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Review on synthesis of acyclic and cyclic oxime ethers

Zohreh Mirjafary⁴, Morteza Abdoli⁵, Hamid Saeidian⁶, Ali Kakanejadifard⁷, S. Morteza F. Farnia⁸

a) Department of Chemistry, Tehran Science and Research Branch, Islamic Azad University, Tehran, Iran
b) Department of Chemistry, Faculty of Science, Lorestan University, Khorramabad, Iran
c) Department of Science, Payame Noor University (PNU), PO Box: 19395-4697, Tehran, Iran
d) Department of Chemistry, University of Tehran, Tehran, Iran

Abstract: Oxime ethers have attracted much attention due to their potential biological activities and wide variety of synthetic applications. Developing more efficient methods for 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.

Keywords: oxime ether, isoxazoline, nitrile oxide, 1,3-dipolar cycloaddition, oxazete

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 variety pesticides.¹² For example, oxiconazole ¹ (Figure 1) with brand name of 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 naphthylmethaneoxime 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 benzoylphenylureas 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, 1,2-aminoalcohols, α- and β-amino acids, hydroxylamines, nitriles, pyridines, benzofuranes, indoles, pyroles, pyrazines, isoquinolines, hydroxytetrahydroquinolines, aminocyclopentitols, aziridines, fluorenones, diarylmethylidenefluorene 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 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 Figure 2.

**Figure 2.** The main methods for synthesis of acyclic and cyclic oxime ethers.

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).76-95

![Scheme 1. Synthesis of oxime ethers from oximes and alkyl(aryl) halides.](image)

A safe method for the preparation of oximes involves reaction of carbonyl compounds (aldehydes and ketones) with hydroxyl amines (Scheme 2).96-101 This type of reaction was introduced by Schiff102 in 1864 and nowadays is the best choice for the synthesis of titled compounds.103-105

![Scheme 2. Synthesis of Oximes via condensation of carbonyl compound with hydroxyl amine.](image)
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/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).

**Table 1.** Synthesis of oxime ether 8 from oxime 7 and methyl 2-chloroacetate in the presence of K₂CO₃ in MeCN

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>K₂CO₃</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1,4-Dioxan</td>
<td>K₂CO₃</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>K₂CO₃</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>K₂CO₃</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Acetonitrile</td>
<td>K₂CO₃</td>
<td>8</td>
<td>70</td>
</tr>
</tbody>
</table>

Recently, an excellent method for generation of oxime ethers 10a,b from oximes 9a,b and epichlorhydrin have been reported by Cerra and co-workers using acetone/water/K₂CO₃ system (Scheme 3).

![Scheme 3. Synthesis of oxime ethers 10a,b from oximes 9a,b and epichlorhydrin](image)

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 benzylation of oximes by combination of phase transfer catalysis and
ultrasound irradiation. They tested several catalysts and solvents, and the system NaOH/benzyldimethyltetradecylammonium chloride/H\textsubscript{2}O 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).\textsuperscript{91} To compare the yields of product 3a (78%) to the same reaction which was reported under toluene/H\textsubscript{2}O/NaOH/TBAB by Wang et al (76.6%),\textsuperscript{86} it can be concluded that the latter system is superior, due to the former method which was carried out under ultrasound irradiation.

**Table 2.** The reaction of oxime 11 with benzyl bromide in aqueous media catalyzed by benzyldimethyltetradecylammoniumchloride in combination with ultrasound irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Time (min)</th>
<th>Product</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-OMe-Ph</td>
<td>H</td>
<td>30</td>
<td>13a</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4-OMe-Ph</td>
<td>H</td>
<td>35</td>
<td>13b</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>2-N02-Ph</td>
<td>H</td>
<td>30</td>
<td>13c</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>2,4-di-Cl-Ph</td>
<td>H</td>
<td>30</td>
<td>13d</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>2-Cl-Ph</td>
<td>H</td>
<td>20</td>
<td>13e</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl-Ph</td>
<td>H</td>
<td>50</td>
<td>13f</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>4-Cl-Ph</td>
<td>H</td>
<td>20</td>
<td>13g</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
<td>30</td>
<td>13h</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>4-Cl-Ph</td>
<td>CH3</td>
<td>60</td>
<td>13i</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>4-OMe-Ph</td>
<td>CH3</td>
<td>60</td>
<td>13j</td>
<td>60</td>
</tr>
</tbody>
</table>

