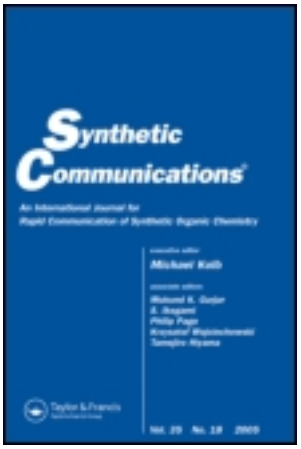

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Hypervalent Iodine-Catalyzed Cycloaddition of Nitrile Oxides to Alkenes

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HYPERVALENT IODINE–CATALYZED CYCLOADDITION OF NITRILE OXIDES TO ALKENES

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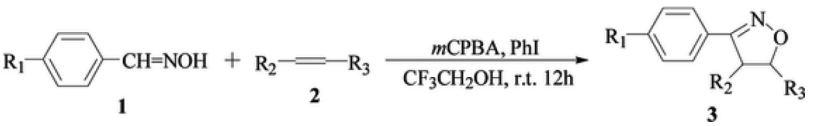
GRAPHICAL ABSTRACT



Abstract *A new and convenient method for preparation of isoxazolines was developed by a catalytic cycloaddition of nitrile oxides generated in situ from aldoximes to alkenes in the presence of a catalytic amount of iodobenzene. In this protocol, iodobenzene was first oxidized into the hypervalent iodine intermediate by* m-*chloroperbenzoic acid, which then transformed aldoximes into nitrile oxides, and a 1,3-dipolar cycloaddition of nitrile oxides to alkenes to provide the isoxazolines in moderate to good yields.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Catalytic reaction; cycloaddition; hypervalent iodine intermediate; iodobenzene; isoxazoline

INTRODUCTION

Isoxazolines are important pharmacophores in several pharmaceutical compounds.[1] They are also useful intermediates for synthesis of natural products and biologically active compounds.[2] A variety of synthetic methods has been developed for preparation of isoxazolines, of which the most convenient and attractive route is probably the 1,3-dipolar cycloaddition of nitrile oxides to alkenes.[3] Nitrile oxides are commonly generated from aldoximes via halogenation using different reagents such as N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), NaOCl, *t*-BuOCl, *t*-BuOI, etc.[4] All of these methods involve two steps and give highly variable yields. Having low toxicity, ready availability, easy handling, and reactivity similar to that of heavy-metal reagents or anodic oxidation, hypervalent iodine compounds have found broad application in organic chemistry and are

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frequently used in synthesis.[5] The hypervalent iodine–induced 1,3-dipolar cycloaddition of nitrile oxides from aldoximes to alkenes is an improved process, in which the stoichiometric hypervalent iodine reagents usually are needed.[6]

In recent years, the catalytic utilization of hypervalent iodine reagents has increased in importance, with growing interest in the development of environmentally benign synthetic transformations.[7] In these catalytic reactions, a catalytic amount of an iodine-containing molecule together with a stoichiometric oxidant are used. The oxidant generates the hypervalent iodine reagent in situ, and after the oxidative transformation, the reduced iodine-containing molecule is reoxidized. Iodobenzene (PhI) is the most utilized iodoarene, and *m*-chloroperbenzoic acid (*m*CPBA) and oxone are usually used as the terminal oxidants.

DISCUSSION AND RESULTS

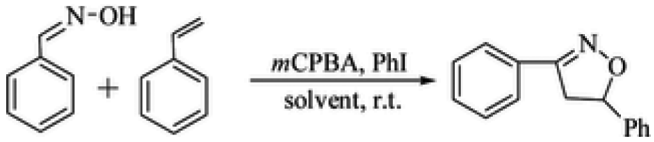
To extend the scope of catalytic use of hypervalent iodine reagents in organic synthesis, we have investigated the catalytic cycloaddition of nitrile oxides generated in situ from aldoximes to alkenes, in which a catalytic amount of PhI and a stoichiometric oxidant *meta*-chloroperbenzoic acid (*m*CPBA) were used. Now we report a new and convenient procedure for preparation of isoxazolines, and to our knowledge the catalytic cycloaddition of nitrile oxides from aldoximes to alkenes using a catalytic amount of PhI has not been reported before.

