Synthesis of Oxazoline and Oxazole Derivatives by Hypervalent-
Iodine-Mediated Oxidative Cycloaddition Reactions

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1 Introduction

Heterocyclic structural blocks can be found in various
biologically active natural and non-natural products and
are widely employed in the synthesis of pharmaceuticals,
agrochemicals, dyes, and polymeric materials.1–8 Numerous
reviews and books on the synthesis and properties of het-
erocyclic compounds have been published.9–23 Five-mem-
bered heterocycles with nitrogen and oxygen atoms in the
ring, such as oxazolines, oxazoles, isoxazolines, and isoxaz-
oles, are particularly important in life-saving drugs, bioac-
tive natural compounds, products of the pharmaceutical in-
dustry, synthetic building blocks, and as metal catalyst li-
gands.10–12,14,16,24–29 Therefore, the reactions forming these
heterocyclic rings and those introducing functional groups
into these rings represent a hot topic, and numerous im-
portant synthetic procedures based on these reactions have
been developed. The known procedures often have serious
drawbacks, such as harsh reaction conditions, long reaction
times, limited substrate scope, or poor yields. In particular,
numerous synthetic procedures utilizing metal reagents
have been developed for efficient and mild syntheses of ox-
azoline and oxazole derivatives.10–12,14,16,23–28,30 However,
some of the metal reagents are expensive, toxic, and rare;
therefore, new synthetic methodologies under metal-free
and mild conditions have been extensively studied.

Organohypervalent iodine compounds are known as
non-toxic and environmentally friendly reagents that are
utilized in many green and sustainable organic reactions.31–
33 The reactivity pattern of hypervalent iodine compounds
is similar to that of transition-metal reagents.34–40 Therefore,
hypervalent iodine compounds have found wide applica-
tion as efficient oxidative reagents and ligand transfer re-
agents in many reactions.41–49 In fact, numerous oxidative
reactions, benzyne-mediated reactions, and new bond-
forming reactions, such as carbon–carbon, carbon–hetero-
atom, or hetero–heteroatom bonds, have been accom-
plished using hypervalent iodine reagents under metal-free
conditions. In particular, these reagents have been used for
various ring construction reactions. Numerous classes of
heterocyclic compounds have been prepared under mild

Abstract

Organohypervalent iodine reagents are widely used for the
preparation of various oxazolines, oxazoles, isoxazolines, and isoxazoles.
In the formation of these heterocyclic compounds, hypervalent iodine
species can serve as the activating reagents for various substrates, as
well as the heteroatom donor reagents. In recent research, both chemi-
cal and electrochemical approaches toward generation of hypervalent
iodine species have been utilized. The in situ generated active species
can react with appropriate substrates to give the corresponding hetero-
cyclic products. In this short review, we summarize the hypervalent-
iiodine-mediated preparation of oxazolines, oxazoles, isoxazolines, and
isoxazoles starting from various substrates.

1 Introduction

1 Synthesis of Oxazolines
2 Synthesis of Oxazoles
3 Synthesis of Isoxazolines
4 Synthesis of Isoxazoles
5 Conclusion

Key words hypervalent iodine, oxidative cyclization, oxidative cyclo-
addition, oxazoles, oxazolines, isoxazolines, isoxazolines
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Akio Saito (second left) received his M.S. (1999) and Ph.D. (2003) degrees from the Tokyo University of Pharmacy and Life Sciences. In 2001, he joined Professor Takeo Taguchi’s group as a research associate at the same university. From 2005, he worked as an assistant professor with Professor Yui Hanzawa at the Showa Pharmaceutical University. In 2012, he moved to his present position as an Associate Professor at the Tokyo University of Agriculture and Technology.

Mekhman S. Yusubov (second right) was born in Georgia. His M.S. (1985), Ph.D. (1991), and Doctor of Chemical Sciences (1998) degrees were earned at Tomsk Polytechnic University in the laboratory of Professor Victor D. Filimonov. He is currently a professor at Tomsk Polytechnic University. Since 1994 he has been involved in intense international collaborative research programs with leading research laboratories in South Korea, Germany, and the United Kingdom. In 2004 he started joint research in the area of hypervalent iodine chemistry with Professor Viktor V. Zhdankin at the University of Minnesota Duluth. His main research interests are in the fields of the chemistry of natural products and hypervalent iodine reagents. Professor Yusubov has published over 100 scientific papers.

