 °C. This method has several advantages such as good to excellent yields, short reaction time and broad substrate scope (Scheme 6). Key to the success of this reaction was the use of bulky biarylphosphine ligands 22 and 23, which promote C–O reductive elimination under relatively mild conditions.

With the objective of designing a comprehensive protocol to O-arylation of oximes, the scope of electrophilic partners was extended to diaryliodonium salts under transition-metal-free cross-coupling conditions. Several bases and solvents were tested and the system t-BuOK/DMF at room temperature was found to be superior. Under optimized conditions, both

### Table 1

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Cs₂CO₃ as base, Na- or K-tartrate as chelating agent, and 1,10-phenanthroline as a ligand in toluene or DMSO and gave corresponding O-aryl oximes 19a,b in moderate to good yields (Scheme 5).
electron-donating and electron-withdrawing groups on either coupling partners were well tolerated and gave desired products in good to high yields (40–96% for 26 examples). The use of Cs$_2$CO$_3$ as base and acetonitrile as solvent provided the same products in comparable yields (Scheme 7).

2.3. From oximes and arylboronic acids

In 2009, Meyer and Feng research teams independently reported the copper catalyzed O-arylation of oximes with arylboronic acids. The reaction was undertaken at room temperature using Cu(OAc)$_2$ as catalyst and pyridine as base in DCE. This method afforded O-arylated acetophenone oximes in moderate yields with various meta and para-substituent arylboronic acids (Scheme 8). It should be noted that using polystyrene supported copper catalyst in aforementioned reaction gave relatively better results.

Recently, Bora and co-workers investigated the efficiency of different bases in titled reaction and showed the system Cu(OAc)$_2$/Cs$_2$CO$_3$ in DMF gave corresponding O-arylated acetophenone oximes in higher yields than previous methods. Coumarins were found to undergo efficient O-arylation with various arylboronic acids in the presence of CuCl$_2$ as catalyst and NEt$_3$ as base (Scheme 9). This system shows good reactivity for a range of arylboronic acids. Para electron-rich aryl boronic acids and phenylboronic acid worked well under these reaction conditions. Meta- and para electron-deficient arylboronic acids gave coupling products in moderate to good yields.

To develop an efficient protocol for the synthesis of O-aryl oximes via cross-coupling reaction, Mulla and co-workers have investigated the O-arylation of acetophenone oximes with arylboronic acids in the presence of recyclable and heterogeneous copper fluorapatite (CuFAP) catalyst in methanol, and good to high yields of desired products was observed (61–96% for 30 examples). A plausible catalytic cycle is depicted in Fig. 4.

2.4. From oximes and olefins

Preparation of oxime ethers from oximes and olefins has been the subject of a number of papers. One of the earliest report of the successful formation of allylic oxime ethers via Michael addition of oximes have been published by Akcamur and Kellenz in 1987 (Scheme 10). This reaction showed an attractive route for the conversion of oximes into oxime ethers in good to high yields at mild reaction conditions and short reaction times.

Meshram et al. expanded the efficiency of this method by using the Triton B as a nonmetallic organic base. All of aliphatic and aromatic oximes with both electron-donating and electron-withdrawing substituents in treatment with $\alpha,\beta$-unsaturated nitriles or $\alpha,\beta$-unsaturated esters gave corresponding oxime ethers in good to high yields (Scheme 11).
A robust process for the synthesis of allylic oxime ethers involves the reaction of oximes with p-allyl metal complexes. Treatment of oximes with a,b-unsaturated acetates in the presence of Pd(PPh₃)₄ as catalyst gave allylic oxime ethers in good to high yields (Table 3). Interestingly, when the reaction was carried out under the [IrCl(cod)]₂/Et₂Zn/THF system, instead of oxime ethers, the branched oxime ethers was observed as desired products in good to high yields (Scheme 12).

Previously, this result has been reported by Takeuchi in allylic amination. With the objective of designing a comprehensive protocol to high regio- and enantioselective synthesis of the branched oxime ethers, the scope of electrophilic partners were extended to a,b-unsaturated phosphates (Scheme 13). The [IrCl(cod)]₂/pybox-H₂O/CH₂Cl₂ system was found to be optimal for this reaction. Notably, the system works well for the allylic substitution of phosphates with amines.