At the onset of the research, benzaldoxime and styrene were chosen as the model substrates. We first investigated the catalytic cycloaddition with 1.0 equiv. of benzaldoxime, 1.5 equiv. of styrene, 0.2 equiv. of PhI, and 0.75 equiv. of *m*CPBA in various solvents at room temperature for 24 h. It was shown from Table 1 that all reactions gave the desired product of 3,5-diphenylisoxazoline, but the yield was variable greatly: When 2,2,2-trifluoroethanol (TFE) was used as solvent, a good yield of 74% was reached; however, other solvents usually led to poor yields (Table 1, entries 1–8). In the same conditions, when another oxidant, oxone, was used in place of *m*CPBA, the reaction provided a moderate yield, so *m*CPBA was more suitable for the reaction (entry 9). When the amount of *m*CPBA was increased from 0.75 equiv. to 1.0 equiv., the yield rose to 76%; however, when more *m*CPBA was added, the yield decreased and some by-products, such as phenyl oxirane, were found (entries 10–13). The reaction was carried out rapidly, and only after 2 h a yield of 63% was recorded; to improve the yield, the reaction time was prolonged to 12 h, which resulted in a good yield of 75% (entries 10, 14–17). The amount of styrene was investigated and 2.0 equiv. of it was the best choice (entries 14, 18–20). The amount of PhI was also checked and when 0.3 equiv. of it was added, the reaction provided the best yield of 81%; however, in the absence of it, no desired product was observed (entries 19, 21–24).

Having established the optimal conditions, the catalytic cycloaddition with 1.0 equiv. of aldoximes (1), 2.0 equiv. of alkenes (2), 0.3 equiv. of PhI, and 1.0 equiv. of *m*CPBA in TFE at room temperature for 12 h was investigated, and a series of corresponding isoxazolines (**3**) were obtained (Scheme 1). The results are summarized in Table 2.

As shown in Table 2, the reaction was compatible with most of alkenes except cyclohexene **2g** and provided the corresponding isoxazolines in moderate to good

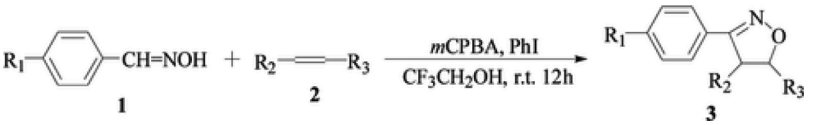
Table 1. Optimization of the catalytic cycloaddition with benzaldoxime and styrene



Entry	*m*CPBA (equiv.)	PhI (equiv.)	$PhCH{=}CH_2$ (equiv.)	Solvent	Time (h)	Yield (%)[a]
1	0.75	0.2	1.5	CH_3OH	24	47
2	0.75	0.2	1.5	EtOAc	24	39
3	0.75	0.2	1.5	THF	24	30
4	0.75	0.2	1.5	EtOH	24	28
5	0.75	0.2	1.5	MeCN	24	48
6	0.75	0.2	1.5	CH_2Cl_2	24	41
7	0.75	0.2	1.5	DMF	24	28
8	0.75	0.2	1.5	CF_3CH_2OH	24	74
9	Oxone (0.75)	0.2	1.5	CF_3CH_2OH	24	58
10	1.0	0.2	1.5	CF_3CH_2OH	24	76
11	1.2	0.2	1.5	CF_3CH_2OH	24	66
12	1.5	0.2	1.5	CF_3CH_2OH	24	58
13	2.0	0.2	1.5	CF_3CH_2OH	24	54
14	1.0	0.2	1.5	CF_3CH_2OH	12	75
15	1.0	0.2	1.5	CF_3CH_2OH	6	68
16	1.0	0.2	1.5	CF_3CH_2OH	4	67
17	1.0	0.2	1.5	CF_3CH_2OH	2	63
18	1.0	0.2	1.0	CF_3CH_2OH	12	71
19	1.0	0.2	2.0	CF_3CH_2OH	12	79
20	1.0	0.2	3.0	CF_3CH_2OH	12	74
21	1.0	0	2.0	CF_3CH_2OH	12	0
22	1.0	0.1	2.0	CF_3CH_2OH	12	49
23	1.0	0.3	2.0	CF_3CH_2OH	12	81
24	1.0	0.4	2.0	CF_3CH_2OH	12	80

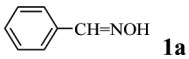
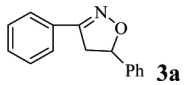
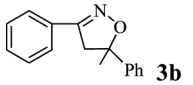
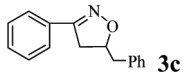
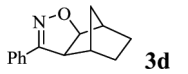
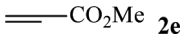
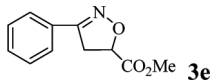
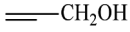
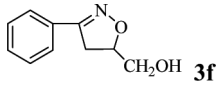
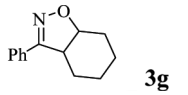
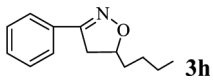
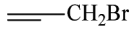
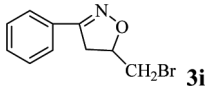
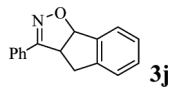
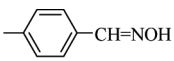
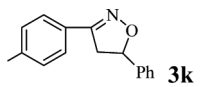
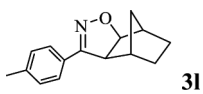
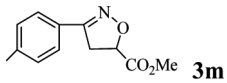
[a]Isolated yield.

yields (entries 1–15). Compared with benzaldoxime **1a**, 4-methylbenzaldoxime **1b** or 4-methoxybenzaldoxime **1c**, which bear electron-donating groups on benzene rings, usually afforded the corresponding products in somewhat poor yields (entries 1, 4, 5, 11–15). *p*-Nitro derivative **1d** with an electron-withdrawing group was not active in the reaction, and the desired isoxazoline was not obtained (entry 16). When phenylacetaldoxime **1e**, an aliphatic aldoxime, was used to treat with styrene in the same conditions, no product was observed.



