



## Copper catalyzed access to functionalized oxazoles from oximes *via* carbenoids

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### ABSTRACT

An operationally simple, economical and straightforward synthesis of diverse oxazoles from oximes possessing a vicinal carbonyl group has been achieved by treatment of the latter with terminal diazo compounds like ethyl/benzyl diazoacetate and diazoacetophenone (which act as carbenoids) in one pot. At least two reducible functional groups (two ester groups or cyano + ester) are simultaneously introduced in one step. This reaction involves expulsion of a molecule each of N<sub>2</sub> and water only as byproducts under copper catalysis. The structure of one of these oxazoles is confirmed by X-ray crystallography. Both the ester groups in the oxazole product could be reduced to alcohol moieties by using NaBH<sub>4</sub>/EtOH.

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Cascade processes that incorporate multiple bond forming events carried out in one-pot are of paramount interest in organic synthesis.<sup>1</sup> Efficient synthetic methods required to assemble complex molecular arrays include reactions that are both selective and economical in atom count (maximum number of atoms of reactants appearing in the products). Transition metal-catalyzed methods that are both selective and economical for the formation of cyclic structures, of great interest for biological purposes, represent an important starting point for this long-term goal.<sup>1c</sup> The synthesis of heterocycles has increasingly attracted the synthetic pursuit of chemists because they are a vital part of new drug discovery and indispensable materials in the implementation of any industrial evolution.<sup>2</sup>

The key core of oxazole skeleton exists in numerous natural products and has potential applications in medicinal and agrochemical fields.<sup>3,4</sup> In particular, 2,4,5-trisubstituted oxazoles exhibit anti-articular rheumatism activity,<sup>3e</sup> hypoglycemic activity<sup>3f</sup> and inhibitory activity on aldose reductases.<sup>3g</sup> Several methods are available for the synthesis of substituted oxazoles such as the reaction of aldehyde with nitrile,<sup>5a</sup> treatment of alkyne with nitrile in the presence of hypervalent iodine,<sup>5b</sup> oxidative cyclization of enamides,<sup>5c</sup> treatment of isocyanide dichlorides aldehydes<sup>5d</sup> and diazoketones with amides<sup>5e</sup> and many others.<sup>5f–o</sup> In the year 2011, Hoarau and coworkers successfully explored the direct C–H arylation of oxazoles with aryl halides by palladium

catalysis (Scheme 1, Eq. (1)).<sup>6</sup> The best yield and selectivity were obtained when a phosphine ligand was used. The synthesis of aryl substituted oxazoles from the readily available amides and ketones by Pd-catalyzed C(sp<sup>2</sup>)-H activation was reported by Jiang and coworkers (Scheme 1, Eq. (2)).<sup>6b</sup> Very recently, Zhang and co-workers developed a method for the synthesis of multisubstituted oxazoles by palladium-catalyzed oxidative cyclization of *N*-acyl enamides (Scheme 1, Eq. (3)).<sup>6c</sup> A highly efficient copper-catalyzed tandem oxidative cyclization gives polysubstituted oxazoles has also been developed by Wang et al. (Scheme 1, Eq. (4)).<sup>6d</sup>

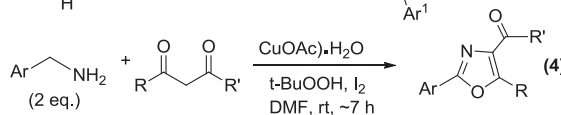
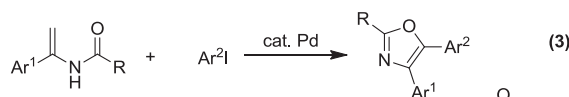
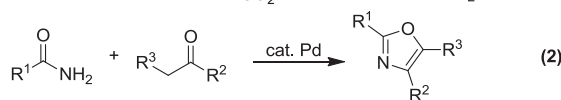
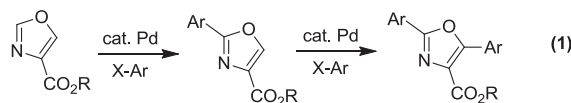
Oximes have been used as important synthons for the construction of nitrogen containing organic compounds.<sup>7</sup> Some reactions of oximes with diazo compounds have been reported.<sup>8</sup> Many of the existing methods for the synthesis of oxazoles have limitations such as poor availability of the starting materials, lack of adequate derivatization, and harsh reaction conditions. These features prompted us to develop a new general and viable route with operational simplicity. Copper salts, which are inexpensive and possess low toxicity, have been widely used as catalysts or mediators in organic reactions.<sup>9,10</sup> We have been interested in the utility of diazo-carbenoids for the synthesis of heterocyclic systems.<sup>11</sup> Herein we report a simple, economical, and straightforward method for the synthesis of diverse functionalized oxazoles from oximes by treatment with terminal  $\alpha$ -diazocarbonyl compounds (cf. Scheme 1, Eq. (5)) in which the byproducts are only water and nitrogen.