Oximes underwent Baylis–Hillman reaction with allyl bromides in the presence of sodium hydride and triethyl amine, and the regioselective products were formed in good yields. The mechanism of the reaction involves the deprotonation of oxime by NaH to generate oxime anion and subsequent reaction of B with intermediate A (derived from the allyl bromide and NEt₃) via path a and path b to produce regioselective oxime ethers and (Scheme 14).

Jia and co-workers established an efficient protocol for radical cation promoted O-alkylation of oximes with N-vinyl-lactams. They showed treatment of oximes with N-vinyl-lactam in the presence of tris(4-bromophenyl)aminium hexachloroantimonate (TBPA+ cSbCl₆) as an initiator and 2,6-di-tert-butyl-pyridine as base afforded corresponding O-alkylated oxime ethers in high to excellent yields at ambient temperature (Scheme 15). Generally, both electron-donating and electron-withdrawing groups in the phenyl ring periphery of oximes were well tolerated.

The use of cerium(IV) ammonium nitrate (10 mol%) in acetonitrile provided the same products in comparable yields (73–95% for 15 examples).

Direct generation of oxime ethers from allylic C(sp³)–H bonds and oxime without a metal catalyst was reported by Bao and co-workers. They tested several oxidants and solvents, and the 2,3-dichloro-5,6-dicyanoquinone (DDQ)/CH₂Cl₂ system was found to be superior. Mechanistically, the reaction involves hydride transfer from the allylic position to DDQ. Good yields were achieved in reaction with both oximes involving electron-donating and electron-withdrawing substituents (Scheme 16).

Following this work, the same group in 2013, extended their methodology to C–O bond formation between oximes and isochroman.

2.5. From oxime and epoxides

The nucleophilic substitution reaction of oxygen atom of oximes with epoxides for preparation of oxime ethers has been the subject of a number of papers. However, in primary reports a mixture of oxime ethers and nitrones have been examined for this reaction in various conditions, such as base and solvent types, etc.

In 2008, Soltani reported a highly efficient regio- and diastereoselective synthetic methodology for preparation of β-hydroxy oxime O-ethers via the O-alkylation of oxime anions

**Scheme 9** CuCl₂-promoted O-arylation of (hydroxyimino)ethylcumarin 31 with arylboronic acids.

**Scheme 10** Formation of allylic oxime ethers 36 via Michael addition of oximes 35.

Fig. 4 Plausible catalytic cycle for O-arylation of acetophenone oximes with arylboronic acids.
with epoxides. This aqueous-mediated reaction carried out in the presence of KOH as base and gave corresponding E-oxime ethers in good to high yields (Scheme 17). Interestingly, in contrast to previous methods, using this methodology gave no products derived from reaction of the nitrogen atom of oximes on epoxides, even in trace amounts. Recently, Crich’s research team performed the same reaction in DMF with a series of epoxides and acetophenone oximes.

2.6. From oximes and alcohols

One-pot O-alkylation of oximes with alcohols employing Ph₃P/CCl₄/DBU/TBAI catalyst system in refluxing acetonitrile was reported in 2010. A wide range of alcohols were efficiently transformed into oximes in good yields (Scheme 18). It is worth to note that the methodology showed excellent regioselectivity for generation of Z-isomers. The selectivity of this method was demonstrated via a competitive reaction of a mixture consisting of primary and secondary alcohols. The results showed high selectivity for the O-alkylation of oximes using the primary alcohols rather than the secondary analogues.

2.7. From oximes and aryl nitro compounds

Baumann demonstrated that oximes can be converted to oxime ethers by treatment with 4-substituted aryl nitro compounds in sodium methoxide at room temperature. The reaction tolerates aryl oximes and gave corresponding O-aryl oximes in moderate yields, but extension of the reaction to aldoximes and alkyl ketoximes bearing a hydrogen at α-position was failed (Table 4).

