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### o-Iodoxy Benzoic Acid-Mediated Synthesis of 3,5-Diarylisoxazoles and Isoxazole-3-carboxylic Acids

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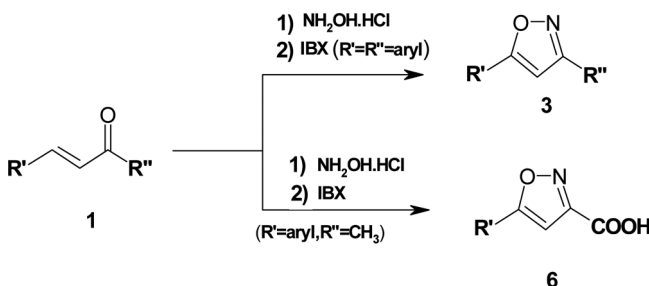


## ***o*-iodoxy benzoic acid-MEDIATED SYNTHESIS OF 3,5-DIARYLSOXAZOLES AND ISOXAZOLE-3-CARBOXYLIC ACIDS**

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### **GRAPHICAL ABSTRACT**



**Abstract** A new, convenient, ecofriendly synthesis of 3,5-diarylisoxazoles is reported from  $\alpha,\beta$ -unsaturated ketoximes. Similarly, a novel synthesis of isoxazole carboxylic acids is also reported. Both the methods use efficient, environmentally friendly, and nontoxic iodoxybenzoic acid (IBX) as an oxidative cyclizing reagent. Easy procedure, environmentally benign reaction conditions, and nontoxicity are advantages to the methodology.

**Keywords** Chalcone; isoxazoles; *o*-iodoxybenzoic acid; oxidative cyclization;  $\alpha,\beta$ -unsaturated ketoxime

## **INTRODUCTION**

In recent years, the organic chemistry of hypervalent iodine compounds<sup>[1–4]</sup> such as *o*-iodoxy benzoic acid (IBX) and iodobenzene diacetate (IBD) has experienced immense development. This growing interest in iodine hypervalent compounds is due to their mild and high chemoselective properties combined with benign environmental character and commercial availability. Hence, numerous new chemical transformations effected by these hypervalent iodine reagents, as powerful reagents, have recently been developed.<sup>[5–7]</sup> Isoxazoles<sup>[8–10]</sup> are an important class

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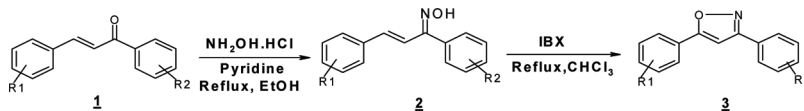
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of heterocycles owing to their diverse applications. They act as intermediates in the synthesis of natural products and as building blocks for construction of new molecular systems.<sup>[11]</sup> Activity includes a wide range of applications as herbicides and fungicides.<sup>[12,13]</sup> There are several routes by which 3,5-diaryl isoxazoles can be synthesized. The [5 + 0] routes involving oxidative cyclization of  $\alpha,\beta$ -unsaturated ketoximes using oxidizing agents such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),<sup>[14]</sup>  $\text{MnO}_2$ ,<sup>[15]</sup>  $\text{I}_2/\text{KI}$  in  $\text{NaHCO}_3$ ,<sup>[16]</sup> tetrakis(pyridine)cobalt dichromate (TPCD),<sup>[17]</sup>  $\text{KOH}$ -dioxane,<sup>[18]</sup>  $\text{N}$ -bromosuccinimide,<sup>[19]</sup> and  $\text{NOBF}_4$ <sup>[20]</sup> are some of the few known. Microwave-assisted synthesis of isoxazoles has also been reported.<sup>[21–24]</sup> There are few reports of one-pot synthesis of isoxazole.<sup>[25–29]</sup> However, the mentioned methods involve use of expensive catalyst or high-temperature reaction conditions and have limited applicability to a variety of substrates. Isoxazole-3-carboxylic acids also possess various biological activities such as antitubercular,<sup>[30,31]</sup> protein tyrosine phosphate IB(PT1B) inhibitory,<sup>[32]</sup> etc. 5-Phenylisoxazole-3-carboxylic acid derivatives are found to be potent xanthine oxidase inhibitors.<sup>[33]</sup> Either it is prepared from previously constructed isoxazole nucleus or by ring-closure methods using appropriate starting compounds containing carboxyl or alkoxy carbonyl groups. In this, ring-construction of isoxazole has been a widely used method. However, few syntheses of isoxazole carboxylic acids have been reported.<sup>[33,34]</sup>