Viktor V. Zhdankin (right) was born in Ekaterinburg, Russian Federation. His M.S. (1978), Ph.D. (1981), and Doctor of Chemical Sciences (1986) degrees were earned at Moscow State University. He moved to the University of Utah in 1990, where he worked for three years as an Instructor of Organic Chemistry and Senior Research Associate with Professor Peter J. Stang. In 1993, he joined the faculty of the University of Minnesota Duluth, where he is currently a professor of chemistry. He has published about 300 research papers, has given over a hundred research presentations in many countries, has edited several books, and co-authored the Handbook of Heterocyclic Chemistry (3rd Edition, 2010) with Professors A. R. Katritzky, C. A. Ramsden, and J. A. Joule, and authored a book on Hypervalent Iodine Chemistry (Wiley, 2013). His main research interests are in the areas of synthetic and mechanistic organic chemistry of hypervalent main-group elements and organofluorine chemistry. In 2011 he received the National Award of the American Chemical Society for Creative Research & Applications of Iodine Chemistry.

2 Synthesis of Oxazolines

The oxazoline nucleus is present in many heterocyclic compounds that have found important applications in medicinal and materials chemistry. Numerous synthetic strategies for the construction of the oxazoline ring have been explored. Particularly important are synthetic approaches using hypervalent iodine reagents, such as (diacetoxyiodo)arenes, iodosylarenes, (difluoroiodo)arenes, in situ generated iodine(III) species, or iodoniylides. This section covers synthetic methodologies for the preparation of various oxazoline derivatives from appropriate substrates using hypervalent iodine species.

The reactions of N-allylamides or N-propargylamides with hypervalent iodine species result in an oxidative cyclization leading to oxazolines with various substituents. For example, Harned’s group reported the oxidative cyclization reaction of N-allylamides 5 using (diacetoxyiodo)benzene in the presence of BF$_3$·Et$_2$O and acetic acid to give the respective oxazoline compounds 6 in moderate to good yields (Scheme 1). The cyclization of chiral N-allylamides afforded the corresponding oxazolines in good yields and diastereoselectivities.

A similar (diacetoxyiodo)benzene-mediated cyclization of N-allylamides 7 in the presence of HF-Py, instead of BF$_3$·Et$_2$O and acetic acid, gave the respective acetoxyethyl-containing oxazolines 8 in moderate to good yields (Scheme 2). Incidentally, when using substituted N-(E)-allylamides under the same conditions, the reaction resulted in endo-cyclization due to the carbocation stability to afford the oxazine products instead of oxazolines.
The reaction of N-allylamides 9 using (diacetoxyiodo)benzene and bis/tosylimide gave 5-amino-oxazolines 10 in moderate to good yields (Scheme 3). The authors proposed that either PhI(OAc)(NTs₂) or PhI(NTs₂)₂ was generated in situ from (diacetoxyiodo)benzene and bis/tosylimide, and the generated active species reacted with the olefin followed by intramolecular cyclization to produce the final oxazoline products.

Recently, synthetic procedures for the preparation of 5-fluoromethyl-2-oxazolines from N-allylamides using in situ generated hypervalent iodine species in the presence of a fluorine source have been developed. For example, Gilmour and co-workers reported the fluorocyclization reaction of imidate compounds leading to the respective oxazolines in good yields. The obtained products could be converted into β-amino alcohols by acidic hydrolysis.

