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# Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or Alkynes

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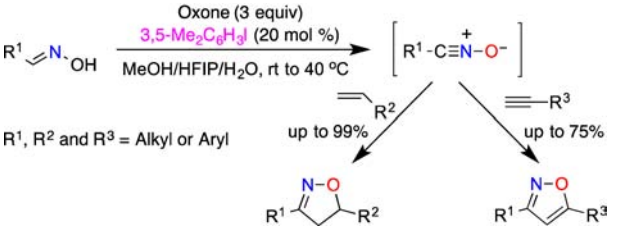
## ABSTRACT




**Hypervalent iodine catalyzed oxidation of aldoximes using oxone as a terminal oxidant generates nitrile oxides, which react with alkenes and alkynes to give the corresponding isoxazolines and isoxazoles in moderate to good yields. This reaction involves active hypervalent iodine species formed in situ from catalytic iodoarene and oxone in the presence of hexafluoroisopropanol in aqueous methanol solution.**

In recent years, hypervalent iodine reagents have emerged as environmentally friendly and efficient oxidizing reagents for various synthetically useful oxidative transformations.[1] One of the most impressive recent achievements in the area of hypervalent iodine chemistry has been the development of numerous catalytic reactions utilizing organohypervalent iodine active species in the iodine(I)/iodine(III) catalytic cycle.[1m,2,3] In particular, several hypervalent iodine catalyzed oxidative cyclization reactions leading to the important heterocyclic systems of carbazoles,[2a] benzimidazoles,[2b] oxoindoles,[2c] and numerous $\gamma$-lactones[2d−g] have recently been reported. Most of the iodine(I)/iodine(III) catalytic cycles utilize iodoarenes as catalysts and *m*-chloroperoxybenzoic acid as the stoichiometric oxidant.[3] Herein, we report the first hypervalent iodine catalyzed synthesis of isoxazole derivatives

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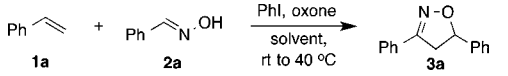
using iodoarene as a catalyst and oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as an inexpensive and environmentally safe terminal oxidant.

Isoxazolines and isoxazoles represent an important heterocyclic system commonly found in natural products, bioactive compounds, and chiral ligands.[4] Previously, several groups reported the preparation of isoxazolines and isoxazoles from aldoximes and alkenes or alkynes using a stoichiometric amount of hypervalent iodine reagents such as [hydroxy(tosyloxy)iodo]benzene,[5] (dichloroiodo)-benzene,[6] iodosylbenzene,[7] [bis(trifluoroacetoxy)iodo]-benzene,[8] and (diacetoxyiodo)benzene.[9] All these reactions involve the initial oxidation of aldoximes to nitrile oxides followed by cycloaddition with the appropriate dipolarophile to give the corresponding isoxazolines and isoxazoles. Several other oxidants and catalysts (e.g., hypoiodite species,[10a,b] 3,3-dimethyldioxirane,[10c] NaOCl,[10d] *N*-chlorosuccinimide,[10e] *N*-bromosuccinimide,[10e] $NaBrO_2$[10f]) have also been previously utilized in this reaction.

Recently, our group reported that activated iodine(III) species, the hydroxy(phenyl)iodonium ion $[PhI(OH)]^+$, generated in situ from PhI and oxone, were effective for the preparation of [bis(trifluoroacetoxy)iodo]arenes and [bis(trifluoroacetoxy)iodo]perfluoroalkanes and for Hofmann rearrangement of carboxamides.[11] Several other groups have also reported a hypervalent iodine catalytic reaction using oxone as the terminal oxidant.[12]

