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Graphical Abstract

Copper-catalyzed synthesis of oxime ethers from iminoxy radical (C=N-O•) and maleimides via radical addition

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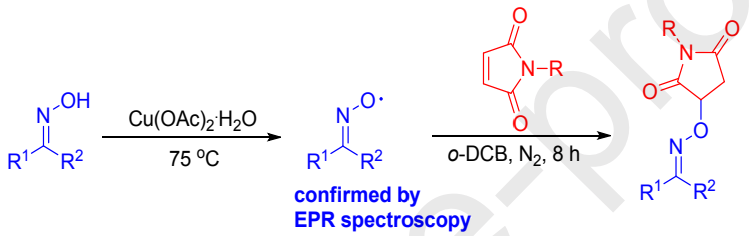

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Copper-catalyzed synthesis of oxime ethers from iminoxy radical (C=N-O•) and maleimides via radical addition

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ABSTRACT

An efficient Cu(II)-catalyzed radical addition of maleimides has been achieved. The identified copper catalyst enables the formation of oxime radicals (N-O•) by cleaving the O-H bond in ketoximes, followed by the radical addition to *N*-substituted maleimides. The oxime radicals (N-O•) were detected and confirmed by EPR spectroscopy and variable-temperature ^{1}H-NMR. The simple one-pot reaction realizes the facile preparation of a variety of oxime ether adduct products in moderate to good yields.

1. Introduction

Ketoximes are readily available and important building blocks for organic synthesis with broad applications in pharmaceutical and biological chemistry [1]. As depicted in Figure 1, there are mainly three types of oximes (Figure 1): hydroxyl oxime **I** (-OH), oxime ether **II** (-OR_3), oxime ester **III** (-$OCOR_4$). In radical chemistry, imine radical (C=N•) appears frequently formed by oxime esters and oxime ethers [2,3], while iminoxy radical (C=N-O•) is less pronounced from hydroxyl oxime by the homolysis of O-H bond [4-9]. Common radical addition reactions of ketoximes mostly involved intramolecular cycloadditions, while the intermolecular radical additions were rarely reported [6,10]. Based on previous reports, we found that ketoximes could readily generate oxime radicals in the presence of Cu(II) catalysts [11], and we also provided evidence in our previous work [12]. An electron transfer process occurs between the Cu(II) and oximes, forming iminoxy radicals with the generation of Cu(I). In the presence of strong bases, traditional Michael addition reactions could easily occur between ketoximes and various olefins, such as α,β-unsaturated nitriles, α,β-unsaturated esters, α,β-unsaturated phosphates [13]. However, the radical addition reactions of ketoximes with unsaturated compounds were lack of attention to this point of view.

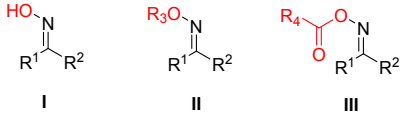
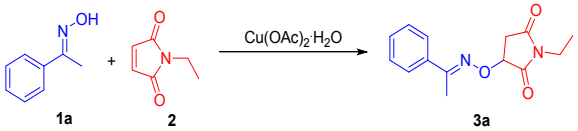


Figure 1 The three types of oxime

As one of the prominent medicinal moieties, the oxime ether group offers very attractive options for drug design in a variety of pharmaceutical preparation and pesticides [14,15], which exhibit excellent anticancer activities and larvicidal activities against pest (Figure 2) [16,17].

Figure 2 Medicine and pesticide containing oxime ether functional group

In the screening of unsaturated compounds to react with iminoxy radical, we surprisingly found that *N*-ethylmaleimide could easily react with ketoximes in the presence of $Cu(OAc)_2{\cdot}H_2O$ catalyst. The corresponding oxime ether products could be smoothly prepared from a variety of ketoximes (Scheme 1). Maleimides are important building blocks in chemical synthesis for biological and material sciences with stiff toroidal structure, providing various functionalized fused-pyrrolidinedione skeletons, and as radical acceptor in radical reaction [18].

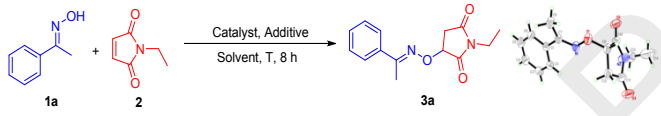


Scheme 1 Cu(II)-catalyzed the radical addition of ketoximes and *N*-ethylmaleimide

2.