The combination of (diacetoxyiodo)benzene and trimethylsilyl iodide promotes intramolecular iodocyclization of N-allylamides 13 leading to the respective 5-iodomethyl-2-oxazoline compounds 14 in good yields (Scheme 5). Trimethylsilyl iodide serves as the iodine source and the activating reagent. When using trimethylsilyl bromide or trimethylsilyl chloride as the halogen source, the respective 5-bromo- or 5-chloromethyl-2-oxazoline compounds were also obtained in good yields. A similar iodocyclization reaction of N-propargylamides 15 using (diacetoxyiodo)benzene with lithium iodide instead of trimethylsilyl iodide gave the corresponding (E)-5-iodomethylene-2-oxazoline compounds 16 in good yields. This reaction probably involved initial generation of acetyl hypoiodite (AcOI) from (diacetoxyiodo)benzene and lithium iodide. Nagib and co-workers reported the use of acetyl hypoiodite generated from (diacetoxyiodo)benzene and elemental iodine in the cyclization reaction of imidate compounds leading to the respective oxazolines in good yields. The obtained products could be converted into β-amino alcohols by acidic hydrolysis.

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of a hypervalent iodine species from stoichiometric amounts of 4-iodotoluene by electrochemical oxidation in the presence of Et₃N·5HF. This active species promotes the oxidative cyclization of N-allylamides 19 to give the respective 5-fluoromethyl-2-oxazolines 20 in moderate yields.71

Moran and co-workers reported the catalytic hypervalent iodine species mediated oxidative cyclization of various N-allylamides 21 or N-propargylamides 23 to give the respective oxazoline compounds 22 and 24 in moderate to good yields (Scheme 7).66,69 The same group also reported that when using β-amidoketones as substrates oxazoline products were obtained in moderate to good yields. A mechanistic investigation of the cyclization of N-allylamides with in situ generated hypervalent iodine reagents by DFT calculations and kinetic experiments was reported. It was found that the rate-limiting step in this reaction was the substrate cyclization.70 Recently, a similar oxidative cyclization of N-allylamides using electrochemically generated hypervalent iodine species was developed by Francke and co-workers.72

An efficient synthetic procedure for the preparation of bicyclic oxazoline compounds mediated by hypervalent iodine reagents has been developed. For example, Zhang and co-workers reported the reaction of N-cyclohexenylamides 25 and 27 with an iodosylarene in the presence of BF₃·Et₂O to give the respective monofluorinated ring-fused oxazolines 26 and 28 in moderate to excellent yields (Scheme 8).56 BF₃·Et₂O served as the Lewis acid and also as a fluorine source in this reaction. The authors proposed that the mechanism of the introduction of fluorine into products 26 and 28 involved initial formation of carbocyclic intermediates from the N-cyclohexenylamides.

In another example of the preparation of oxazoline compounds, an iodonium ylide was used for the construction of a bicyclic oxazoline (Scheme 9). Koser and co-workers reported the preparation of ring-fused 4-oxazoline 31 from cyclic iodonium ylide 29 and phenyl isocyanate (30).74

Our group has also reported the cycloaddition reaction of carbodiimides 33 mediated by cyclic iodonium ylide 32 to give the corresponding ring-fused 4-oxazolines 34 in moderate to good yields.75

3 Synthesis of Oxazoles

Oxazoles have found numerous applications in chemical and biomedical sciences, and many synthetic procedures for oxazole ring formation from various precursors have been developed.10,16,28,30,51 Particularly important are methods based on the use of hypervalent iodine reagents such as (diacetoxiiodo)benzene,76–87 [bis(trifluoroacetoxy)iodo]benzene,79,88–91 iodosylbenzene,92–95 [hydroxy(tosyloxy)iodo]arenes,96–99 recyclable iodine(III) compounds,100 in situ generated iodine(III) species,101,102 and iodonium ylides,107–113

The hypervalent-iodine(III)-mediated cyclization of N-propargylamides represents a useful synthetic methodology for the construction of the oxazole nucleus. This methodology is applicable to the synthesis of substituted oxazoles bearing nitrogen-containing groups,76 fluoride,101,102 iodide,95 or acetoxo groups.77 For example, the reaction of...
N-propargylamides 35 with (diacetoxyiodo)benzene in the presence of bis(sulfonfyl)imides affords the respective oxazoles 36 bearing sulfonamide groups in moderate to good yields (Scheme 10).76 The sulfonfyl group in products 36 can be easily removed to give the respective amines. The reaction mechanism has been investigated by NMR spectroscopy using the deuterated alkyne variant of N-propargylamide. This cyclization reaction of N-propargylamides has also been accomplished using the in situ generated catalytic hypervalent iodine species derived from iodobenzene and Oxone. Similar oxidative cyclizations of hypervalent iodine species derived from iodobenzene and PhI(OTf)2, is probably generated from bis(trifluoroacetoxido)arene, which gave the fluorinated products 38 in moderate yields.102