**Table 1.** Optimization of Catalytic Heterocyclization[a]




| entry | ArI (equiv) | solvents (ratio) | **3a** (%)[b] |
|---|---|---|---|
| 1 | none | MeOH-HFIP-$H_2O$ (10:10:1) | 0 |
| 2 | PhI (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 74 (73) |
| 3 | PhI (0.2) | MeOH-$H_2O$ (20:1) | 35 |
| 4 | PhI (0.2) | MeOH-TFE-$H_2O$ (10:10:1) | 40 |
| 5 | PhI (0.2) | MeOH−$CH_2Cl_2$−$H_2O$ (10:10:1) | 12 |
| 6 | PhI (0.2) | MeOH−MeCN-$H_2O$ (10:10:1) | 11 |
| 7 | PhI (0.2) | MeOH-AcOEt-$H_2O$ (10:10:1) | 6 |
| 8 | PhI (0.2) | MeOH-hexane-$H_2O$ (10:10:1) | 49 |
| 9 | PhI (0.2) | MeOH-THF-$H_2O$ (10:10:1) | 4 |
| 10 | PhI (0.2) | MeOH-toluene-$H_2O$ (10:10:1) | 13 |
| 11 | PhI (0.2) | MeOH-HFIP (1:1) | 1 |
| 12 | 4-$MeC_6H_4I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 71 |
| 13 | 3,5-$Me_2C_6H_3I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 85 |
| 14 | 4-$ClC_6H_4I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 44 |
| 15 | 4-$CF_3C_6H_4I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 17 |
| 16[c] | 3,5-$Me_2C_6H_3I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 87 (88) |
| 17[c] | 3,5-$Me_2C_6H_3I$ (0.1) | MeOH-HFIP-$H_2O$ (10:10:1) | 66 |
| 18[c,d] | 3,5-$Me_2C_6H_3I$ (0.2) | MeOH-HFIP-$H_2O$ (10:10:1) | 65 |

[a] The cyclization of aldoxime and styrene was performed at 40 °C for 4 h by using styrene **1a** (1.2 equiv), aldoxime **2a** (1 equiv), ArI (0−0.2 equiv), and oxone (2−3 equiv). [b] Yields of **3a** determined from $^1H$ NMR spectra of reaction mixture (numbers in parentheses show yields of isolated **3a**). [c] Reaction was performed at rt for 24 h. [d] 2 equiv of oxone were used.

In the search for the organohypervalent iodine(III)-catalyzed oxidative cycloaddition of aldoxime and alkene, we have investigated the reaction of styrene **1a** (1.2 equiv), benzaldoxime **2a** (1 equiv), and oxone as a terminal oxidant in the presence of catalytic amounts of iodoarenes under different conditions and using various solvents (see Table 1; for additional details, see Table S1).

In the absence of iodoarene as a precatalyst, the desired isoxazoline product was not formed from alkene, aldoxime, and oxone (Table 1, entry 1). A study of different solvent systems (Table 1, entries 2−10) has demonstrated that the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in the reaction mixture dramatically changes the results of this cyclization. The accelerating effect of HFIP on the reactions of hypervalent iodine species was previously reported by several groups.[13] The addition of a small amount of water is required to increase the solubility of oxone in the reaction mixture (Table 1, entry 11). Out of several iodoarenes tested, 3,5-$Me_2C_6H_3I$ was found to be