We chose the simple and readily available acetophenone oxime **1a** and N-ethylmaleimide **2** as our starting materials for our initial studies. In the presence of 20 mol% $Cu(OAc)_2·H_2O$, *O*-(*N*-ethyl-2,5-dicarbonyl pyrrolidine)-oxime ether **3a** was already realized in 54% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by single crystal X-ray diffraction analysis [19]. Continuous optimization of reaction conditions was carried to improve the conversion yield, including temperatures, catalysts and additives (see in supplementary material). The reaction temperature was found to be important for the reaction (Table 1, entries 1-4). At 75 °C, the reaction yield was further improved to 82% by employing excesses of acetophenone oxime (Table 1, entry 5). However, the radical reactions were dramatically inhibited in the aerobic atmospheres (Table 1, entries 6-7). Among the common copper catalysts, $Cu(OAc)_2·H_2O$ showed higher catalytic effect than others (Table 1, entries 8-11). Control reaction indicated that copper catalyst is crucial for the process (Table 1, entry 12). It is not surprised that the same product could be obtained in the presence of a base *via* Michael addition, but in a relative lower yield compared to the copper-catalyzed radical addition (Table 1, entries 13-14). Screening on other bases and additives could not realize higher yields (Table 1, entries 15-24). Thus the optimized reaction conditions were achieved as below: in the presence of 20 mol% of $Cu(OAc)_2·H_2O$, a mixture of acetophenone oxime **1a** and N-ethylmaleimide **2** (1.75:1) was refluxed in anhydrous *o*-DCB at 75 °C for 8h under N_2, giving *O*-(*N*-ethyl-2,5-dicarbonyl pyrrolidine)-oxime ether **3a** in 82% yield.