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/H\textsubscript{2}O 9:1 resulted in products with higher than 86% yield (Scheme 4).\textsuperscript{106}

**Scheme 4.** \(O\)-propargylation of oximes 14a,b
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.\textsuperscript{107} Oximes 17a,b were found to undergo O-H arylation with various iodo- and bromoarenes 18 in the presence of CuI as catalyst, Cs\textsubscript{2}CO\textsubscript{3} 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)\textsubscript{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.\textsuperscript{108}

Scheme 5. a) Cross-coupling of ketoximes with haloarenes/ catalytic CuI in refluxing toluene; b) cross-coupling of aldoximes with haloarenes/ catalytic CuI in DMSO at 30 °C.
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 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).

Scheme 7. The $O$-arylation of oximes 1a-e with diaryliodonium salts

### 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.$^{111,112}$ 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 29 in moderate yields with various meta and para-substituent arylboronic acids 28 (Scheme 8). It should be noted that using polystyrene supported copper catalyst 30 (Figure 3) in aforementioned reaction gave relatively better results.$^{113}$
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 33 in higher yields than previous methods. Coumarins 31 were found to undergo efficient $O$-arylation with various arylboronic acids 32 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 Figure 4.\textsuperscript{116}

![Figure 4. Plausible catalytic cycle for O-arylation of acetophenone oximes with arylboronic acids](image)

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 Kollenz in 1987 (Scheme 10).\textsuperscript{117} 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.

![Scheme 10. Formation of allylic oxime ethers 36 via Michael addition of oximes 35.](image)

Meshram\textit{ et al.} expanded the efficiency of this method by using the Triton B as a nonmetallic organic base. All of aliphatic and aromatic oximes 37 with both electron-donating and electron-withdrawing substituents in treatment with α,β-unsaturated nitriles 38 or α,β-unsaturated esters 40 gave corresponding oxime ethers in good to high yields (Scheme 11).\textsuperscript{118}
A robust process for the synthesis of allylic oxime ethers involves the reaction of oximes with π-allyl metal complexes. Treatment of oximes 42 with α,β-unsaturated acetates 43 in the presence of Pd(PPh₃)₄ as catalyst gave allylic oxime ethers 44 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 44, the branched oxime ethers 45 was observed as desired products in good to high yields (Scheme 12). Previously, this result has been reported by Takeuchi in allylic amination.

Table 3. Palladium-Catalyzed Reaction of 42A–D with Acetates 43a–e

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime</th>
<th>Acetate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42A</td>
<td>43b</td>
<td>44Ab</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>42A</td>
<td>43c</td>
<td>45Ac</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>42A</td>
<td>43d</td>
<td>45Ad</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>42A</td>
<td>43e</td>
<td>45 Ae</td>
<td>73</td>
</tr>
</tbody>
</table>

A: R¹ = Ph, R² = H  
B: R¹ = Ph, R² = Ph  
C: R¹ = H, R² = (CH₂)₅  
D: R¹ = CO₂Me, R² = H  

a: Ar = Ph  
b: Ar = 4-F₃C-Ph  
c: Ar = 4-OMe-Ph  
d: Ar = 1-Naph  
e: Ar = 2-Naph
Reactions were carried out with 42A–D (1 equiv) and 43a–e (1.5 equiv) in the presence of Pd(PPh₃)₄ (6 mol%) and K₂CO₃ (1 equiv) in CH₂Cl₂.

Scheme 12. Iridium-catalyzed reaction of 42A–D with acetates 43a–e.