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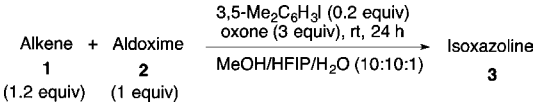
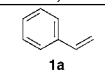
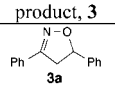
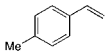
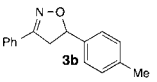
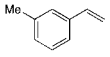
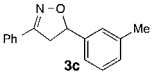
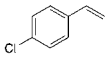
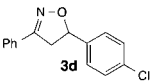
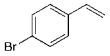
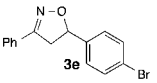
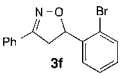
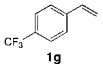
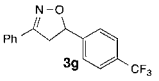
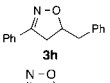
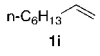
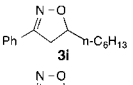
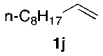
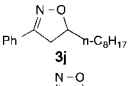
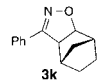
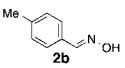
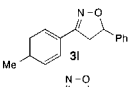
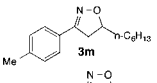
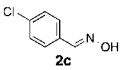
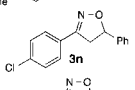
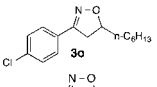
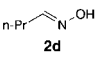
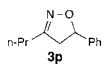
(12) (a) Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933. (b) Schulze, A.; Giannis, A. *Synthesis* **2006**, 257. (c) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251. (d) Ojha, L. R.; Kudugunti, S.; Maddukuri, P. P.; Kommareddy, A.; Gunna, M. R.; Dokuparthi, P.; Gottam, H. B.; Botha, K. K.; Parapati, D. R.; Vinod, T. K. *Synlett* **2009**, 117. (e) Uyanik, M.; Fukatsu, R.; Ishihara, K. *Org. Lett.* **2009**, *11*, 3470. (f) Thottumkara, A. P.; Vinod, T. K. *Org. Lett.* **2010**, *12*, 5640. (g) Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem.* **2011**, *9*, 2258.

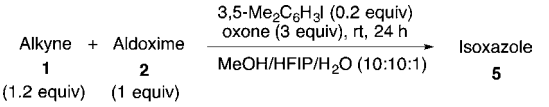
**Table 2.** Catalytic Heterocyclization of Aldoximes with Alkenes under Optimized Conditions[a]

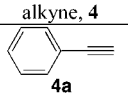
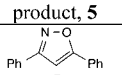
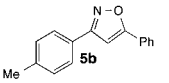
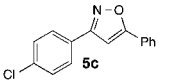
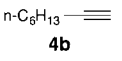
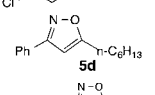
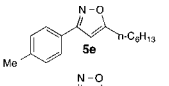



| entry | alkene, **1** | aldoxime, **2** | product, **3** | yield %[b] |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 88 |
| 2 |  **1b** | **2a** |  **3b** | 78 |
| 3 |  **1c** | **2a** |  **3c** | 81 |
| 4 |  **1d** | **2a** |  **3d** | 92 |
| 5 |  **1e** | **2a** |  **3e** | 87 |
| 6 |  **1f** | **2a** |  **3f** | 89 |
| 7 |  **1g** | **2a** |  **3g** | 99 |
| 8 |  **1h** | **2a** |  **3h** | 78 |
| 9 |  **1i** | **2a** |  **3i** | 69 |
| 10 |  **1j** | **2a** |  **3j** | 71 |
| 11 |  **1k** | **2a** |  **3k** | 30 |
| 12 | **1a** |  **2b** |  **3l** | 71 |
| 13 | **1i** | **2b** |  **3m** | 54 |
| 14 | **1a** |  **2c** |  **3n** | 77 |
| 15 | **1i** | **2c** |  **3o** | 79 |
| 16 | **1a** |  **2d** |  **3p** | 17 |

[a] All reactions of alkene **1** (1.2 equv), aldoxime **2** (1 equiv), 3,5-$Me_2C_6H_3I$ (0.2 equiv), and oxone (3 equiv) were performed in MeOH-HFIP-$H_2O$ at rt for 24 h. [b] Isolated yields of products **3**.