Table 1 The optimization of reaction conditions



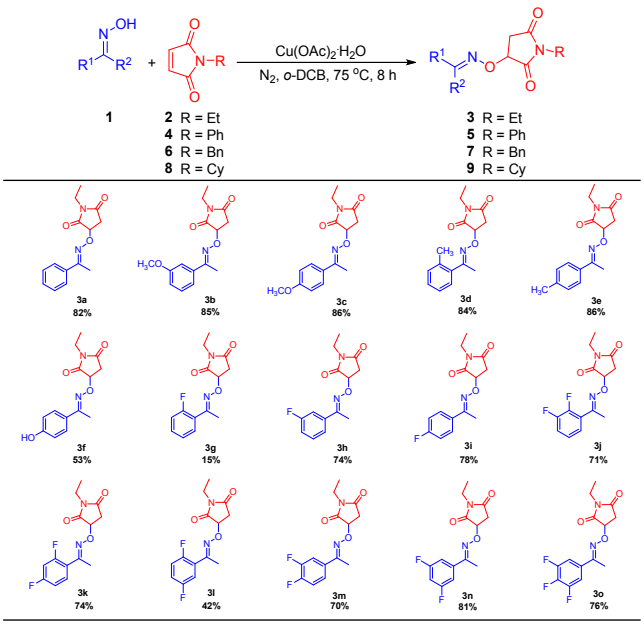
1a 2 3a

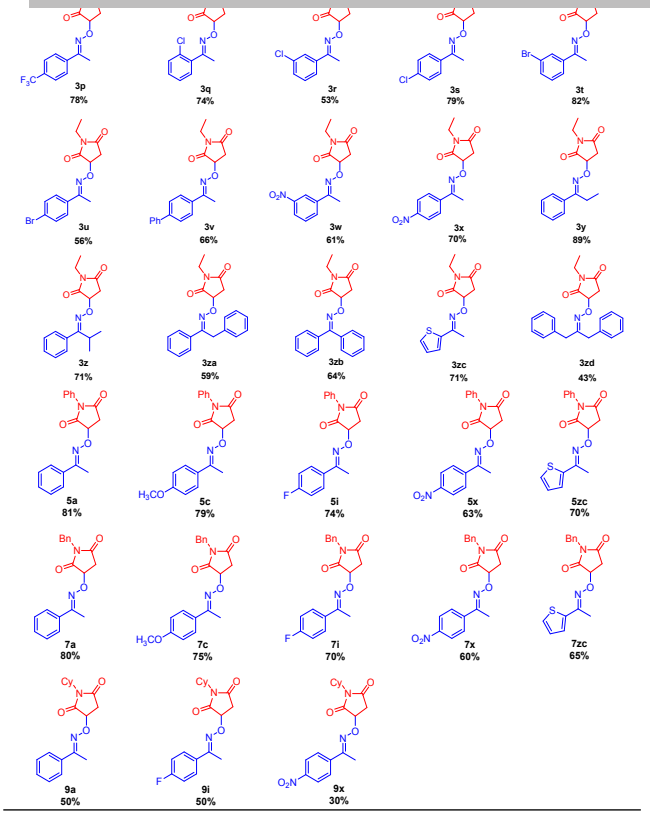
Entry	Cat.	Additive	Solvent	T (°C)	Atm.	Yield[b] (%)
1	$Cu(OAc)_2·H_2O$	/	*o*-DCB	90	N_2	54 [a]
2	$Cu(OAc)_2·H_2O$	/	*o*-DCB	60	N_2	49 [a]
3	$Cu(OAc)_2·H_2O$	/	*o*-DCB	75	N_2	69 [a]
4	$Cu(OAc)_2·H_2O$	/	*o*-DCB	120	N_2	40 [a]
5	$Cu(OAc)_2·H_2O$	/	*o*-DCB	75	N_2	**82**
6	$Cu(OAc)_2·H_2O$	/	*o*-DCB	75	Air	21 [c]
7	$Cu(OAc)_2·H_2O$	/	*o*-DCB	75	O_2	12 [d]
8	$Cu(OAc)_2$	/	*o*-DCB	75	N_2	69
9	Cu	/	*o*-DCB	75	N_2	45
10	CuI	/	*o*-DCB	75	N_2	2
11	CuCl	/	*o*-DCB	75	N_2	21
12	/	/	*o*-DCB	75	N_2	5
13	$Cu(OAc)_2·H_2O$	K_2CO_3	*o*-DCB	75	N_2	85
14	/	K_2CO_3	*o*-DCB	75	N_2	51
15	$Cu(OAc)_2·H_2O$	Cs_2CO_3	*o*-DCB	75	N_2	0
16	/	Cs_2CO_3	*o*-DCB	75	N_2	0
17	/	DIPEA	*o*-DCB	75	N_2	50
18	/	Et_3N	*o*-DCB	75	N_2	40
19	/	DBU	*o*-DCB	75	N_2	47
20	$Cu(OAc)_2·H_2O$	$K_2S_2O_8$	*o*-DCB	75	N_2	39
21	$Cu(OAc)_2·H_2O$	$K_2S_2O_8$	*o*-DCB	75	N_2	71
22	$Cu(OAc)_2·H_2O$	$NaHSO_3$	*o*-DCB	75	N_2	73
23	$Cu(OAc)_2·H_2O$	M.S.	*o*-DCB	75	N_2	74
24	$Cu(OAc)_2·H_2O$	1,10-Phenanthroline	*o*-DCB	75	N_2	66

[a] Condation: **1a** (0.15 mmol), **2** (0.1 mmol), $Cu(OAc)_2·H_2O$ (0.02 mmol), *o*-DCB (0.3 mL), 8 h in the atmosphere of N_2. [b] Condation: **1a** (0.175 mmol), **2** (0.1 mmol), catalyst (0.02 mmol), solvent (0.3 mL), additive (1.5 mmol), 8 h in the atmosphere of N_2. [c] Condation: in the atmosphere of Air. [d] Condation: in the atmosphere of O_2.