Enamides have been converted into the corresponding oxazole compounds using hypervalent iodine reagents under metal-free conditions.78,79,88–90 Nachtsheim and Hempel developed an efficient method for the oxidative cyclization of N-styrylbenzamides 39 to give the corresponding oxazoles 40 using bis(trifluoroacetoxido)iodobenzene in the presence of TMSOTf (Scheme 11).90 The key active iodine(III) species in this reaction, Ph(OOTf)2, is probably generated from bis(trifluoroacetoxido)iodobenzene and TMSOTf. A one-pot synthesis of oxazoles 42 from N-acetylamido acids 41 was reported by Boto and co-workers.80 In this reaction, the enamide intermediates were initially formed from N-acetylamido acids 41 via decarboxylation and were further converted into the respective oxazole compounds 42 by iodine-mediated oxidative cyclization.

Very recently, Nagib and co-workers reported the reaction of arylimidates 43 with (diacetoxyiodo)benzene in the presence of cesium iodide under fluorescent light irradiation leading to the corresponding oxazole products 44 in moderate to good yields (Scheme 12).114 The key step in this reaction involved the double hydrogen atom transfer (HAT) reaction by in situ generated radical species. The same group has also achieved a one-pot procedure for the synthesis of oxazoles from alcohols and nitriles.

Du and co-workers reported the reaction of enamines 45 with bis(trifluoroacetoxido)iodobenzene giving β-trifluoroacetoxy enamines, which were further converted into 2-(trifluoromethyl)oxazoles 46 in moderate to good yields (Scheme 13).91 The same group has also developed the acylation reaction of enamines using iodosylbenzene with various carboxylic acids. The obtained β-acyloxylated products can be further transformed into the corresponding oxazoles under acetic acid reflux conditions.92

The reaction of 3-hydroxybut-2-enimidates 39 with (diacetoxyiodo)benzene in the presence of benzotriazole (BTA) as an additive affords the rearranged 2,4,5-trisubstituted oxazoles 48 in moderate to good yields (Scheme 14).81 The product structure was confirmed by X-ray crystallography. This reaction proceeds via initial isoxazole formation leading to the corresponding oxazole products 48 in moderate to good yields (Scheme 14).81 The product structure was confirmed by X-ray crystallography. This reaction proceeds via initial isoxazole formation followed by ring opening and recyclization to produce oxazoles 48.
Convenient practical approaches for the preparation of oxazoles from monocarbonyl substrates and nitrile solvents as the nitrogen source in the presence of hypervalent iodine reagents have been reported by several groups.\textsuperscript{86,87,93,96,97,100,103–105} Furthermore, the reaction of dicarbonyl compounds\textsuperscript{49} using iodosylbenzene in the presence of bis[(trifluoromethanesulfonyl)]imide also proceeded as an oxidative cycloaddition reaction to give the respective carbonyl-substituted oxazoles\textsuperscript{50} (Scheme 15).\textsuperscript{93} The reaction of carbonyl compounds with amides as the nitrogen source instead of nitrile afforded the respective oxazoles in moderate to good yields.\textsuperscript{98,99} Iodosylbenzene works in this reaction as the oxygen source.

