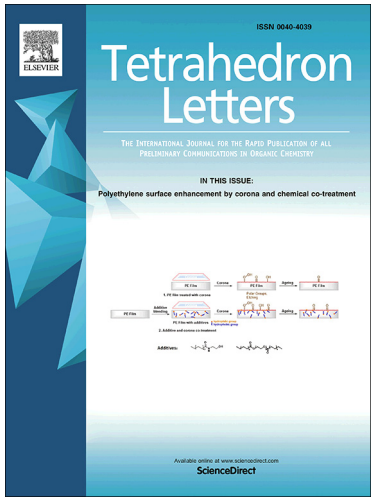


# A Convenient one-pot synthesis of 3,5-diarylisoxazoles via oxidative cyclisation using catalytic $CuBr_2$ and Oxone

Ashish Bhatt, Rajesh K. Singh, Ravi Kant

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## Graphical Abstract

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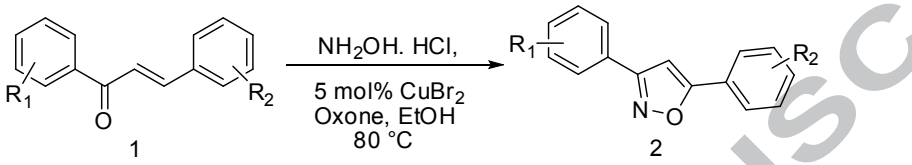
Ashish Bhatt[a], Rajesh K. Singh[b], Ravi Kant[a]




$R_1$ = H, 4-Me, 4-OMe, 4-$OC_2H_5$, 2,4-$Me_2$, 4-Cl, 2-Cl, 4-Br, 3,4-$Cl_2$, 4-$NO_2$, $R_2$ = H
$R_1$ = H, $R_2$ = 4-Me, 3-Me, 3-OMe, 4-Cl, 3-Cl, 2-Cl, 4-Br, 3-Br, 2-$NO_2$

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# A Convenient one-pot synthesis of 3,5-diarylisoxazoles via oxidative cyclisation using catalytic $CuBr_2$ and Oxone

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ABSTRACT

A facile one-pot synthesis of 3,5-diarylisoxazoles from *α,β*-unsaturated ketones and hydroxylamine hydrochloride is reported. The reaction is efficiently promoted by catalytic $CuBr_2$ and Oxone to afford the desired products mostly in high yields and in relatively short time. The mild nature of the synthesis and short reaction time are notable advantages of the developed protocol. This protocol is effective toward various substrates having different functionalities.



## Introduction

Isoxazole derivatives represent a privileged class of five membered nitrogen heterocycles and are extensively found in numerous biologically active molecules with anticancer, antidepressant, antibiotic, and analgesic activities [1–4]. Moreover, they are used as key building blocks in materials science and as various complex synthetic intermediate in organic synthesis [5,6]. By capitalizing on the presence of a comparatively weak N-O bond, for example, isoxazoles can be transformed into such useful structures as those found in α-hydroxy-β-diketones and other β-dicarbonyl compounds [7-10]. Owing to their good reactivity and synthetic utility, the development of more efficient synthetic methods for isoxazoles is of great importance to organic chemists [11–15].

Isoxazoles are often synthesized through a [3+2] cycloaddition of nitrile oxides with alkynes or alkenes followed by oxidation [16-18]. As van Delft has noted, the thermal [3+2] cycloaddition method can suffer from low yields, side-reactions and poor regioselectivity [19]. While transition metal mediated preparations of 3,5-disubstituted and 3,4-disubstituted isoxazoles have been reported to provide satisfactory yields [20,21].