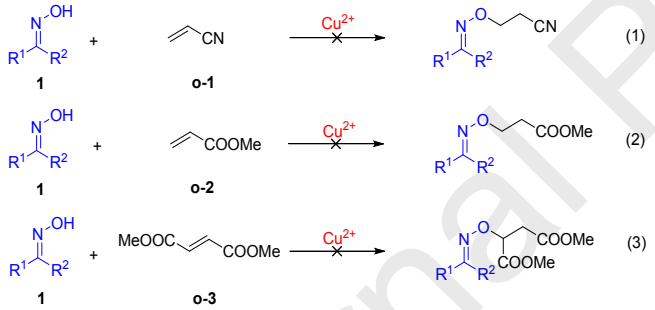
Then the investigation on the substrate scope of this reaction was carried out. Different substituted ketoximes **1** were used to react with *N*-ethylmaleimide **2**. As shown in Table 2, a series of *O*-(*N*-ethyl-2,5-dicarbonyl pyrrolidine)-oxime ethers were readily accessed in moderate to good yields. By applying the optimal reaction conditions, substrates with electron-donating groups, such as methoxyl, methyl, hydroxy, could give the corresponding products in good yields, up to 86% (**3b-3f**). Electron-withdrawing groups, including fluorine, chlorine, bromine, trifluoromethyl, phenyl and even strong electron-deficient nitro group were tolerated with the catalytical radical addition process (**3g-3x**). Ketoximes with more sterically hindered groups were also successfully converted into the desired products in moderate to good yields (**3y**, **3z**, **3za**, **3zb**, **3zd**). Even the heterocyclic substrate with thiophene moiety could also generate the product in 71% yield (**3zc**). After the replacement of ethly of maleimides with phenyl, benzyl and cyclohexyl, the reactions still successfully took place to gain the desired oxime ethers (**5a-5zc**, **7a-7zc**, **9a-9x**). However, aliphatic ketone oximes had too weak responses to gain the target products because of its low activity. In addition, the radical reactions could not occur between ketoximes and other electron-deficient olefins such as α,β-unsaturated nitriles, α,β-unsaturated esters and so on (Scheme 2) [18d]. The failures in such traditional α,β-unsaturated Michael acceptors were probably due to their inferior tolerances with oxime radicals.

Table 2 $Cu(OAc)_2·H_2O$ catalyzed one-pot synthesis of *O*-(*N*-substituted-2,5-dicarbonyl pyrrolidine)-oxime ethers





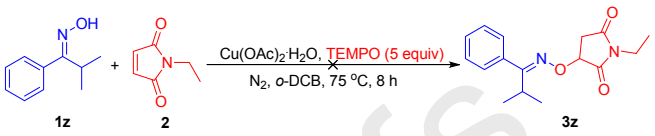
[a] Condition: ketoximes **1** (1.05 mmol), *N*-substituted maleimides (0.6 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.12 mmol) in *o*-DCB (1.8 mL) at 75 °C for 8 h in N_2.



Scheme 2 Cu(II)-catalyzed the radical addition of ketoximes and other electron-withdrawing olefins

Control experiments were performed to gain some insight into the reaction mechanism. When a strong radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction, the reaction was totally blocked (Scheme 3). Furthermore, the oxime radical was also confirmed by EPR spectroscopy. Each individual component of the used raw materials could not give any radical signals in the EPR test (Figure 3). When the ketoxime **1z** was treated by catalyst $Cu(OAc)_2{\cdot}H_2O$ under elevated temperature 90 °C, strong radical signal was observed in the EPR spectroscopy (Figure 4). As shown in Figure 5, the signals of radical **A** generated from **1z** (g = 2.01746, g = 1.99899, g = 1.97980, $\bar{g}$ = 1.99875, aN= 30.84 G) appeared, and they are quite coincident with the reported literatures [20]. Variable-temperature ^{1}H-NMR was simultaneously carried out to monitor possible intermediates **A**. At room temperature, the two peaks at 11-10 ppm shift indicate a pair of cis-trans isomers [21] of the ketoxime structure (Figure 6). However, these signals became faint during raising temperatures, and disappeared completely at 90 °C. Over the temperature range from room temperature to 90 °C, the H (-OH) intensities decreased continuously, indicating that the O-H bond was

ketoxime **1z** to radical **A**. These facts were consistent with our assumption about the proposed radical mechanism as follows (Scheme 4): under the catalysis of $Cu(OAc)_2{\cdot}H_2O$, the homolytic cleavage of O-H bonds of ketoxime releases oxime radicals **A**, and $Cu^{I}H$ *via* single electron transfer from Cu^{II}. Then the oxime radical **A** attacks the double bond of *N*-ethyl maleimide **2** to generate the free radical intermediate **B**, which captures the hydrogen radical released by single electron transfer from the previously generated $Cu^{I}H$. The desired product **3z** is eventually afforded together with regeneration of the Cu(II) catalyst.