2.8. From oximes and Morita–Baylis–Hillman (MBH) carbonates

An excellent method for generation of oxime ethers is the reaction of oximes with Morita–Baylis–Hillman (MBH) carbonates. Chen and co-workers showed acetophenone oxime and MBH carbonates in the presence of commercially available hydroquinidine 1,4-phthalazinediyldiether 72 as a chiral catalyst at 50 °C gave O-allylic alkylated acetophenone oxime in moderate to excellent yields with high enantiomeric excess.
2.9. From condensation of carbonyl compounds with aminooxy groups

As it is mentioned in Section 2.2, oximes are syntheses from the reaction of carbonyl compounds (ketones or aldehydes) with hydroxyl amines, in a two-step reaction (Scheme 20, route a). The reaction of carbonyl compounds with aminooxy groups is a one-step route for the synthesis of titled compounds (Scheme 20, route b).\(^ {139,140}\) However the synthesis of aminooxy groups requires another step.\(^ {145-147}\)

Synthesis of oxime ethers \(\text{via}\) condensation of carbonyl compounds with aminooxy groups are well described in the literature.\(^ {145-156}\) This reaction is usually conducted in various solvents and in the presence of an acid, which influence the yield of oxime ethers. Usual solvents which have been used are water,\(^ {145-147}\) methanol,\(^ {148,149}\) ethanol,\(^ {150}\) aqueous tetrahydrofuran,\(^ {146,147}\) chloroform,\(^ {151}\) and common acids include hydrochloric acid,\(^ {147,148}\) acetic acid,\(^ {148,150}\) piperazine-\(N,N'\)-bis(2-ethanesulfonic acid),\(^ {152}\) pyridinium \(\text{para}\)-toluenesulfonate.\(^ {153}\)

The system MeOH/aqueous HCl gave excellent yield for the synthesis of \(O\)-aryl oximes at room temperature (Scheme 21).\(^ {149}\) The reaction of carbonyl compounds with benzyl hydroxylamines in absolute ethanol without catalyst gave superior result for preparation of \(O\)-benzyl oximes (Scheme 22).\(^ {153}\) Indeed, the reaction rate is accelerated by using acid catalyst in aforementioned reactions. The acidic conditions are not compatible with biological systems and can damage biomolecules.\(^ {157}\) In 2008, to overcome this difficulty, Dirksen and Dawson introduced aniline as an efficient catalyst for condensation of carbonyl group with aminooxy group at neutral pH.\(^ {158}\) Crisalli and Kool\(^ {159}\) reported anthranilic acids and 3,5-diaminobenzoic acid (Fig. 5) as superior catalysts for oxime ether formation under neutral pH conditions. Using the same catalysts, Palandoken and co-workers synthesized sugar oxime ether surfactant 85 in moderate to excellent yields (Scheme 23).\(^ {149}\)

2.10. Miscellaneous

Reaction of oximes with acetylenes is a potential route for synthesis of novel oxime ethers. The example for this type of reaction have been reported by Tighelaar-Lutjeboer \(\text{et al.}\)\(^ {\text{143-144}}\) It is shown that, the reaction of oximes \(86\) with ethoxyethyne \(87\) at 75–90°C rise to the formation of di-oxime ethers \(88\) in moderate yields (Scheme 24). However the products are unstable.
compounds and in the case of aldoximes, corresponding di-oxime ethers were decomposed immediately.\textsuperscript{160}

Reaction of oximes with cyclic peroxides is an efficient route for the synthesis of oxime ethers. 1-Methoxy-2,3,7-trioxabicyclo[2.2.1]hept-5-enes 90, derived from photooxygenation of 2-methoxyfurans 89, were converted into oxime ether hydroperoxides 93 by treatment of 4-nitrobenzaldehyde oxime 92. The reaction proceed via the oxygen nucleophilic trapping reaction of intermediate carbonyl oxides 91. However, in the most cases the products are unstable and rearrange into N-hydroperoxy alkynitrones (Table 5).\textsuperscript{163}

Treatment of methylglyoximes 94 with trialkyl orthoformate 95 resulted in the formation of a mixture of corresponding bis-

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme16}
\caption{Formation of oxime ether with oxime 58 and 1,3-diphenylpropene 59.}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme17}
\caption{β-Hydroxy oxime O-ethers synthesized by the ring opening of epoxides with oximes.}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme18}
\caption{One-pot O-alkylation of oximes via alcohols in refluxing acetonitrile.}
\end{scheme}
Table 4  Synthesis of oxime ethers 69 via treatment of oximes 67 with 68

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Scheme 19  Asymmetric  O-allylic alkylation of acetophenone oxime 70 with MBH carbonates 71.

Scheme 20  General route for synthesis of oxime ethers.

Scheme 21  Preparation of oxime ethers 7Aa–7He in the presence of aqueous HCl as catalyst in MeOH.

Scheme 22  Preparation of oxime ethers 78 and 79 in EtOH without catalyst.