Iodonium ylides and various nitriles can be converted into the corresponding oxazoles in moderate to good yields.\textsuperscript{107–113} For example, dimesone-derived iodonium ylide\textsuperscript{29}, reacting with nitriles in the presence of a metal catalyst, can be easily transformed into ring-fused oxazole compounds bearing a monocarbonyl group\textsuperscript{51} (Scheme 16).\textsuperscript{108} The key nitrilium intermediates are initially formed from iodonium salts reacting with nitrile in the presence of bis(trifluoromethanesulfonyl)imide also proceeded as an oxidative cycloaddition reaction to give the respective oxazoles in moderate to good yields.\textsuperscript{93,96,97,100,103–105}

Scheme 15 Oxidative cycloaddition of dicarbonyl compounds with nitriles

![Scheme 15](image)

The metal-free, regioselective hypervalent-iodine-mediated\textsuperscript{2} cycloaddition of alkenes, nitriles and oxygen atoms leading to substituted oxazoles have been developed.\textsuperscript{94,108} Reactions of alkenes\textsuperscript{52} with iodosylbenzene in nitrile solution in the presence of trifluoromethanesulfonic acid or bis[(trifluoromethane)sulfonyl]imide gave the corresponding oxazole products\textsuperscript{53} (Scheme 17).\textsuperscript{94} Iodosylbenzene works as this reaction as the oxygen source and also as the activating reagent. Deuterium labeling experiments indicate that alkenyliodonium and alkynyliodonium intermediates are initially formed from iodosylbenzene and alkenes. A catalytic version of this\textsuperscript{[2+2+1]} cycloaddition was also reported.\textsuperscript{106} The oxygen source in the catalytic version of this reaction was mCPBA, and the yields of products\textsuperscript{53} were comparable to those of the stoichiometric reaction. According to the deuterium labeling experiments, this catalytic\textsuperscript{[2+2+1]} cycloaddition involved only alkenyliodonium intermediates.

Scheme 16 Rhodium-catalyzed cycloaddition of iodonium ylides with nitriles

![Scheme 16](image)

4 Synthesis of Isoxazolines

The isoxazoline ring is present in many important heterocycles that are widely used in several areas of chemistry and biomedical sciences.\textsuperscript{24–26,52} Hypervalent iodine reagents such as (diacetoxyiodo)benzene,\textsuperscript{115–129} [hydroxy(tosyloxy)iodo]benzene,\textsuperscript{130,131} iodosylbenzene\textsuperscript{132–135} [bis(trifluoroacetoxy)iodo]benzene,\textsuperscript{136} (dichloroiodo)benzene,\textsuperscript{137} and also in situ generated iodine(III) species,\textsuperscript{138–141} can be used as efficient tools for construction of the isoxazoline ring.

The hypervalent-iodine-mediated oxidative cycloaddition of aldoximes with unsaturated substrates represents a powerful methodology for the synthesis of isoxazoline compounds.\textsuperscript{52,115–120,134,136,137} For example, the reactions of various aldoximes\textsuperscript{54} with alkenes\textsuperscript{55} and (diacetoxyiodo)benzene afford the corresponding isoxazolines\textsuperscript{56} in generally high yields (Scheme 18).\textsuperscript{110} The key intermediate in this reaction, nitrile oxide, is generated by oxidation of the aldoxime with (diacetoxyiodo)benzene, and then the generated nitrile oxide reacts with alkenes to produce the isoxazoline products. The reactions of disubstituted or trisubstituted alkenes with aldoximes using hypervalent iodine reagents can proceed through oxidative cycloaddition leading to the corresponding substituted isoxazolines.\textsuperscript{120,133}

Scheme 17 Metal-free [2+2+1] oxidative cycloaddition reactions

![Scheme 17](image)

Scheme 18 Iodine(III)-mediated preparation of isoxazolines

![Scheme 18](image)
The treatment of aldoxime-bearing pyridine structures and various alkenes with an iodine(III) reagent also leads to the respective isoxazoline products in moderate to good yields.\textsuperscript{116,117,122–124} Likewise, the treatment of heterocyclic alkenes with various aldoximes using hypervalent iodine reagents also produces products \textsuperscript{59} in good yields.\textsuperscript{132} This reaction involves initial formation of aldoximes from aldehydes and hydroxylamine, followed by oxidative cycloaddition with alkenes to give the final products (Scheme 18).