**Table 3.** Catalytic Heterocyclization of Aldoximes with Alkynes under Optimized Conditions[a]




| entry | alkyne, **4** | aldoxime, **2** | product, **5** | yield %[b] |
|---|---|---|---|---|
| 1 |  **4a** | **2a** |  **5a** | 75 |
| 2 | **4a** | **2b** |  **5b** | 70 |
| 3 | **4a** | **2c** |  **5c** | 70 |
| 4[c] |  **4b** | **2a** |  **5d** | 49 |
| 5[c] | **4b** | **2b** |  **5e** | 39 |
| 6[c] | **4b** | **2c** |  **5f** | 42 |
| 7 |  **4c** | **2a** |  **5g** | 27 |
| 8 |  **4d** | **2a** |  **5h** | 44 |

[a] All reactions of alkyne **4** (1.2 equv), aldoxime **2** (1 equiv), 3,5-$Me_2C_6H_3I$ (0.2 equiv), and oxone (3 equiv) were performed in MeOH/HFIP/$H_2O$ at rt for 24 h. [b] Isolated yields of products **5**. [c] Performed at 40 °C.

the best precatalyst in this reaction (Table 1, entries 12–15). We have also found that this reaction can be performed at rt for a longer reaction time (Table 1, entry 16). Decreasing the amount of 3,5-$Me_2C_6H_3I$ from 0.2 to 0.1 equiv and oxone from 3 to 2 equiv leads to decreased yields of product **3a** (Table 1, entries 17, 18).

Using the optimized reaction conditions with 20 mol % 3,5-$Me_2C_6H_3I$, we have investigated the conversion of various substituted alkenes **1** to the respective isoxazolines **3** (Table 2). In general, all styrenes with either electron-donating or -withdrawing substituents afforded corresponding isoxazolines **3** in good yields (Table 2, entries 2–7). This reaction also gave good yields for aliphatic alkenes (Table 2, entries 8–10). However, the reaction of norbornene **1k** with aldoxime **2a** gave isoxazoline **3** in only a 30% yield (Table 2, entry 11). As expected, *p*-methylbenzaldoximes **2b** or *p*-chlorobenzaldoximes **2c** also reacted smoothly with styrene **1a** or 1-octene **1i** giving the respective isoxazolines in moderate to good yields. The reaction of an aliphatic aldoxime, butylaldoxime **2d**, with styrene **1a** gave a low yield of the product (Table 2, entry 16).

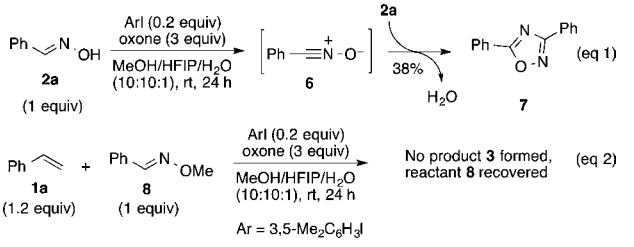
Compared to previously reported methods of the oxidative cyclization of alkenes and aldoximes using stoichiometric hypervalent iodine reagents,[5–9] the new catalytic procedure affords isoxazolines in similar yields. Next, we tried to prepare isoxazoles by replacing alkenes with alkynes. The reaction of phenylacetylene **4a** with benzaldoxime under the optimized reaction conditions gave the desired isoxazoles

(13) (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (b) Miyamoto, K.; Tada, N.; Ochiai, M. *J. Am. Chem. Soc.* **2007**, *129*, 2772. (c) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775. (d) Gurard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Menard, M.-A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121. (e) Zhu, C.; Yoshimura, A.; Wei, Y.; Nemykin, V. V.; Zhdankin, V. V. *Tetrahedron Lett.* **2012**, *53*, 1438. (f) Samanta, R.; Lategahn, J.; Antonchick, A, P. *Chem. Commun.* **2012**, *48*, 3194.

**5a** in 75% yield (Table 3, entry 1). As expected, the reaction of phenylacetylene **4a** and benzaldoximes with *p*-Me or *p*-Cl substituents afforded corresponding isoxazoles in good yields (Table 3, entries 2, 3). However, the reaction with aliphatic alkynes and various benzaldoximes required heating and gave corresponding isoxazoles in moderate yields (Table 3, entries 4–6). The reaction with *para*-substituted arylacetylenes and benzaldoximes **2a** also gave low yields of isoxazoles (Table 3, entries 7, 8).