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 α,β-unsaturated phosphates (Scheme 13). The [IrCl(cod)]₂/pybox 48/ Ba(OH)₂·H₂O/CH₂Cl₂ system was found to be optimal for this reaction. Notably, the system works well for the allylic substitution of phosphates with amines.¹²⁰,¹²³

Scheme 13. Iridium-pybox-catalyzed allylic substitution with oximes

Oximes 50 underwent Baylis-Hillman reaction with allyl bromides 51 in the presence of sodium hydride and triethyl amine, and the regioselective products 52 were formed in good yields. The mechanism of the reaction involves the deprotonation of oxime by NaH to generate oxime anion B and subsequent reaction of B with intermediate A (derived from the allyl bromide 51 and NEt₃) via path a and path b to produce regioselective oxime ethers 52 and 53 (Scheme 14).¹²⁴
Scheme 14. The proposed mechanism for the formation of 52 via Baylis-Hillman reaction of 50 with 51.

Jia and co-workers established an efficient protocol for radical cation promoted $O$-alkylation of oximes with $N$-vinylactams. They showed treatment of oximes 54 with $N$-vinylactam 55 in the presence of tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{+}$ SbCl$_6^-$) as an initiator and 2,6-di-tertbutyl-pyridine 56 as base afforded corresponding $O$-alkylated oxime ethers 57 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).

Scheme 15. TBPA$^{+}$ SbCl$_6^-$ initiated addition of oxime 54 with $N$-vinylactam 55

Direct generation of oxime ethers from allylic C(sp$^3$)-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)/CH$_2$Cl$_2$ 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.

![Diagram](image)

**Scheme 16.** Formation of oxime ether with oxime 58 and 1,3-diphenylpropene 59

### 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 63 via the O-alkylation of oxime anions 61 with epoxides 62. This aqueous-mediated reaction carried out in the presence of KOH as base and gave corresponding E-oxime ethers 63 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 Ph$_3$P/CCl$_4$/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.\textsuperscript{136}
2.7. From oximes and aryl nitro compounds

Bauman demonstrated that oximes can be converted to oxime ethers by treatment with 4-substituted aryl nitro compounds 68 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). 137

**Table 4.** Synthesis of oxime ethers 69 via treatment of oximes 67 with 68.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-C(H₂)₃-</td>
<td>CO₂Me</td>
<td>7</td>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>PhCO</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-C(H₂)₃-</td>
<td>CN</td>
<td>22</td>
<td>8</td>
<td>Ph</td>
<td>Ph</td>
<td>CHO</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>CO₂Me</td>
<td>12</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Me</td>
<td>CN</td>
<td>24</td>
<td>10</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>CO₂Me</td>
<td>28</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>CN</td>
<td>61</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 70 and MBH carbonates 71 in the presence of commercially available hydroquinidine 1,4-phthalazinediyli diether 72 as a chiral catalyst at 50 °C gave O-allylic alkylated acetophenone oxime 73 in moderate to excellent yields with high enantiomeric excess (Scheme 19). However, the MBH carbonates bearing alkyl-substitution were incompatible in this type of reaction. 138
2.9. From condensation of carbonyl compounds with aminooxy groups

As it is mentioned in section 2.2., oximes are synthesized 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). However the synthesis of aminooxy groups requires another step.

Scheme 20. General route for synthesis of oxime ethers

Synthesis of oxime ethers via condensation of carbonyl compounds with aminooxy groups are well described in the literature. 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, methanol, ethanol, aqueous tetrahydrofuran, chloroform and common acids include hydrochloric acid, acetic acid, piperazine-\(\text{N},\text{N}'\)-bis(2-ethanesulfonic acid), pyridinium para-toluenesulfonate.
The system MeOH/aqueous HCl gave excellent yield for the synthesis of \( O \)-aryl oximes at room temperature (Scheme 21).\(^{148}\) The reaction of carbonyl compounds with benzyl hydroxyamines in absolute ethanol without catalyst gave superior result for preparation of \( O \)-benzyl oximes (Scheme 22).\(^{153}\)