Despite the various methods of synthesis reported for disubstituted isoxazole and isoxazole-3-carboxylic acid, development of newer ecofriendly and green methodologies remains a challenging task for synthetic organic chemists. In our earlier approaches we have developed novel strategies for synthesis of important heterocycles.<sup>[14,15]</sup> *o*-Iodoxy benzoic acid (IBX) is a well-known, nontoxic, environmentally benign reagent which has been extensively used for various organic functional group transformations.<sup>[5–7,35]</sup> In view of this, we thought of trying IBX as a reagent for oxidative cyclization.

## RESULTS AND DISCUSSION

Herein, we describe a convenient methodology toward the synthesis of 3,5-diaryl isoxazoles from  $\alpha,\beta$ -unsaturated ketoximes. The parent chalcone (**1a**) prepared by Claisen–Schmidt condensation was first converted into its corresponding oxime by a reported literature procedure<sup>[36]</sup> via hydroxylamine hydrochloride treatment under weakly basic conditions in good yield. The oxime, after isolation and purification, was then subjected to oxidative cyclization in refluxing chloroform using 1 equivalent of IBX. The reaction mixture was continuously monitored and the thin-layer chromatography (TLC) was checked with the authentic sample for the completion of the reaction. The reaction reached completion in 4 h as indicated by TLC. The crude mixture was then concentrated to remove chloroform, adsorbed over silica gel, and loaded for column chromatographic separation. The product, 3,5-diphenylisoxazole, was obtained as a white solid, which was recrystallized using ethanol to give pure isoxazole (**3a**) in 78% yield. In its  $^1\text{H}$  NMR spectrum, it showed a singlet at  $\delta$  6.8 ppm, a characteristic signal indicating the presence of C–H at the 4-position of the isoxazole ring. To check the generality of this reaction, various  $\alpha,\beta$ -unsaturated ketoximes were tried for oxidative cyclization using IBX as reagent. Besides the parent 3,5-diphenylisoxazole, 11 more differently substituted 3,5-diaryl isoxazoles were synthesized in moderate to



**Scheme 1.** IBX-mediated synthesis of 3,5-disubstituted isoxazole **3a–l** from  $\alpha,\beta$ -unsaturated ketoximes.

good yields after chromatographic separation (Scheme 1, Table 1). It was observed that the nature and position of the substituent on the aryl ring did not make much difference in reactivity. All the compounds have been well characterized by comparison with authentic sample melting points as well as spectroscopic data (IR, NMR). Having successfully prepared the diarylisoxazoles, we thought of synthesizing isoxazole-3-carboxylic acids starting from benzalacetone oxime and 3 equivalents of IBX. Chromatographic separation and recrystallization gave 5-phenyl isoxazole-3-carboxylic acid in 67% yield. Although the actual mechanistic pathway is not known, we thought to propose the following putative mechanism<sup>[38,39]</sup> (Scheme 2) for the conversion. Intramolecular Michael-type addition, insertion of hypervalent iodine across the double bond, followed by the oxidation of the methyl group to carboxylic acid group with the elimination of iodosobenzoic acid were performed. In its <sup>1</sup>H NMR spectrum, it showed a singlet at  $\delta$  9.33 ppm, indicating the presence of a proton of carboxylic acid, while in its <sup>13</sup>C NMR spectrum, it showed a singlet at  $\delta$  171 ppm, indicating the carbonyl carbon of the carboxylic acid. This prompted us to extend this methodology toward synthesizing more isoxazole carboxylic acids. We synthesized in all five such isoxazole-3-carboxylic acids (Table 2). The melting points obtained for the products compare well with the reported synthesis of isoxazole carboxylic acids (Scheme 3). None of the reactions led to any kind of by product formation.