In order to gain additional information on the mechanism of this catalytic reaction, we have performed several control experiments (Scheme 1). It is known from the literature that nitrile oxides, generated from aldoximes in the absence of alkenes or alkynes, undergo cyclodimerization or cycloaddition with nitrile oxide and aldoxime.[8a,14] We have found that the reaction of **2a** in the absence of alkenes and alkynes under our conditions gave the cycloaddition product, oxadiazole **7**, in 38% preparative yield (Scheme 1, eq 1). This result implies that nitrile oxide **6** can be generated under our conditions.[14] As expected, the reaction with protected benzaldoxime, *O*-methyloxime **8**, and **1a** did not proceed, and **8** was recovered from the reaction mixture (Scheme 1, eq 2). This result indicates that the ligand exchange of aldoxime and hypervalent iodine active species is important in this reaction.

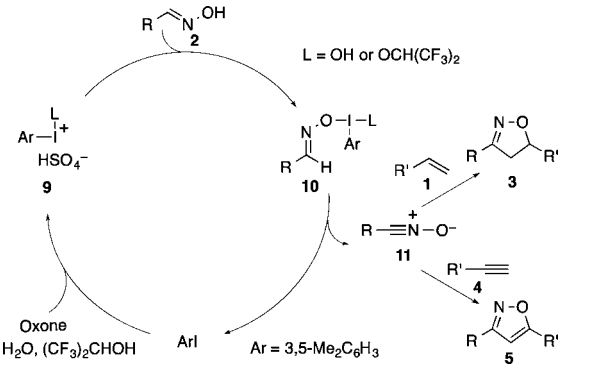
**Scheme 1.** Control Experiments




From these control experiments and based on previously reported cyclizations of aldoximes with alkenes or alkynes using stoichiometric hypervalent iodine reagents,[5–9] we propose the catalytic cyclization mechanism outlined in Scheme 2. The activated hypervalent iodine species,

(14) (a) Kelly, D. R.; Baker, S. C.; King, D. S.; de Silva, D. S.; Lord, G.; Taylor, J. P. *Org. Biomol. Chem.* **2008**, *6*, 787. (b) Ghosh, H.; Patel, B. K. *Org. Biomol. Chem.* **2010**, *8*, 384. (c) Schmidt, M. A.; Katipally, K.; Ramirez, A.; Soltani, O.; Hou, X.; Zhang, H.; Chen, B.-C.; Qian, X.; Deshpande, R. P. *Tetrahedron Lett.* **2012**, *53*, 3994.

**Scheme 2.** Proposed Reaction Mechanism




[hydroxy(aryl)iodonium ion $[ArI(OH)]^+$ **9**, which is generated from ArI and oxone in aqueous HFIP, further reacts with aldoxime **2** to give the hypervalent alkoxy iodane **10** via ligand exchange. The intermediate **10** then undergoes reductive elimination of ArI to give nitrile oxide **11**. The regenerated ArI continues the next catalytic cycle. The intermediate **11** reacts with alkene or alkyne to give the corresponding isoxazoline **3** or isoxazole **5**. The presence of HFIP may help to generate the highly reactive electron-deficient hypervalent species **9** or **10**, which accelerate further steps of this catalytic cycle, such as ligand exchange and oxidation of aldoxime.

In summary, we have developed a new procedure for the cyclization of aldoxime and alkene or alkyne using catalytic hypervalent iodine and oxone as a terminal oxidant in aqueous HFIP. This reaction proceeds via initial formation of nitrile oxides, which react with alkenes and alkynes to give corresponding isoxazolines and isoxazoles. The reaction mechanism probably involves the electron-deficient hypervalent iodine species formed from the hydroxy(aryl)-iodonium ion and HFIP.

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**Supporting Information Available.** Experimental procedures, spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.