Hypervalent-iodine-mediated oxidative cycloadditions of aldoximes with cyclic alkenes has been used for the preparation of bicyclic isoxazoline compounds in moderate to good yields.\textsuperscript{116,117,122–124} For example, the oxidative cycloaddition of various aldoximes \textsuperscript{60} with sultone \textsuperscript{61} in the presence of \([\text{hydroxy(tosyloxy)}\text{iodo}]\text{benzene}\) proceeds smoothly to produce the corresponding products \textsuperscript{62} (Scheme 19). A similar reaction using cyclic phospholene-oxide instead of sultone resulted in the respective bicyclic products in moderate yields.\textsuperscript{123} Yang and co-workers reported a practical procedure for the preparation of fulleroisoxazolines \textsuperscript{65} from various aldoximes \textsuperscript{63} and fullerene \textsuperscript{64} using (diacetoxyiodo)benzene.\textsuperscript{124} This procedure can also be used for the synthesis of fulleropyrazolines from various hydrazones and fullerene.

The intramolecular cyclization of aldoximes to produce fused isoxazolines was reported by several research groups.\textsuperscript{116,117,122–124} In the reaction of 2-(allyloxy)benzaldoximes \textsuperscript{72} with [hydroxy(tosyloxy)iodo]benzene in water, an intramolecular cyclization of the aldoximes led to the tricyclic fused products \textsuperscript{73} (Scheme 21).\textsuperscript{131} Das and co-workers reported a similar intramolecular oxidative cyclization reaction of a furanose-based aldoxime using (diacetoxyiodo)benzene leading to furopyrano-2-isoxazoline products in good yields.\textsuperscript{123} Sorensen and co-workers reported a tandem oxidative cyclization reaction forming a pentacyclic product \textsuperscript{75} by the treatment of aldoxime \textsuperscript{74} with (diacetoxyiodo)benzene.\textsuperscript{124} This reaction mechanism probably involved initial formation of quinone derivatives from the phenol moiety and nitrile oxide species, then followed by cyclization of the quinone and nitrile oxide to give the desired pentacyclic compound.

Ciufolini and co-workers have reported the (diacetoxyiodo)benzene-mediated generation of nitrile oxide species from \(\alpha\)-oxo-oximes.\textsuperscript{125} The reaction of \(\alpha\)-oxo-\(\alpha\)-ketoximes \textsuperscript{76} with norbornene (\textsuperscript{77}) and (diacetoxyiodo)benzene in methanol gave the corresponding isoxazolines \textsuperscript{78} in moderate yields (Scheme 22). This reaction mechanism involved initial formation of the nitrile oxide from the \(\alpha\)-oxo-\(\alpha\)-ketoximes via ligand exchange and solvolysis, followed by the cycloaddition with the alkene to form the final products.
The reaction of \( \alpha,\alpha'- \text{dioxo-ketoximes} \) 79 with norbornene under the same conditions also gave the corresponding isoxazoline compounds 80.

The oxidative cyclization of allyl ketoximes using (diacetoxyiodo)benzene can produce the corresponding isoxazolines bearing various functional groups.\(^\text{126–129}\) For example, the reaction of allyl ketoximes 81 using (diacetoxyiodo)benzene in the presence of HF·Py as the fluoride source gave the corresponding oxyfluorination compounds 82 (Scheme 23).\(^\text{128}\) The obtained isoxazolines 82 can be converted into the monofluoromethyl-substituted \( \beta \)-hydroxy ketones via a ring-opening reaction. Cai and Yu reported a (diacetoxyiodo)benzene-induced oxidative cycloaddition of allyl ketoximes 83 in the presence of disulfides 84, which produced the corresponding isoxazolines 85.\(^\text{129}\) A similar reaction using diselenides instead of disulfides afforded the selenium-containing isoxazolines in good yields. The authors suggested that this oxidative cyclization of allyl ketoximes proceeds via a radical mechanism.

## 5 Synthesis of Isoxazoles

Isoxazoles belong to an important class of heteroaromatic compounds with many practical applications.\(^\text{52}\) Hypervalent iodine reagents such as (diacetoxyiodo)benzene,\(^\text{116,122,142–147}\) [bis(trifluoroacetoxy)iodo]benzene,\(^\text{136,148–151}\) iodosylbenzene,\(^\text{134,135}\) [hydroxy(tosyloxy)iodo]benzene,\(^\text{152,153}\) and in situ generated iodine(III) species\(^\text{138,154}\) have been commonly used for isoxazole ring construction.