\[
\begin{align*}
| R^1 | & \text{H, } o\text{-Me, } m\text{-Me, } p\text{-Me, } m\text{-OMe, } o\text{-Br, } m\text{-Br, } p\text{-Br} \\
| R^2 | & \text{H, Me, } -(\text{CH}_2)_n \\
| R^3 | & \text{Me, Et, Ph, } o\text{-OH-Ph, } o\text{-OMe-Ph, } o\text{-Br-Ph, } o\text{-NO}_2\text{-Ph, } m\text{-OH-Ph, } m\text{-OMe-Ph, } m\text{-Br-Ph, } m\text{-NO}_2\text{-Ph, } p\text{-OH-Ph, } p\text{-OMe-Ph, } p\text{-Br-Ph, } p\text{-NO}_2\text{-Ph} \\
\end{align*}
\]

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

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 aminoxy group at neutral pH.\(^{158}\) Crisalli and Kool\(^{159}\) reported anthranilic acids and 3,5-diaminobenzoic acid (Figure 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).\(^{149}\)

\[
\begin{align*}
&\text{Figure 5. Chemical structure of anthranilic acids and 3,5-diaminobenzoic acid.}
\end{align*}
\]
Scheme 23. Sugar oxime ether surfactant (SOESurf) synthesis.

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 Tigchelaar-Lutjeboer et al. 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 effi cient route for the synthesis of oxime ethers. 1-Methoxy-2,3,7-trioxa-bicyclo[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 alkynitrone (Table 5).\textsuperscript{161}
Table 5. Reaction of oximes with cyclic peroxides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂Me</td>
<td>H</td>
<td>Ph</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>CO₂Me</td>
<td>H</td>
<td>4-Me-Ph</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>CO₂Me</td>
<td>H</td>
<td>4-OMe-Ph</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>CO₂Me</td>
<td>H</td>
<td>4-Br-Ph</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
<td>H</td>
<td>Ph</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>CO₂Me</td>
<td>Me</td>
<td>Ph</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>Ph</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>CO₂Me</td>
<td>CO₂Me</td>
<td>Ph</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment of methylglyoximes 94 with trialkyl orthoformate 95 resulted in the formation of a mixture of corresponding bis-O-alkylated oximes 96a in moderate yields and mono-O-alkylated analogues 96b in poor yields (Scheme 25).\(^\text{162}\)

**Scheme 25.** Synthesis of \(O\)-dialkoxydimethyloximes from oximes and trialkyl orthoformate

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

Generally, 4H-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).\(^\text{163-168}\)

**Scheme 26.** Fragmentation of 4H-1,2-oxazetes to carbonyl compounds and nitrile oxides.

However, there are some reports for preparation of relatively stable derivatives of 4H-1,2-oxazetes. Wiese and Berndt reported two different routes for generation of two family of stable 4H-1,2-oxazete derivatives\(^\text{169,170}\): 1) treatment of 3-\textit{tert}-butyl-1-chloro-4,4-
dimethylpenta-1,2-diene 97 with N₂O₄ 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).

Scheme 27. Synthesis of stable oxazetes from 3-t-butyl-1-chloro-4,4-dimethylpenta-1,2-diene

Corkins and co-workers reported an efficient protocol for the synthesis of stable 3-tert-butyl-4,4-bis-(methylthio)-4H-1,2-oxazete 109 (Scheme 29). Addition of m-chloroperbenzoic acid to oxime 108 in CH₂Cl₂ leads directly to oxazete 109 after 16 hours at 0 °C in 90% yield.

Scheme 28. Synthesis of stable oxazetes from oximes.