With the growing need to follow the trend of green chemistry, we also attempted one-pot synthesis of 3,5-disubstituted isoxazole (Scheme 4). Herein the substituted

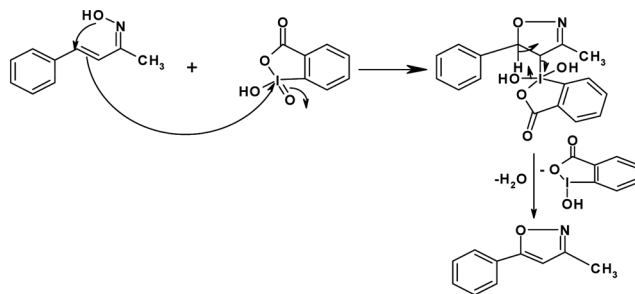
**Table 1.** IBX-mediated green synthesis of 3,5-disubstituted isoxazole **3a–l** from  $\alpha,\beta$ -unsaturated ketoximes

Entry	Product <sup>a</sup>		Isolated yield (%) <sup>b</sup>	Mp (°C)	Lit. mp <sup>c</sup> (°C)
	<i>R1</i>	<i>R2</i>			
<b>3a</b>	H	H	78	140–142	141–142 <sup>[14]</sup>
<b>3b</b>	2-Cl	4-OMe	69	85–86	85–86 <sup>[21]</sup>
<b>3c</b>	4-OMe	4-OMe	73	142–143	142–144 <sup>[20]</sup>
<b>3d</b>	4-Cl	4-OMe	61	185–186	185–186 <sup>[28]</sup>
<b>3e</b>	H	4-OMe	61	120–122	120–122 <sup>[14]</sup>
<b>3f</b>	4-OMe	4-Br	86	130–132	130–132 <sup>[27]</sup>
<b>3g</b>	4-Cl	4-Br	68	121–122	120–122 <sup>[24]</sup>
<b>3h</b>	4-Cl	H	72	171–172	170–172 <sup>[17]</sup>
<b>3i</b>	H	4-Br	81	178–179	178–180 <sup>[27]</sup>
<b>3j</b>	H	4-Cl	76	176–178	176–178 <sup>[27]</sup>
<b>3k</b>	H	4-NO <sub>2</sub>	60	227–228	226–228 <sup>[18]</sup>
<b>3l</b>	4-OMe	4-NO <sub>2</sub>	64	176–178	176–178 <sup>[37]</sup>

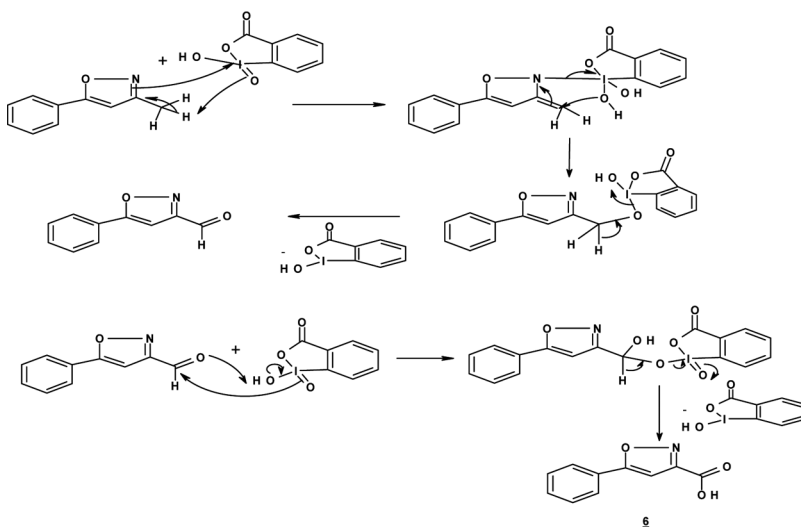
<sup>a</sup>All products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR data.