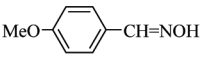
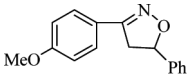
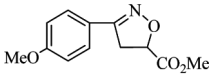
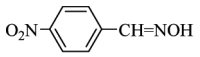
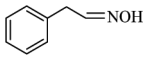
Scheme 1. Catalytic cycloaddition of nitrile oxides from aldoximes to alkenes.

Table 2. Result of catalytic cycloaddition of nitrile oxides from aldoximes to alkenes

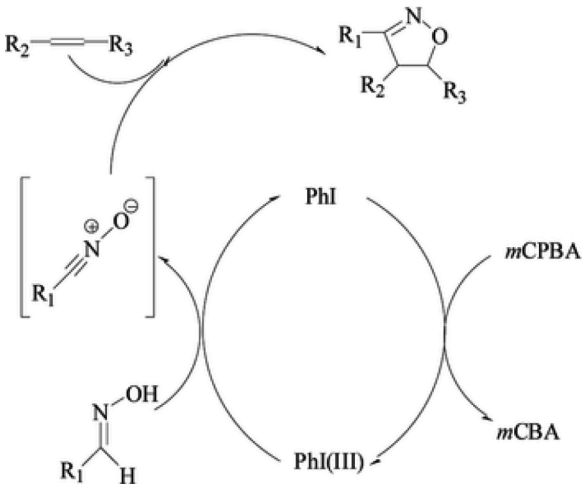
Entry	Aldoxime **1**	Alkene **2**	Isoxazoline **3**	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	81
2	**1a**	 **2b**	 **3b**	83
3	**1a**	 **2c**	 **3c**	82
4	**1a**	 **2d**	 **3d**	70
5	**1a**	 **2e**	 **3e**	76
6	**1a**	 **2f**	 **3f**	51
7	**1a**	 **2g**	 **3g**	40
8	**1a**	 **2h**	 **3h**	81
9	**1a**	 **2i**	 **3i**	68
10	**1a**	 **2j**	 **3j**	53
11	 **1b**	**2a**	 **3k**	62
12	**1b**	**2d**	 **3l**	54
13	**1b**	**2e**	 **3m**	53

(*Continued*)

Table 2. Continued

Entry	Aldoxime **1**	Alkene **2**	Isoxazoline **3**	Yield (%)[a]
14	 **1c**	**2a**	 **3n**	63
15	**1c**	**2e**	 **3o**	65
16	 **1d**	**2a**	—	—
17	 **1e**	**2a**	—	—

[a]Isolated yield.



Scheme 2. Reaction mechanism for the catalytic cycloaddition.

A plausible reaction pathway for the present reaction is shown in Scheme 2. The iodobenzene is first oxidized into the hypervalent iodine intermediate by *m*CPBA, which then transforms aldoximes into nitrile oxides, and finally a 1,3-dipolar cycloaddition of nitrile oxides to alkenes is carried out and provides the corresponding isoxazolines. The reduced by-product iodobenzene is reoxidized into hypervalent iodine reagent by *m*CPBA in the recycling reaction.

CONCLUSIONS

In summary, we have developed a new and efficient method for preparation of isoxazolines by the catalytic cycloaddition of nitrile oxides generated in situ from

aldoximes to alkenes using a catalytic amount of iodobenzene, and a series of corresponding isoxazolines was prepared in moderate to good yields. This method has some advantages such as mild reaction conditions and simple procedure. Furthermore, the scope of hypervalent iodine reagents in organic synthesis could be extended.

EXPERIMENTAL

Melting points were measured with an XT-4 melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Thermo-Nicolet 6700 instrument, ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III (500 M) spectrometer, and mass spectra were determined on a Thermo-ITQ 1100 mass spectrometer. Aldoximes, alkenes, *m*CPBA, and PhI were commercially available.

Aldoxime **1** (1.0 mmol), *m*CPBA (1.0 mmol), and PhI (0.3 mmol) were added to a 2,2,2-trifluoroethanol (TFE) solvent (5 mL). The resulting mixture was stirred at rt for about 25 min, alkene **2** (2.0 mmol) was added, and the mixture was continuously stirred at rt for another 12 h. After the reaction, TFE was evaporated under reduced pressure, and then H_2O (6 mL), saturated aqueous $Na_2S_2O_3$ (4 mL), and saturated aqueous Na_2CO_3 (4 mL) were added. The mixture was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified on a silica-gel plate (3:1 petroleum ether–ethyl acetate) to provide the corresponding pure isoxazoline **3**.

ACKNOWLEDGMENT

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