Fig. 5  Chemical structure of anthranilic acids and 3,5-diaminobenzoic acid.

Scheme 23  Sugar oxime ether surfactant (SOESurf) synthesis.

Scheme 24  Addition of oximes to ethoxyethyne.
O-alkylated oximes 96a in moderate yields and mono-O-alkylated analogues 96b in poor yields (Scheme 25).

### 3. Synthesis of four membered cyclic oxime ethers (4\(H\)-1,2-oxazete)

Generally, 4\(H\)-1,2-oxazetes and their highly strained derivatives are known as reactive intermediates in thermal and photochemical reactions. These compounds undergo facile fragmentation to carbonyl compounds and nitrile oxides (Scheme 26).\(^{163-168}\)

However, there are some reports for preparation of relatively stable derivatives of 4\(H\)-1,2-oxazetes. Wieser and Berndt reported two different routes for generation of two family of stable 4\(H\)-1,2-oxazete derivatives:\(^{169,170}\) (1) treatment of 3-tert-butyl-1-chloro-4,4-dimethylpent-1,2-diene 97 with \(\text{N}_2\text{O}_4\) readily gave crystalline oxazete N-oxide 99. This compound undergoes partial transformation to 100 and stable 101 (Scheme 27); (2) elimination of H-X from oximes 102 and 103, followed by intramolecular cyclization of unsaturated nitro intermediates 104 and 105, gave corresponding stable oxazete 106 and 107 in good to excellent yields (Scheme 28).

Corkins and co-workers reported an efficient protocol for the synthesis of stable 3-tert-butyl-4,4-bis-(methylthio)-4\(H\)-1,2-oxazete 109 (Scheme 29). Addition of \(m\)-chloroperbenzoic acid to oxime 108 in \(\text{CH}_2\text{Cl}_2\) leads directly to oxazete 109 after 16 hours at 0 °C in 90% yield.\(^{171}\)

### Table 5 Reaction of oximes with cyclic peroxides

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<th>(\text{R}^3)</th>
<th>Yield (%)</th>
</tr>
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<td>(\text{H})</td>
<td>(\text{Ph})</td>
<td>26</td>
</tr>
<tr>
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<td>(\text{H})</td>
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<td>(\text{CO}_2\text{Me})</td>
<td>(\text{H})</td>
<td>4-OMe–Ph</td>
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<td>(\text{H})</td>
<td>4-Br–Ph</td>
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<td>(\text{Me})</td>
<td>(\text{Ph})</td>
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</tr>
<tr>
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<td>(\text{Ph})</td>
<td>(\text{Ph})</td>
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</tr>
<tr>
<td>9</td>
<td>(\text{CO}_2\text{Me})</td>
<td>(\text{CO}_2\text{Me})</td>
<td>(\text{Ph})</td>
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4. Synthesis of five-membered cyclic oxime ethers

4.1. 1,3-Dipolar cycloaddition of nitrile oxides to carbon–carbon double bonds

The 1,3-dipolar cycloaddition of nitrile oxides to C=C bond is a fundamental tool and straightforward route to isoxazoline rings.\textsuperscript{172–228} The same reaction with carbon–carbon triple bonds is one of the most efficient protocols for generation of isoxazoles.\textsuperscript{229–233} Hydroxamic acid chlorides 110 are the commonly used precursors for generation of nitride oxides 112. Nitro compounds can also serve as convenient nitride oxides precursors.\textsuperscript{211–220} However, nitro compounds are commonly used for the synthesis of isoxazoline N-oxides.\textsuperscript{233–246} The conversion of 110 to 112 and 1,3-dipolar cycloaddition of 112 to alkenes 111 usually carried out in a one-pot reaction sequence (Scheme 30a). This reaction is conducted with various bases, such as NaHCO\textsubscript{3},\textsuperscript{172,173} KHCO\textsubscript{3},\textsuperscript{174} AgNO\textsubscript{3} (ref. 173) and NEt\textsubscript{3}.\textsuperscript{174–180} The sequence in Scheme 30b shows how hydroxamic acid chlorides can be converted into nitride oxides.