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. The same reaction with carbon-carbon triple bonds is one of the most efficient protocols for generation of isoxazoles. Hydroxamic acid chlorides are the commonly used precursors for generation of nitrile oxides. Nitro compounds can also serve as convenient nitrile oxides precursors. However, nitro compounds are commonly used for the synthesis of isoxazoline N-oxides. The conversion of to and 1,3-dipolar cycloaddition of to alkenes usually carried out in a one-pot reaction sequence (Scheme 30a). This reaction is conducted with various bases, such as NaHCO$_3$, KHCO$_3$, AgNO$_3$ and NEt$_3$. The sequence in Scheme 30b shows how hydroxamic acid chlorides can be converted into nitrile oxides.

It is noteworthy that nitrile oxide can be generated in situ from the corresponding aldoxime by chlorination with bleach and then dehydrochlorination.

![Scheme 30](image)

Scheme 30. a) 1,3-dipolar cycloaddition of nitrile oxides to C=C bond; b) The mechanism of generation of nitrile oxides from hydroxamic acid chlorides.

The impressive methods have been developed for direct use of aldoximes instead of hydroxamic acid chlorides as nitrile oxides precursor. In these methods, generation of nitrile oxides and then a 1,3-dipolar cycloaddition to alkenes performed in single step using hypervalent iodine as oxidants. Recently, a more robust protocol for the synthesis of 4,5-dihydroisoxazoles was introduced by Yoshimura 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. In 2014, Yan improved the efficiency of Yoshimura protocol by using potassium chloride/oxone as oxidation system in water.
Following Yan, Bharate and co-workers have investigated the same reaction using DBU/NCS/DMF system and achieved better results.\(^{253}\)

\[
\text{Alkene} + \text{Aldoxime (1.2 equiv.)} \rightarrow \text{3,5-Me}_2\text{C}_6\text{H}_3\text{I} (0.2 \text{ equiv.) oxone (3 equiv.) r.t., 24 h}} \rightarrow \text{4,5-dihydroisoxazole (17-99\%)}
\]

\[\begin{align*}
\text{Scheme 31. Iodine catalyzed generation of nitrile oxides from oximes and their cycloaddition with alkenes.}
\end{align*}\]

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 110 and dialkylamine 114; 2) condensation of aldehyde 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 116 containing dialkylamino moiety at C-5 position in good to excellent yields (77-99\% for 18 examples).\(^{254}\)

\[\begin{align*}
\text{Scheme 32. Tri-component reaction for the synthesis of 4,5-dihydroisoxazole rings.}
\end{align*}\]

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

Metal catalyzed cross-coupling reaction is a straightforward route for formation of =N-O-R linkage \textit{via} reaction of oximes (=N-OH) with an electrophilic partner (X-R). The
intramolecular version of this reaction is a highly effective protocol for generation of isoaxazolines. The first example, was reported by Coffen and co-workers in 1984.\textsuperscript{255} Coupling of iodoxime 117 with propargyl alcohol using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}/CuI/Et\textsubscript{3}N/CH\textsubscript{2}Cl\textsubscript{2} system, resulted in isoaxazoline 118 in 95% yield (Scheme 33).

![Scheme 33. Synthesis of isoaxazoline 118 from iodo oxime 117 via metal-catalyzed cross-coupling reaction.](image)

Subsequently Wailes reported the same cyclization using CuI/Et\textsubscript{3}N/CH\textsubscript{2}Cl\textsubscript{2} system and obtained isoaxazoline 120 in 80% yield. Two other examples utilizing this protocol is depicted in Scheme 34.\textsuperscript{107}

![Scheme 34. Intramolecular cross-coupling of ketoximes 119a,b with catalytic Cul in refluxing toluene.](image)

4.3. Miscellaneous

In 2010, Knight and co-workers were able to take advantage of a new route for the synthesis of isoaxazolines in their efforts to develop novel cyclization of O-propargylic hydroxylamines. It was shown that hydroxylamines 121 in treatment with 10% w/w silver nitrate/silica gel as a catalyst in CH\textsubscript{2}Cl\textsubscript{2} at 20 °C underwent intramolecular hydroamination to give corresponding isoaxazolines 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 isoxazolines 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 isoxazoline. 

