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# An environmentally benign synthesis of isoxazolines and isoxazoles mediated by potassium chloride in water

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ABSTRACT

An effective and environmentally benign procedure for the synthesis of isoxazolines and isoxazoles has been developed by a cycloaddition of nitrile oxides with alkenes or alkynes in water. In this approach, potassium chloride is first oxidized into chlorine in water by the environmentally friendly oxidant Oxone®, then aldoximes are oxidized into nitrile oxides by the in situ generated hypochlorous acid, finally a 1,3-dipolar cycloaddition between nitrile oxides and alkenes or alkynes occurs to provide the corresponding isoxazolines and isoxazoles in good yields.

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## Introduction

Isoxazolines and isoxazoles are two major classes of five-membered nitrogen containing heterocycles, which are found in a large number of natural products and biologically active compounds.[1] A variety of synthetic methods has been developed for preparation of isoxazolines and isoxazoles, of which the most convenient and attractive route is probably the 1,3-dipolar cycloaddition of nitrile oxides to alkenes or alkynes.[2] Nitrile oxides are commonly generated from aldoximes via oxidations using different oxidants. Organic hypervalent iodine reagents, due to their low toxicity, ready availability, easy handling, and reactivity similar to that of heavy metal reagents, have been recently used as effective oxidants for the above purpose.[3] Other oxidants, such as NBS, NCS, NaOCl, *t*-BuOCl, and *t*-BuOI also have been used in the cycloaddition.[4] Due to most of the 1, 3-dipolar cycloadditions of nitrile oxides to alkenes or alkynes usually occurring in organic solvents or mixed solvent systems, utilization of water as a medium, an environmentally benign system, is less common. Hailes and Bala have investigated an intramolecular 1,3-dipolar cycloaddition in water albeit longer time is required to get good yield.[5] Rohloff et al. have reported a one-pot 1,3-dipolar cycloaddition in water but only tolerating water-soluble olefins and acetylenes as substrates.[6] Sarma group have developed a one-pot high-throughput synthesis of isoxazolines in bleach with moderate or low yield.[7] Therefore, from both environmental and economic viewpoints, to develop an efficient synthesis of isoxazolines and isoxazoles using water as the sole solvent is still desired.

Potassium hydrogen persulfate ($KHSO_5$), or Oxone® ($2KHSO_5$–$KHSO_4$–$K_2SO_4$), is an effective oxidant. Due to its good stability, water-solubility, ease of transport, nontoxic 'green' nature, nonpolluting byproducts, and cost-effectiveness, this solid reagent has become a popular reagent for oxidative transformations.[8] Recently, Zhdankin and co-workers have developed a novel cycloaddition of nitrile oxides with alkenes using KI as the catalyst and Oxone® as the terminal oxidant, which occurred in MeOH–$H_2O$ (20:1) and provided isoxazolines in good yields.[9] However, this protocol is not suitable to prepare isoxazoles since alkynes were not active in the reaction when they were used in place of alkenes. In order to improve the application of Oxone® and develop a new process for the synthesis of isoxazolines and isoxazoles, we have investigated the reaction of nitrile oxides with alkenes or alkynes in the presence of potassium chloride (KCl) and Oxone® in water. Herein, an environmentally benign synthesis of isoxazolines and isoxazoles has been developed.

## Discussion and results

At first, an inexpensive and readily available KCl was attempted to mediate the cycloaddition of nitrile oxides and alkenes, and a mixture of benzaldoxime (1.0 equiv), styrene (2.0 equiv), Oxone® (2.0 equiv) and KCl (1.0 equiv) in methanol was stirred at room temperature for 12 h, the desired cycloaddition product 3,5-diphenylisoxazoline was observed with only a trace amount (Table 1, entry 1). With the observation of the bad solubility of KCl and Oxone®

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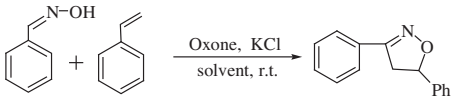
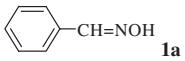
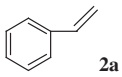
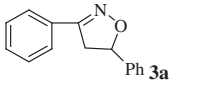
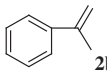
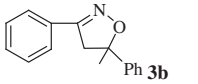
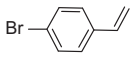
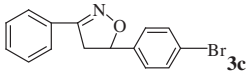
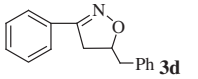
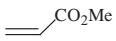
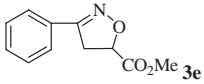
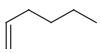
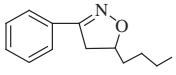
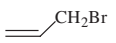
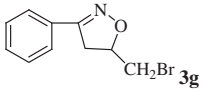
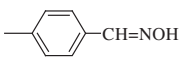
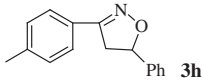
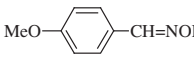
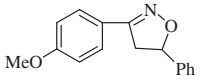
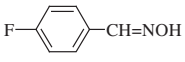
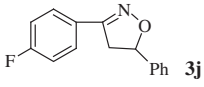
**Table 1**
Optimization of the cycloaddition of nitrile oxide from benzaldoxime with styrene mediated by KCl