<sup>b</sup>Yields after purification by chromatography.

<sup>c</sup>Identified by comparison with authentic samples (14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, and 37).



## Step 1



## Step 2

**Scheme 2.** Proposed stepwise mechanism for the synthesis of isoxazole-3-carboxylic acids. Step 1: synthesis of 3-methyl-5-phenyl isoxazole; Step 2: synthesis of 5-phenyl isoxazole-3-carboxylic acid.

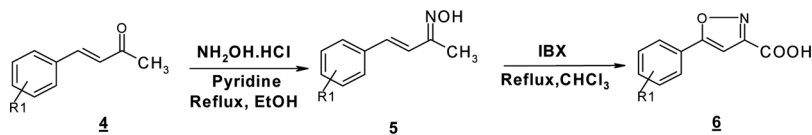
**Table 2.** One-pot synthesis of isoxazole-3-carboxylic acid from benzalacetone oximes

Entry	Product <sup>a</sup>	Isolated yield (%) <sup>b</sup>	Mp (°C)	Lit. mp <sup>c</sup> (°C)
<b>6a</b>	5-Phenylisoxazole-3-carboxylic acid	67	162–163	161–163 <sup>[33]</sup>
<b>6b</b>	5-(4-Methoxyphenyl)isoxazole-3-Carboxylic acid	75	156–157	156–157 <sup>[34]</sup>
<b>6c</b>	5-(4-Chlorophenyl)isoxazole-3-Carboxylic acid	70	180	180 <sup>[34]</sup>
<b>6d</b>	5-(2-Chlorophenyl)isoxazole-3-Carboxylic acid	61	(decomposes) 162–163	(decomposes) 162–162 <sup>[34]</sup>
<b>6e</b>	5-(4-Nitrophenyl)isoxazole-3-Carboxylic acid	62	176–177	176–178 <sup>[31]</sup>

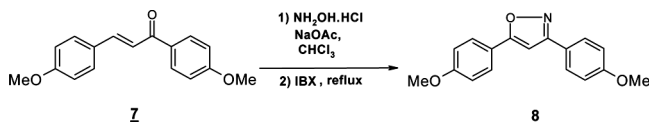
<sup>a</sup>All products were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and IR data.

<sup>b</sup>Yields after purification by chromatography.

<sup>c</sup>Identified by comparison with authentic samples (31, 33, 34, and 36).



Scheme 3. Synthesis of isoxazole-3-carboxylic acid (**6a–e**) from benzalacetone oximes.



Scheme 4. One-pot synthesis of 1,3-diaryl isoxazoles.

chalcone (**7**) was treated with excess of hydroxylamine under weakly basic conditions in chloroform. After 4 h, TLC indicated the formation of oxime. To this, 3 equivalents of IBX was added and the reaction mixture was further refluxed. After 15 h the reaction reached completion and after purification gave the corresponding isoxazole in 88% yield. Herein, this one-pot methodology involved three reactions: oxime formation, cyclization, and oxidation. The method was tried for only one example. All the products obtained were characterized by comparing melting points with literature and spectroscopic data (IR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR).