Hypervalent-iodine-mediated oxidative cycloadditions of aldoximes with unsaturated substrates represents an efficient procedure for the construction of isoxazoles. For example, the reaction of aldoximes 86 with terminal alkynes...
3.5-Disubstituted oxazole compounds 97 can be prepared from the respective alkyneiodonium salts 96 and a nitrile oxide generated from aldoxime 95 and iodosylbenzene (Scheme 25). The mechanism of this reaction involves oxidative cycloaddition and loss of the iodonium group.

Very recently, our group reported the regioselective cycloaddition reaction of aldoximes with enaminones.153 The reaction of aldoximes 98 with enaminones 99 and [hydroxy(tosyloxy)iodo]benzene afforded the 3,4-disubstituted isoxazoles 100 (Scheme 26). This reaction involves the regioselective cycloaddition of enaminones with the generated nitrile oxide followed by elimination of dialkylamine to produce 3,4-disubstituted isoxazole products 100. The reaction of β-substituted enaminones under similar conditions afforded the respective 3,4,5-trisubstituted isoxazoles in moderate yields.

The hypervalent-iodine-mediated preparation of ring-fused isoxazoles from aldoximes and cyclic alkynes has been reported.142,145,146,151 For example, the reaction of bicyclo[6.1.0]nonyne 102 with various aldoximes 101 and [bis(trifluoroacetoxy)iodo]benzene gave the corresponding bicyclic 3,4,5-trisubstituted isoxazole compounds 103 in good yields (Scheme 27). A one-pot synthesis of bicyclic isoxazoles has been developed by Boons and co-workers.145 The reaction of aldehydes 104 with hydroxylamine and cyclic alkyne 105 using (diacetoxyiodo)benzene gave isoxazoles 106 in generally good yields. Another convenient one-pot synthetic approach to bicyclic isoxazoles using phenolic compounds (instead of cyclic alkynes) was reported by Liu and co-workers.147 The reaction of aldoximes 107 with 2,3-dimethylphenol (108) and (diacetoxyiodo)benzene gave the corresponding isoxazoles 109 (Scheme 27). In this reaction, the hypervalent iodine reagent serves as the oxidant for both the aldoxime and the phenol.
Catalytic procedures for the hypervalent-iodine-mediated synthesis of isoxazoles have been developed.\textsuperscript{138,154} For example, the reaction of aldoximes 110 with alkenes 111, in the presence of an iodoarene and Oxone, affords the respective 3,5-isoxazole products 112 in low to good yields (Scheme 28).\textsuperscript{138} This reaction probably involves initial formation of a nitrile oxide, which further reacts with the alkyne to give the final isoxazole. Recently, Kaliappan and Subramanian reported the oxidation of a cyclic α-ketoimine to a nitrile oxide using an in situ generated hypervalent iodine species.\textsuperscript{154} The reaction of cyclic α-ketoimine 113 and alkenes 114 with a catalytic amount of iodosobenzene using mCPBA in methanol solution afforded the corresponding isoxazole compounds 115 bearing a cyclopentyl group in low to excellent yields. The key intermediate in this reaction, the nitrile oxide, is probably generated by iodine(III)-mediated methanolysis of the α-ketoimine, and then the resulting nitrile oxide is converted into product 115 by oxidative cycloaddition with the alkyne.

6 Conclusion

This short review summarizes organohypervalent-iodine-mediated synthetic procedures for the preparation of five-membered heterocycles with oxygen and nitrogen atoms in the ring. Intramolecular or intermolecular oxidative cyclization reactions of appropriate substrates provide efficient synthetic approaches to oxazoles, oxazolines, isoxazolines, and isoxazoles. Various hypervalent iodine compounds have been utilized as efficient reagents for the preparation of these heterocyclic compounds. Furthermore, the preparation of heterocyclic compounds using in situ generated hypervalent iodine species has been developed. We expect that hypervalent-iodine-mediated syntheses of heterocyclic compounds will continue to attract significant research activity in the future.

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