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## Convenient Synthesis of 3,5-Disubstituted Isoxazoles

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**Abstract:**  $\alpha,\beta$ -Unsaturated oximes obtained from the corresponding  $\alpha,\beta$ -unsaturated ketones on treatment with 2 equivalents of manganese dioxide in refluxing chloroform gives 3,5-disubstituted isoxazoles in good yields.

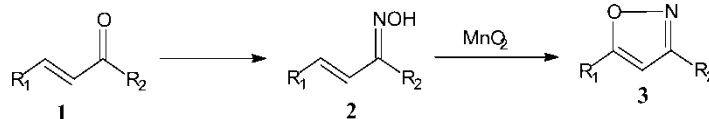
**Keywords:** heterocycle, isoxazole,  $\text{MnO}_2$ , oxidative cyclisation

Isoxazoles<sup>[1]</sup> form an important class of aromatic heterocycles and have diverse applications. Their range of uses includes medicinal, herbicidal, fungicidal, pesticidal applications; dyes; insulating oils and lubricants. Isoxazoles contain a weak nitrogen–oxygen bond, which has been exploited to provide difunctionalized compounds such as 1,3-dicarbonyl, enamino ketone,  $\gamma$ -aminoalcohols, and  $\beta$ -hydroxy ketone. Thus, isoxazoles serve as building blocks in organic synthesis.

Earlier, we had reported dichloro dicyano benzoquinone (DDQ) as an oxidative cyclizing agent for the synthesis of 3,5-diaryl isoxazoles from the oximes of corresponding ketones.<sup>[2]</sup> Recently,  $\text{MnO}_2$  has been used as a

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Scheme 1.

tandem oxidation process (TOP) agent<sup>[3]</sup> in a variety of synthetic manipulations including synthesis of heterocycles. Because  $\text{MnO}_2$  is a mild, nontoxic, and cheaply available reagent, we thought of using this for the synthesis of isoxazoles (Scheme 1). Our initial attempt at oxidative cyclisation of the chalcone oxime **1a** in  $\text{CH}_2\text{Cl}_2$  failed. When refluxing chloroform was used, we could get the corresponding 3,5-diphenyl isoxazole (**2a**) in 60% yield after 2 h. Similarly the other unsaturated oximes (Table 1, entries **2a–j**) yielded the corresponding isoxazoles. To check the feasibility of the TOP sequence,<sup>[3]</sup> a mixture of chalcone **1a**,  $\text{MnO}_2$ ,  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , and triethylamine (TEA) in refluxing  $\text{CHCl}_3$  was attempted, but without success. When tetrahydrofuran (THF) was used as a solvent, some amount of direct formation of product was observed, but under the varying conditions tried, complete conversion could not be obtained. However, it was possible to obtain the isoxazole in a one-pot experiment wherein initially chalcone **1a**, 3 equivalents of  $\text{NH}_2\text{OH} \cdot \text{HCl}$ , and 3 equivalents of TEA were stirred for 30 min, followed by the addition of  $\text{MnO}_2$  (5 equivalents) and refluxing for 2 h.

In conclusion, we have developed a convenient method for the synthesis of 3,5-disubstituted isoxazoles from  $\alpha,\beta$ -unsaturated ketones. The procedure works well for differently substituted 3,5-diaryl isoxazoles (Table 1, entries **2a–h**). It also works well when one of the group is alkyl (entries **2i–j**). It fails to work when both the groups are alkyl and also with  $\alpha,\beta$ -unsaturated aldehydes or

Table 1. Preparation of 3,5-disubstituted isoxazoles **3a–j**

Compound 1–3	R <sub>1</sub>	R <sub>2</sub>	Yield of 3 (%)	Mp (°C) (lit.mp)
<b>a</b>	Ph	Ph	67	141 (140–141 <sup>[4]</sup> )
<b>b</b>	Ph	4-MeOC <sub>6</sub> H <sub>4</sub>	62	122 (122 <sup>[5]</sup> )
<b>c</b>	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	69	175 (172–178 <sup>[6]</sup> )
<b>d</b>	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	75	178 (178–180 <sup>[6]</sup> )
<b>e</b>	Ph	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	65	228 (226–228 <sup>[7]</sup> )
<b>f</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	79	209 (210 <sup>[7]</sup> )
<b>g</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4-BrC <sub>6</sub> H <sub>4</sub>	65	130 (130–132 <sup>[6]</sup> )
<b>h</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	60	175 (172–175 <sup>[6]</sup> )
<b>i</b>	Ph	CH <sub>3</sub>	70	67 (67 <sup>[8]</sup> )
<b>j</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	75	113 (111–112 <sup>[9]</sup> )

their oximes. Also, extending the method for the one-pot synthesis of corresponding pyrazoles using hydrazine did not work well in our hands.

## EXPERIMENTAL

All melting points are uncorrected and were measured by the normal Thiels tube (paraffin) method. Column chromatography was performed on silica gel G (13% CaSO<sub>4</sub> as binder). IR spectra were recorded on a Shimadzu FT-IR spectrophotometer (KBr pellets). <sup>1</sup>H NMR and <sup>13</sup>CMR were recorded on a Bruker 300-MHz instrument. The multiplicities of carbon signals were obtained from distortionless enhancement by polarization transfer (DEPT) experiments.

### General Procedure

A mixture of  $\alpha,\beta$ -unsaturated oxime **2** (1 mmol), MnO<sub>2</sub> (2 mmol), and chloroform (15 mL) was refluxed for 2 h (or until the reaction was completed). After cooling, it was filtered and the black residue was washed with chloroform (5 × 5 mL). The combined filtrate after concentration was further purified by passing through a small column of silica gel using ethyl acetate–hexane (5:95) as an eluent.

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