The reaction of hydroxylamine with 1,3-dicarbonyl or *α,β*-unsaturated carbonyl compounds, followed by an intramolecular oxidative cyclization provides another approach to isoxazoles [22-23]. Since the oximes can be conveniently generated in high yield, the oxidative cyclization of *α,β*-unsaturated oximes or *β*-keto oximes constitutes the essential step for the successful construction of the isoxazole framework.Various oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) [24], $MnO_2$ [25], $I_2$/KI in $NaHCO_3$ [26], tetrakis(pyridine)cobalt dichromate (TPCD) [27], KOH-dioxane [28], N-bromosuccinimide [29], $NOBF_4$ 30 and hypervalent iodine reagents, such as $PhI(OCOCH_3)_2$ [31,32], $PhI(OCOCF_3)_2$ [33] are widely employed to initiate the intramolecular oxidative cyclization. Microwave-assisted synthesis of isoxazoles has also been reported [34,35]. There are few reports of one-pot synthesis of isoxazole [36–38]. However, the mentioned methods involve the use of expensive catalyst, tedious synthetic procedures, time taking reactions and unsatisfactory yields. Hence, the development of milder and more general procedures to access isoxazole derivatives with high yields in short reaction time remains desirable.

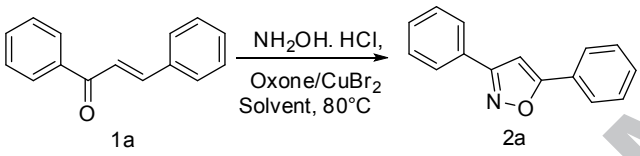
Oxone is a versatile reagent and is becoming increasingly popular because of its commercial availability at low cost and lesser corrosiveness. The combination of $CuBr_2$/Oxone has been used for the several oxidative transformations. Our continued interest in the development of useful synthetic methodologies prompted us to explore the feasibility of $CuBr_2$/Oxone for the one-pot synthesis of isoxazole derivatives with high yields. However, it has not been investigated as a catalyst in the synthesis of isoxazole until now.

## Result and Discussion

Herein, we describe a convenient one-pot synthesis of 3,5-diaryl isoxazoles from *α,β* -unsaturated ketones. The parent chalcone **1a** was prepared by Claisen–Schmidt condensation as per the reported literature procedure [39-40]. Our preliminary investigation began with the reaction of Chalcone **1a** and hydroxylamine hydrochloride in the presence of Oxone (1 equiv.) and a catalytic amount of $CuBr_2$ (2 mol%) in methanol at 80 °C. We were delighted to observe the formation of the desired

product **2a**, albeit in a low yield of 55% (Table 1, entry 1). Next, we optimized the reaction conditions in order to increase the yield. Thus, different solvents were screened and the results are summarized in Table 1. It was found that ethanol was the most superior solvent in terms of the reaction time and yield of the product (Table 1, entry 2). Once we had established a suitable solvent for the synthesis of isoxazole, we then focused on the quantity of Oxone and $CuBr_2$. An increase in the amount of Oxone (from 1 equiv. to 2 equiv.) and $CuBr_2$ (from 2 mol% to 5 mol%) not only decreased the reaction time from 1.5 h to 30 min., but also increased the product yield from 55% to 85% (Table 1, entry 8). Further increasing the quantity of Oxone to 3 equiv. and $CuBr_2$ (10 mol%) led to a decrease in the yield to 65% (Table 1, entry 9). Therefore, we decided to perform the subsequent reactions of the various chalcones with hydroxylamine hydrochloride in the presence of Oxone (2 equiv.) and $CuBr_2$ (5 mol%) as the catalyst in ethanol at 80 °C. The effect of temperature on the reaction rate as well as on the yields of the products were also investigated. Faster reactions occurred on increasing the temperature but the product yields were not satisfactory. The progress of the reactions was monitored by TLC analysis (using EtOAc–hexane as the eluent).