## EXPERIMENTAL

The IR spectra were recorded on an IR Prestige-21 Shimadzu FTIR spectrophotometer.  $^1\text{H}$  NMR spectra were obtained on a Avance Bruker 400-MHz spectrometer and  $^{13}\text{C}$  NMR were obtained on a Avance Bruker 75-MHz spectrometer. Samples were analysed in  $\text{CDCl}_3$ , and the chemical shift values are expressed relative to  $\text{Me}_4\text{Si}$  as an internal standard. The product isoxazoles were purified using glass column and silica gel (60–120 Mesh). *o*-Iodoxybenzoic acid was prepared from *o*-iodobenzoic acid by a literature known procedure.<sup>[40]</sup>

### General Procedure for the Synthesis of 3,5-Disubstituted Isoxazole (**3**)

Ketoxime **2a** (0.223 g, 1 mmol), IBX (0.280 g, 1 mmol), and chloroform (5 mL) were placed in a 100-mL round-bottom flask. The reaction mixture was refluxed for 4 h. The product **3a** was purified using column chromatography with petroleum ether and ethyl acetate (9:1) as an eluent. The product was further recrystallized using ethanol. 3,5-Diphenylisoxazole (**3a**)<sup>[14–20]</sup>: White solid, 78%, mp 140–141 °C; IR (KBr),  $\nu$  ( $\text{cm}^{-1}$ ): 1250, 1430, 3010.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ),  $\delta$  (ppm): 6.8 (s, 1H), 7.21–8.05 (m, 10H).

### General Procedure for the Synthesis of Isoxazole-3-carboxylic Acid (**6**)

Ketoxime **5a** (0.161 g, 1 mmol), IBX (0.840 g, 3 mmol), and chloroform (5 mL) were placed in a 100 mL round-bottom flask. The reaction was refluxed for 4 h. The

reaction was continuously monitored using TLC. The product **6a** was purified using column chromatography with petroleum ether and ethyl acetate (9:1) as an eluent.

5-Phenylisoxazole-3-carboxylic acid (**6a**)<sup>[34]</sup>: White solid, 67%, mp 162–163 °C; IR (KBr),  $\nu$  (cm<sup>-1</sup>): 1450, 1550, 1690, 3000, 3200. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 7.202–8.145 (m, 5H), 9.33(s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 30.21, 97.88, 134–124, 142.45, 162.56, 171.54.

### Procedure for One-Pot Synthesis of 3,5-(Bis-P-methoxyphenyl)-isoxazole (**8**)

Chalcone **7** (0.268 g, 1 mmol), hydroxylamine hydrochloride (0.416 g, 6 mmol), sodium acetate (0.5 g, 6 mmol), and chloroform (5 mL) were placed in a 100-mL, round-bottom flask and refluxed for 4 h. Oxime formation was observed on TLC. This was followed by addition of IBX (0.840 g, 3 mmol) for reaction. The reaction was continuously monitored using TLC. After completion of the reaction, the product **8** was separated and purified using column chromatography with petroleum ether and ethyl acetate (9:1) as an eluent.

3,5-Bis (4-methoxyphenyl)isoxazole (**8**)<sup>[14,20]</sup>: White solid, 88%, mp 144 °C; IR (KBr),  $\nu$  (cm<sup>-1</sup>): 1250, 1460, 1590, 3050. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 3.84 (s, 3H), 5.45 (s, 3H), 6.80 (s, 1H), 7.20–7.78 (m, 8H).

### CONCLUSION

In conclusion, a convenient and an efficient method for the synthesis of 3,5-diarylisoxazoles from  $\alpha,\beta$ -unsaturated ketoximes have been developed for various substrates. The significance of our synthesis of isoxazole carboxylic acid is that it involves three reactions: cyclization, followed by oxidation, leading to isoxazole ring, and then oxidation of side chain methyl group to carboxylic acid group. Also the one-pot synthesis of 3,5-diarylisoxazole has been carried out effectively. Use of IBX for oxidative cyclization signifies nontoxicity and ecofriendliness of the methodology. All the reagents are used in stoichiometric amounts in view of the need for environmentally benign synthesis. The sequence exhibits wide scope and is tolerant of various substituted aromatic substrates.

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### SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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