It is noteworthy that nitride oxide can be generated \textit{in situ} from the corresponding aldoxime by chlorination with bleach and then dehydrochlorination.\textsuperscript{221–228} The impressive methods have been developed for direct use of aldoximes instead of hydroxamic acid chlorides as nitride oxides precursor. In these methods, generation of nitride oxides and then a 1,3-dipolar cycloaddition to alkenes performed in single step using hypervalent iodine as oxidants.\textsuperscript{247–253} Recently, a more robust protocol for the synthesis of 4,5-dihydroisoxazoles was introduced by Yoshimura \textit{et al.} They have exemplified the direct reaction of aldoximes with variety of alkenes in the presence of iodoarenes as catalyst and oxone as a terminal oxidant (Scheme 31). The similar reaction with alkynes gave the corresponding isoxazoles.\textsuperscript{241} In 2014, Yan improved the...
efficiency of Yoshimura protocol by using potassium chloride/oxone as oxidation system in water.\textsuperscript{252}

Following Yan, Bharate and co-workers have investigated the same reaction using DBU/NCS/DMF system and achieved better results.\textsuperscript{253}

Recently, Wang and co-workers reported a beautiful three-component reaction for the synthesis of 4,5-dihydroisoxazole rings with secondary amine at C-5 position (Scheme 32). Most of the applied secondary amines failed to participate in the reaction, whereas, pyrrolidine was well tolerated. Mechanistically, the reaction involves: (1) the formation of nitrile oxide by hydroxamic acid chloride \textsuperscript{110} and dialkylamine \textsuperscript{114}; (2) condensation of aldehyde \textsuperscript{115} with pyrrolidine to give enamine; (3) 1,3-dipolar cycloaddition of nitrile oxides to carbon–carbon double bonds of enamine to produce 4,5-dihydroisoxazole rings \textsuperscript{116} containing dialkylamino moiety at C-5 position in good to excellent yields (77–99% for 18 examples).\textsuperscript{254}

### 4.2. Intramolecular metal catalyzed cross-coupling reactions

Metal catalyzed cross-coupling reaction is a straightforward route for formation of \(=\text{N}–\text{O}–\text{R}\) linkage via reaction of oximes \(=\text{N}–\text{OH}\) with an electrophilic partner \(\text{X}–\text{R}\). The intramolecular version of this reaction is a highly effective protocol for generation of isoxazolines. The first example, was reported by Coffen and co-workers in 1984.\textsuperscript{255} Coupling of iodo oxime \textsuperscript{117} with propargyl alcohol using \(\text{Pd(PPh}_3\text{)_2Cl}_2/\text{CuI/\text{Et}_3\text{N/CH}_2\text{Cl}_2}\) system, resulted in isoxazoline \textsuperscript{118} in 95% yield (Scheme 33).

Subsequently Wailes reported the same cyclization using \(\text{CuI/\text{Et}_3\text{N/CH}_2\text{Cl}_2}\) system and obtained isoxazoline \textsuperscript{120} in 80% yield. Two other examples utilizing this protocol is depicted in Scheme 34.\textsuperscript{107}

### 4.3. Miscellaneous

In 2010, Knight and co-workers were able to take advantage of a new route for the synthesis of isoxazolines in their efforts to develop novel cyclization of O-propargylic hydroxylamines. It was shown that hydroxylamines \textsuperscript{121} in treatment with 10% w/w silver nitrate/silica gel as a catalyst in \(\text{CH}_2\text{Cl}_2\) at 20 \(^\circ\)C underwent intramolecular hydroamination to give corresponding isoxazolines \textsuperscript{122} in good to excellent yields (Scheme 35).\textsuperscript{256}
Regioselective intramolecular carbon–hydrogen bond oxygenation at β-position of oxime moiety with activation of hydroxyl group is the newest route for generation of isoaxolizines which have been introduced by Chiba et al. in 2013. The cyclization has been conducted using 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) in DMF and gave desired products in moderate to high yields (Scheme 36). Mechanistically, it involves: (1) the reaction of oxime moiety with TEMPO to give iminoxyl radical; and (2) 1,5-H radical shift of iminoxyl radical result in the formation of corresponding isoaxolizine.257

5. Conclusion

This review provides concise overview on the synthesis of acyclic and cyclic oxime ethers. The new strategies in this area such as synthesis of oxime ethers via metal-catalyzed cross-coupling reactions and intramolecular carbon–hydrogen bond oxygenation have further potential for development. We believed that the highly versatile and novel procedures for the synthesis of oxime ethers will be attainable in the near future.

References