**Table-1 Optimization of the Reaction Conditions**




1a 2a

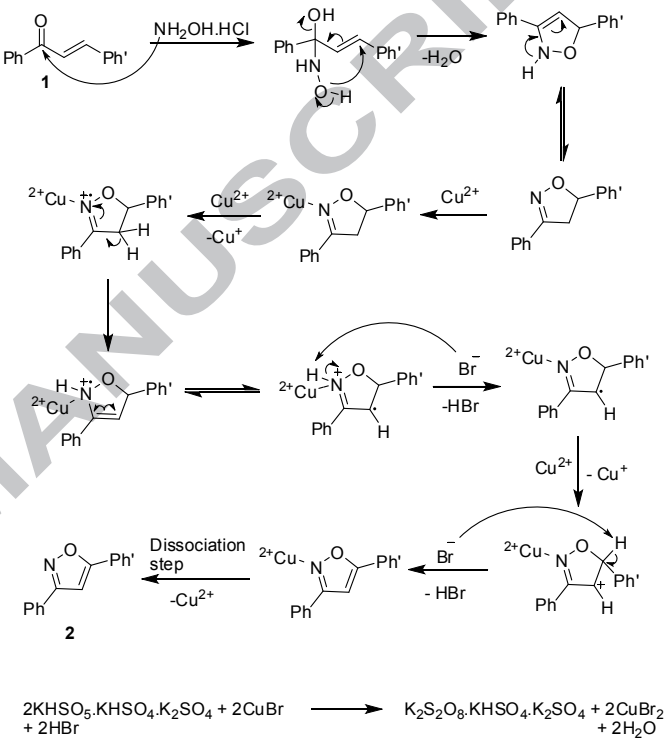
| Entry | Solvent | Oxone (eq.) | $CuBr_2$ (mol%) | Time | Yield (%) |
|---|---|---|---|---|---|
| **1** | MeOH | 1 | 2 | 1.5 h | 55 |
| **2** | EtOH | 1 | 2 | 1h | 65 |
| **3** | IPA | 1 | 2 | 2.5 h | 40 |
| **4** | Toluene | 1 | 2 | 3 h | 40 |
| **5** | AcOH | 1 | 2 | 1.5 h | 45 |
| **7** | EtOH | 1.5 | 5 | 45 min. | 70 |
| **8** | EtOH | 2 | 5 | 30 min. | 85 |
| **9** | EtOH | 3 | 10 | 15 min. | 65 |

With the optimized reaction conditions established, the scope of this protocol was investigated as listed in Tables 2 and 3. A variety of substituents on the chalcone ($R^1$) were explored firstly. As shown in Table 2, either electron-donating groups such as methoxy, ethoxy and methyl or electron-withdrawing groups such as chloro, bromo and nitro on the aryl rings were well tolerated, affording the corresponding 3,5-diarylisoxazole products in good yields (Table 2, 2a–2j). The reaction is insensitive to steric hindrance, for substrate with ortho-substituent resulted in similar yield with the para-substituted one (2f vs 2g). High efficiency was performed for the reaction of chalcone with strong electron deficient nitro group (2j). Notably, the tolerance of halide substituents such as Cl and Br, provides possibilities for further functionalizations (Table 2, 2f–2i).

Next, various substituents on the chalcone ($R^2$) were tested. Substrates with electron donating or withdrawing group all reacted smoothly to generate the desired 3,5 diarylisoxazoles in good yields (Table-3).

**Mechanism**

Based on our experimental data and previous report, [41–42] a plausible reaction mechanism for the formation of 3,5-disubstituted isoxazole **2** is proposed (Scheme 1). According to this route, chalcone on treatment with hydroxyl amine hydrochloride first provides 3,5-diaryl isoxazoline and form Cu(II) complex of isoxazoline with $CuBr_2$ which finally oxidizes to isoxazole via the formation of isoxazolinium radical cation through a single electron transfer to $Cu^{2+}$. Finally, the nucleophile bromide ion ($Br^-$) abstract proton form isoxazolinium cation to give the product. CuBr formed in reaction oxidizes by Oxone to regenerate the $CuBr_2$.

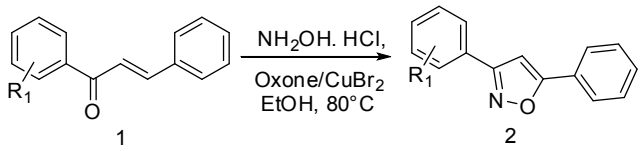



**Scheme 1**. Plausible mechanism for oxidative cyclisation of Chalcone with hydroxyl amine hydrochloride

**Conclusion**

In conclusion, we have developed a short and efficient synthesis of 3,5-diarylisoxazoles using a mild and straightforward one-pot oxidative cyclization method using the combination of $CuBr_2$/Oxone, which is a low cost commercially available reagent. A variety of substituents are tolerated allowing the synthesis of diverse products in good to excellent yields. The main advantage of this procedure is to access 3,5-diarylisoxazoles with high yields and short reaction time. The newly developed synthetic route is believed to be valuable for the construction of building blocks but also for medicinal chemistry studies comprising isoxazole moiety.