Scheme 3 The reaction of ketoxime and N-ethylmaleimide with TEMPO

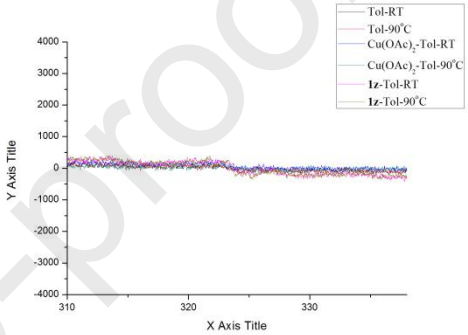


Figure 3 EPR spectrum of individual components

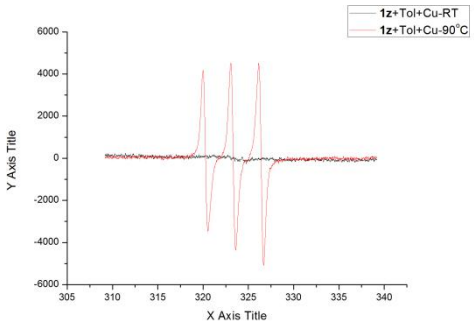


Figure 4 EPR spectrum of oxime radical generated by **1z** with Cu(II)-catalyst in toluene

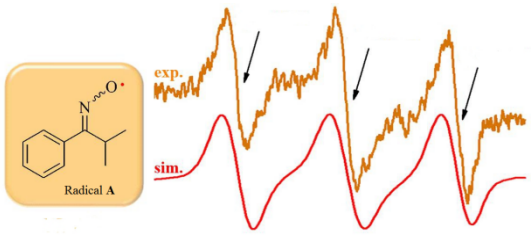


Figure 5 EPR detection of radical **A**

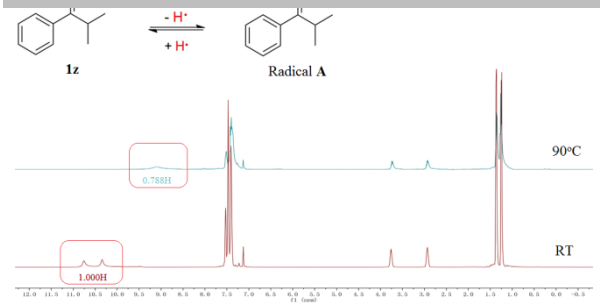
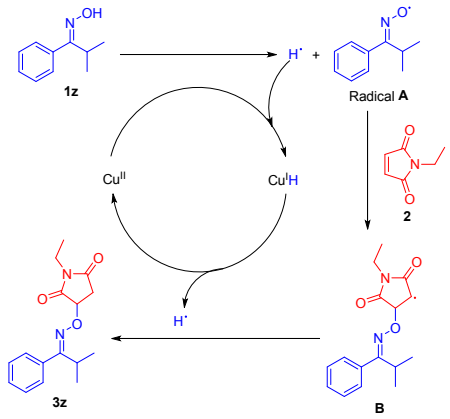


Figure 6 Monitoring of radical **A** by variable-temperature ^{1}H-NMR



Scheme 4 Plausible mechanism for the radical addition reaction

Conclusions

In summary, we have developed an efficient Cu(II)-catalyzed radical addition reaction of ketoximes with *N*-substituted maleimides. In the presence of $Cu(OAc)_2 \cdot H_2O$ catalyst , the reaction of readily available ketoximes and *N*-substituted maleimides could easily access to a series of *O*-(*N*-substituted-2,5-dicarbonyl pyrrolidine)-oxime ether products in moderate to good yields. The oxime radical has been confirmed by EPR spectroscopy. Furthermore, variable-temperature ^{1}H-NMR indicates the radical addition reaction mechanism. Further evaluations on other radical reactions using ketoximes as well as the studies of the insight into the reaction mechanism are ongoing in our laboratory.

Acknowledgments

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[19] CCDC 1868576 contains the supplementary crystallographic data for **3a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.

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Highlights

1) An efficient Cu(II)-catalyzed radical addition reaction of ketoximes with *N*-substituted maleimides.

2) Synthesis of *O*-(*N*-substituted-2,5-dicarbonyl pyrrolidine)-oxime ether products in moderate to good yields.

3) The evidence of oxime radical confirmed by EPR spectroscopy.

4) The radical addition reaction mechanism indicated by variable-temperature ^{1}H-NMR.