| Entry | Oxone® (equiv) | KCl (equiv) | PhCH=CH$_2$ (equiv) | Solvent | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | 2.0 | 1.0 | 2.0 | $CH_3OH$ | 12 | Trace |
| 2 | 2.0 | 1.0 | 2.0 | MeOH–$H_2O$ (4:1) | 12 | 21 |
| 3 | 2.0 | 1.0 | 2.0 | MeOH–$H_2O$ (3:1) | 12 | 33 |
| 4 | 2.0 | 1.0 | 2.0 | MeOH–$H_2O$ (2:1) | 12 | 36 |
| 5 | 2.0 | 1.0 | 2.0 | MeOH-$H_2O$ (1:1) | 12 | 71 |
| 6 | 2.0 | 1.0 | 2.0 | $H_2O$ | 2 | 85 |
| 7 | 2.0 | 0 | 2.0 | $H_2O$ | 24 | Trace |
| 8 | 2.0 | 0.2 | 2.0 | $H_2O$ | 4 | 68 |
| 9 | 2.0 | 0.5 | 2.0 | $H_2O$ | 4 | 72 |
| 10 | 2.0 | 1.0 | 2.0 | $H_2O$ | 4 | 86 |
| 11 | 2.0 | 1.5 | 2.0 | $H_2O$ | 4 | 32 |
| 12 | 2.0 | NaCl (1.0) | 2.0 | $H_2O$ | 4 | 80 |
| 13 | 2.0 | $NH_4Cl$ (1.0) | 2.0 | $H_2O$ | 4 | 84 |
| 14 | 2.0 | 1.0 | 1.0 | $H_2O$ | 4 | 56 |
| 15 | 2.0 | 1.0 | 1.2 | $H_2O$ | 4 | 52 |
| 16 | 2.0 | 1.0 | 1.5 | $H_2O$ | 4 | 64 |
| 17 | 2.0 | 1.0 | 2.5 | $H_2O$ | 4 | 98 |
| 18 | 2.0 | 1.0 | 3.0 | $H_2O$ | 4 | 96 |
| 19 | 1.2 | 1.0 | 2.5 | $H_2O$ | 4 | 78 |
| 20 | 1.5 | 1.0 | 2.5 | $H_2O$ | 4 | 96 |
| 21 | 2.5 | 1.0 | 2.5 | $H_2O$ | 4 | 94 |
| 22 | 1.5 | 1.0 | 2.5 | $H_2O$ | 2 | 94 |
| 23 | 1.5 | 1.0 | 2.5 | $H_2O$ | 3 | 98 |
| 24 | 1.5 | 1.0 | 2.5 | $H_2O$ | 5 | 97 |

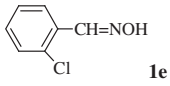
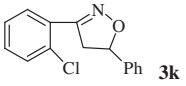
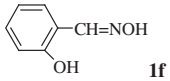
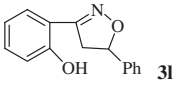
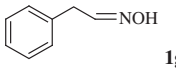
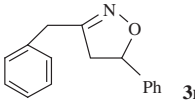
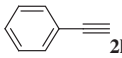
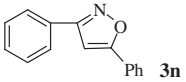
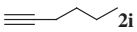
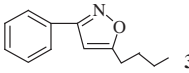
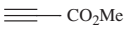
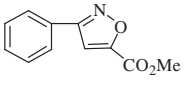
[a] Isolated yield.

**Table 2**
The result of cycloaddition of nitrile oxides from aldoximes to alkenes or alkynes

| Entry | Aldoxime **1** | Alkene/alkyne **2** | Isoxazoline/isoxazole **3** | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** |  **3a** | 98 |
| 2 | **1a** |  **2b** |  **3b** | 81 |
| 3 | **1a** |  **2c** |  **3c** | 85 |
| 4 | **1a** |  **2d** |  **3d** | 79 |
| 5 | **1a** |  **2e** |  **3e** | 88 |
| 6 | **1a** |  **2f** |  **3f** | 73 |
| 7 | **1a** |  **2g** |  **3g** | 92 |
| 8 |  **1b** | **2a** |  **3h** | 92 |
| 9 |  **1c** | **2a** |  **3i** | 83 |
| 10 |  **1d** | **2a** |  **3j** | 89 |

(*continued on next page*)

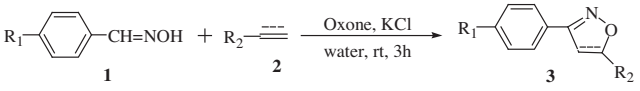
**Table 2** (*continued*)

| Entry | Aldoxime **1** | Alkene/alkyne **2** | Isoxazoline/isoxazole **3** | Yield[a] (%) |
|---|---|---|---|---|
| 11 |  **1e** | **2a** |  **3k** | 77[b] |
| 12 |  **1f** | **2a** |  **3l** | 87 |
| 13 |  **1g** | **2a** |  **3m** | 56[b] |
| 14 | **1a** |  **2h** |  **3n** | 87 |
| 15 | **1a** |  **2i** |  **3o** | 80 |
| 16 | **1a** |  **2j** |  **3p** | 85 |