**Table-2 Synthesis of Various 3,5-diarylisoxazoles with the scope of substituents ($R^1$) on the chalcone**




1 2

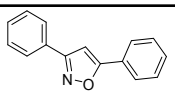
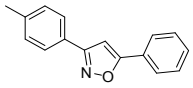
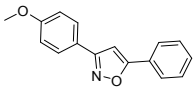
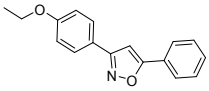
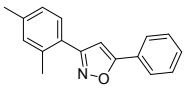
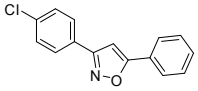
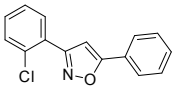
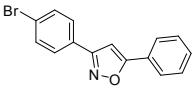
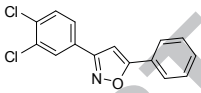
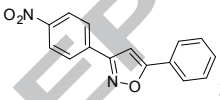
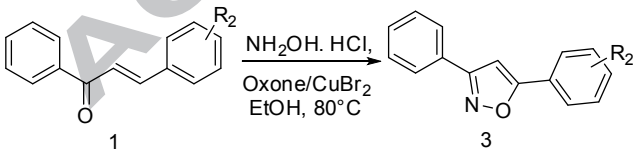
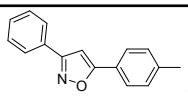
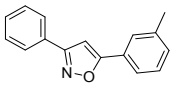
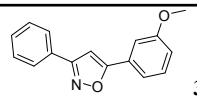
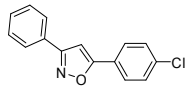
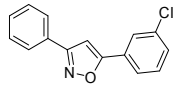
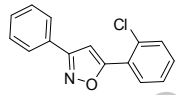
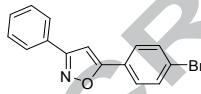
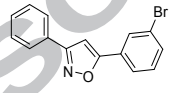
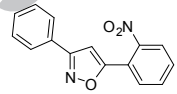
| Entry | $R^1$ | Product | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | Hydrogen |  **2a** | 30 | 85 |
| 2 | 4-Me |  **2b** | 35 | 83 |
| 3 | 4-OMe |  **2c** | 30 | 81 |
| 4 | 4-$OC_2H_5$ |  **2d** | 35 | 85 |
| 5 | 2,4-$Me_2$ |  **2e** | 40 | 82 |
| 6 | 4-Cl |  **2f** | 35 | 83 |
| 7 | 2-Cl |  **2g** | 40 | 81 |
| 8 | 4-Br |  **2h** | 35 | 84 |
| 9 | 3,4-$Cl_2$ |  **2i** | 40 | 79 |
| 10 | 4-$NO_2$ |  **2j** | 45 | 79 |

**Table-3 Synthesis of Various 3,5-diarylisoxazoles with the scope of substituents ($R^2$) on the chalcone**




1 3

| Entry | $R^2$ | Product | Time (min) | Yield (%) |
|---|---|---|---|---|
| 1 | 4-Me |  **3a** | 30 | 78 |
| 2 | 3-Me |  **3b** | 30 | 80 |
| 3 | 3-OMe |  **3c** | 35 | 77 |
| 4 | 4-Cl |  **3d** | 35 | 83 |
| 5 | 3-Cl |  **3e** | 30 | 81 |
| 6 | 2-Cl |  **3f** | 40 | 80 |
| 7 | 4-Br |  **3g** | 40 | 78 |
| 8 | 3-Br |  **3h** | 40 | 75 |
| 9 | 2-$NO_2$ |  **3i** | 40 | 77 |

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/xxxx/j.tetlet.xxxxxxxx.

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## Highlights

- $CuBr_2$ catalysed one-pot synthesis of 3,5-diarylisoxazole from chalcone and $NH_2OH.HCl$
- Oxone is used as an oxidant to oxidise CuBr (formed in the reaction) to $CuBr_2$
- Various substituted chalcones tolerated and gave 3,5-diarylisoxazole in good yields.