The oxime precursors used in the present study were synthesized in good yields by a reported procedure.<sup>7f</sup> Initially we

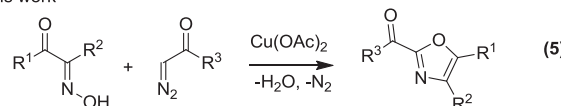
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Selected examples from previous work



This work



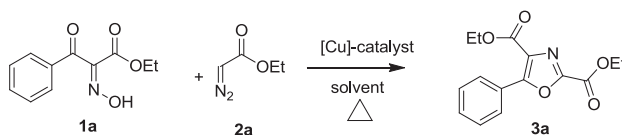
Scheme 1. Synthesis of functionalized oxazoles.

envisioned to develop azirine moiety by reacting oxime with terminal carbenoids such as ethyl diazoacetate (EDA), benzyl diazoacetate (BDA) and diazoacetophenone (DAP). In this context, we hypothesized that the oxime upon treatment with a copper complex formed from the elimination of  $\text{N}_2$  from EDA should give aziridine ring which will be followed by rearrangement and insertion of oxygen of adjacent carbonyl could leading to the oxazole.

In order to optimize the reaction conditions for the synthesis of oxazoles, ethyl 2-(hydroxyimino)-3-oxo-3-phenylpropanoate **1a** and EDA **2a** were taken as model substrates. Initially, the solution of **1a** (0.5 mmol) in 1.5 ml of dichloroethane (DCE) was treated with EDA (0.5 mmol, 15% in toluene) in the presence of  $\text{Cu(OAc)}_2$  (10 mol %) at  $80^\circ\text{C}$  for 24 h. The work-up followed by isolation of the

reaction provided **3a** in 30% yield, characterized as diethyl 5-phenyloxazole-2,4-dicarboxylate with the help of satisfactory spectral ( $^1\text{H}$  &  $^{13}\text{C}$  NMR, mass) studies. Encouraged by this, the effect of various parameters such as EDA loading, catalyst, solvent and temperature were examined and the results are shown in Table 1. Entry 1 corresponds to the above reaction conducted at  $80^\circ\text{C}$ . In the next attempt, the temperature was raised to  $100^\circ\text{C}$ , and to our delight the yield of product **3a** increased to 79% 8 h (entry 2). Further raise in temperature did not improve the yield (entry 3). Then we have focused on the effect of solvent by using chloroform, DCM, 1,2-dichlorobenzene and DMSO (entries 4–7). The best one was still DCE (entry 2). The effect of different catalysts like  $\text{Cu(OTf)}_2$ ,  $\text{CuBr}_2$ ,  $\text{CuBr}$  and  $\text{CuI}$  were also explored (entries 8–11), but  $\text{Cu(OAc)}_2$  was found to be the best. Further, no improvement in the yield was

Table 1  
Optimization of reaction conditions.<sup>a</sup>



| Entry | Catalyst (10 mol%)   | Solvent (ml)    | Temp ( $^\circ\text{C}$ ) | Time (h) | Yield <sup>b</sup> (%) |
|-------|----------------------|-----------------|---------------------------|----------|------------------------|
| 1     | $\text{Cu(OAc)}_2$   | DCE             | 80                        | 24       | 30                     |
| 2     | $\text{Cu(OAc)}_2$   | DCE             | 100                       | 8        | 79                     |
| 3     | $\text{Cu(OAc)}_2$   | DCE             | 110                       | 6        | 60                     |
| 4     | $\text{Cu(OAc)}_2$   | DCM             | 40                        | 24       | 40                     |
| 5     | $\text{Cu(OAc)}_2$   | $\text{CHCl}_3$ | 60                        | 24       | 45                     |
| 6     | $\text{Cu(OAc)}_2$   | DCB             | 120                       | 8        | 70                     |
| 7     | $\text{Cu(OAc)}_2$   | DMSO            | 100                       | 24       | 10                     |
| 8     | $\text{Cu(OTf)}_2$   | DCE             | 100                       | 24       | 40                     |
| 9     | $\text{CuBr}$        | DCE             | 100                       | 24       | 50                     |
| 10    | $\text{CuBr}_2$      | DCE             | 100                       | 24       | 40                     |
| 11    | $\text{CuI}$         | DCE             | 100                       | 24       | 45                     |
| 12    | $\text{Cu(OAc)}_2^c$ | DCE             | 100                       | 24       | 65                     |
| 13    | $\text{Cu(OAc)}_2^d$ | DCE             | 100                       | 20       | 70                     |

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), DCE (1.5 ml).

<sup>b</sup> Isolated yields.

<sup>c</sup> 5 mol%.

<sup>d</sup> 15 mol%.

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