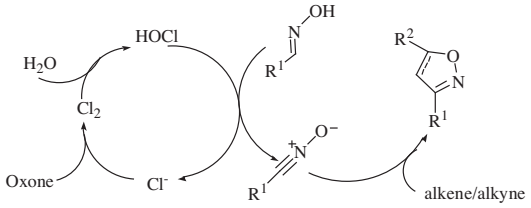
[a] Isolated yield; the reaction time was 5 h.
[b] The reaction time was 5 h.

in methanol, water was added in methanol to form mixed solvent in different ratios. With the ratio of water increased, the reaction yield increased as well (entries 2–5). If only water was utilized, the cycloaddition provided a good yield (85%) in 2 h although the reaction was a biphasic process (entry 6). Encouraged by this result, we optimized other reaction conditions. As shown in Table 1, if KCl was absent, only a trace amount of product was observed (entry 7) and 1.0 equivalent of KCl was found to result the highest yield (86%) after 4 h (entries 8–11). Other chlorides, such as NaCl and $NH_4Cl$ were also active under the same reaction conditions (entries 12, 13). The amounts of styrene and Oxone® were also optimized to 2.5 equiv of styrene and 1.5 equiv of Oxone® (entries 14–21). The reaction completed in 3 h in the scales of our experiments, in which the product 3,5-diphenylisoxazoline was obtained in near quantitative yield (entries 21–24).

Having established the optimal conditions, the cycloaddition of 1.0 equiv of aldoximes (1), 2.5 equiv of alkenes (2), 1.5 equiv of Oxone®, and 1.0 equiv of KCl in water at room temperature for 3 h, a series of corresponding isoxazolines (3) were thus obtained, and the results are summarized in Table 2. When benzaldoxime (**1a**) was used as starting substrate, the reaction was compatible with the studied alkenes and provided the corresponding isoxazolines in good to excellent yields (Table 2, entries 1–7). Other benzaldoximes with various electron-donating and electron-withdrawing groups on the benzene ring (**1b**–**1f**) also reacted smoothly with styrene (**2a**), giving the respective isoxazolines in good to excellent yields (entries 8–12). Phenylacetaldoxime (**1g**), an aliphatic aldoximes, could react with **2a** and afforded the desired product in a moderate yield after 5 h (entry 13). Encouraged by the results obtained with alkene, we then tried to prepare isoxazoles from alkynes. Three different alkynes were attempted to react with **1a** and finally the corresponding isoxazoles were obtained in good




**Scheme 1.** The cycloaddition of nitrile oxides from aldoximes to alkenes or alkynes mediated by KCl.




**Scheme 2.** Proposed mechanism for the synthesis of isoxazolines and isoxazoles.

yields (entries 14–16). Thus, the new procedure could be applied in the synthesis of both isoxazolines and isoxazoles (Scheme 1).[10]

A plausible mechanism is proposed, which is similar to that reported by Zhdankin and co-workers[9] (Scheme 2). It includes that potassium chloride is first oxidized into chlorine in water by Oxone®, then aldoximes are oxidized into nitrile oxides by the in situ generated hypochlorous acid. Finally, a 1,3-dipolar cycloaddition between the nitrile oxides and alkenes or alkynes furnishes the corresponding isoxazolines or isoxazoles.

## Conclusions

We have developed a convenient and environmentally benign procedure for the synthesis of isoxazolines and isoxazoles. Compared to previously reported methods, this procedure utilizes the readily available and inexpensive KCl and 'green' oxidant Oxone® to mediate the 1,3-dipolar cycloaddition between nitrile oxides and alkenes or alkynes in water. The advantages of this procedure include mild reaction conditions, simple and environmentally benign procedure, short reaction time, and good yields. Furthermore, this method is suitable for the synthesis of not only isoxazolines but also isoxazoles, which extends the scope of 1,3-dipolar cycloaddition between nitrile oxides and alkenes or alkynes in water.

## Acknowledgment

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.118.

## References and notes


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10. *A typical procedure for the synthesis of isoxazolines and isoxazoles*: Aldoxime **1** (0.5 mmol), alkene **2** (1.25 mmol), and KCl (0.5 mmol) were added to a flask before water (3 ml) was added. Oxone® (0.75 mmol) was then added into the stirred mixture. The mixture was stirred at room temperature for 3 h after the reaction completed. The mixture was transformed into a separating funnel, and the flask was washed with $CH_2Cl_2$ (4 ml). Extraction of the mixture with $CH_2Cl_2$ ($2 \times 4$ ml), the combined organic phase was dried over anhydrous $Na_2SO_4$, filtered, and the filtration was concentrated under reduced pressure. The residue was purified on a silica gel plate with Thin-Layer Chromatography technique (10:1 petroleum ether–EtOAc) to provide the corresponding isoxazoline **3**.