Scheme 36. TEMPO-mediated C-H oxygenation of oximes 123.

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 has 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

197. J. Desai, C. Desai and K. Desai, 
196. P. de la Cruz, E. Espíldora, J. García, A. de la Hoz, F. Langa, N. Martín and L. Sánchez, 
188. Y. J. Chung, E. J. Ryu, G. Keum and K. B. Han, 
190. S. A. Popov, A. Y. Denisov, Y. V. Gatilov, I. Y. Bagryanskaya and A. V. Tkachev, 
194. P. Conti, C. Dallanoce, M. De Amici, C. De Michelis and K. N. Klotz, 
192. T. Bosanac, J. Yang and C. S. Wilcox, 
189. L. N. Zhang, J. Chung, T. Costello, I. Valvis, P. Ma, S. Kauffman and R. Ward, 
187. B. H. Kim, Y. J. Chung, G. Keum, J. Kim and K. Kim, 
181. C. Balsamini, G. Spadoni, A. Bedini, G. Tarzia, M. Lanfranchi and M. Pellinghelli, 
186. M. J. Kurth and M. J. Rodriguez, 
185. R. Shotter, D. Sesardić and P. Wright, 
184. K. Eichinger, M. Wokurek, B. Zauner and M. R. Rostami, 
183. T. Shah and V. Desai, 
201. S. Kobayashi and R. Akiyama, 
207. P. N. Zhang, X. N. Li, H. Chen, Y. N. Li and R. Wang, 

180. C. Dallanoce, P. Magrone, P. Bazza, G. Grazioso, L. Rizzi, L. Riganti, C. Gotti, F. Clementi, K. Frydenvang and M. De Amici, 
199. S. Castellano, D. Kuck, M. Viviano, J. Yoo, F. López-N-Vallejo, P. Conti, L. Tamborini, A. Pinto, J. L. Medina-N-Vallejo, P. Conti, 
204. M. S. Meier and M. Poplawska, 

192. M. L. Quan, C. D. Ellis, A. Y. Liauw, R. S. Alexander, R. M. Knabb, G. Lam, M. R. Wright, P. C. Wong and R. R. Wexler, 

199. S. A. Mousa and J. Wityak, 


180. C. Dallanoce, P. Magrone, P. Bazza, G. Grazioso, L. Rizzi, L. Riganti, C. Gotti, F. Clementi, K. Frydenvang and M. De Amici, 
199. S. Castellano, D. Kuck, M. Viviano, J. Yoo, F. López-N-Vallejo, P. Conti, L. Tamborini, A. Pinto, J. L. Medina-N-Vallejo, P. Conti, 
204. M. S. Meier and M. Poplawska, 


Review on synthesis of acyclic and cyclic oxime ethers

Zohreh Mirjafary, Morteza Abdoli, Hamid Saeidian, Ali Kakanejadifard, Sayed Morteza Farnia

\[
\begin{align*}
R_1 & \quad N \quad R_2 \\
R_1, R_2 = \text{alkyl, aryl} \\
R & \quad = \text{alkyl, aryl}
\end{align*}
\]

- Ketone or aldehydes + hydroxylamines
- Oximes + alkyl halides
- Oximes + aryl halides
- Oximes + aryloboronic acids
- Oxime + alcohols
- Oximes + olefines
- Oxime + Morita-Baylis-Hillman carbonates

- M-chloroperbenzoic acid + oximes
- Intramolecular carbon-hydrogen bond oxygenation
- Cyclization of \(O\)-propargylic hydroxylamines
- Intramolecular metal catalyzed cross-coupling reactions

- Aldoximes + olefines
- Hydroxamic acid chlorides + olefines
- Nitrile oxides + olefines

\(3\text{-tert-butyl-1-chloro-4,4-dimethylpenta-1,2-diene} + N_2O_4\)