Convenient One-Pot Synthesis of 2,5-Disubstituted Oxazoles via a Catalytic Oxidative Dehydrogenation of $F_3CSO_3H \cdot SiO_2$ -DDQ/CuCl₂/LiCl

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A facile one-pot synthesis of 2,5-disubstituted oxazoles was developed via cyclization of aldoximes and phenylacetylene then dehydrogenation oxidation. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was studied for the selective oxidation of oxazolines using Cu^{2+}/Li^+ as catalyst and O_2 as indirect oxidant. The reaction results showed that this catalyst system can effectively catalyze the oxidation of oxazolines to the corresponding oxazoles. Thus, a variety of polysubstituted oxazoles was easily synthesized in high yields by catalytic oxidation of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone/CuCl₂/LiCl/O₂.

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INTRODUCTION

Oxazoles are well known as important structural units in a wide variety of biologically active natural products as well as useful synthetic intermediates [1]. In particular, many efforts have been focused for the synthesis of 2,5-substituted oxazoles because of their existence in substructures of many pharmaceuticals [2]. Classical procedure for the synthesis of them includes two steps: (1) cyclization of acyclic precursors and (2) dehydrogenation oxidation of oxazolines.

Now, major cyclizations have the reaction of amide with olefinic bond [3] or acetylene bond [4] and amine with carbonyl compounds [5]. The main dehydrogenation oxidation methods are (1) direct halogenation with a halogen then dehydrohalogenation [6], (2) bromination with NBS [7] then eliminating hydrogen bromide, and (3) direct dehydrogenation with specific oxidation [8].

However, these methods always suffered from the limitation of utilization of the toxic transition-metal catalysts, such as $Pd(OAc)_2$ [9], $Ru(PPh)_3$ [10], $PbCl_2(PPh_3)_2$ [11], or inaccessible starting materials [12]. Therefore, the development of more efficient and practical protocols still would be highly desirable.

RESULTS AND DISCUSSION

Herein, we report a novel tandem synthetic method for preparation of 2,5-substituted oxazoles from facile aldoximes and phenylacetylene with effective catalytic oxidation reaction.

As is well known that oxazole ring is readily oxidized and leads to open in the presence of oxidants, so only specific oxidants could be qualified for dehydrogenation oxidation. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a highly active and selective oxidant and is widely used to the dehydrogenation and aromatization in organic synthesis, especially suitable for the dehydrogenation of benzylic and allylic oxidations. In oxidation reaction, DDQ is reduced to DDQH₂ (2,3-dichloro-5,6-dicyano-1,4-hydroquinone). However, DDQH₂ is reductant; the oxidation capacity of DDQ gradually decreases with increasing concentration of DDQH₂, so decreasing the concentration of DDQH₂ will help to enhance the oxidation capacity of DDQ. Undoubtedly, the best way to decrease the concentration of DDQH₂ is that DDQH₂ could be oxidized to DDQ by desired oxidant.

To initiate our study, we have optimized the reaction conditions for the formation of oxazole with benzaldoxime (1a) and phenylacetylene (2a) as substrates (Scheme 1). The results are listed in Table 1.

As shown in Table 1, we could have access to optimum conditions of synthesis:

1. Influence of catalysts

First, various catalysts were examined; it has been observed that heterogeneous catalysts (Table 1, entries 4–8) were more effective than homogeneous catalysts (Table 1, entries 1–3). The mixture of trifluoromethanesulfonic acid and silica $[F_3CSO_3H\cdot SiO_2 \ (0.15+0.15\,g)]$ was the most efficient catalyst for synthesis of substituted oxazoles (Table 1, entries 8–10).

2. Influence of oxidants

In the absence of Cu^{2+} and only by using DDQ, DDQ/ O₂, and DDQ/LiCl/O₂ as the oxidants, the yields of



 Table 1

 Optimization of reaction conditions.^{a,b}

Entry	Catalyst Oxidant		Yield (3aa , %) ^c
1	H ₂ SO ₄ (98%)	DDQ	36
2	4-CH ₃ C ₆ H ₄ SO ₃ H(0.1 g)	DDQ	41
3	Sulfamic acid (0.1 g)	DDQ	43
4	Phosphotungstic acid (0.1 g)	DDQ	47
5	Montmorillonite (0.1 g)	DDQ	46
6^{d}	ASR (D001, 0.1 g)	DDQ	47
7	$F_3CSO_3H(0.1 g)$	DDQ	51
8	$F_3CSO_3H \cdot SiO_2(0.1 + 0.1 g)$	DDQ	55
9	$F_3CSO_3H \cdot SiO_2(0.15 + 0.15 g)$	DDQ	57
10	$F_3CSO_3H \cdot SiO_2(0.2 + 0.2 g)$	DDQ	56
11 ^e	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/O ₂	59
12	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ (1:1)/O ₂	67
13	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuSO ₄ (1:1)/O ₂	63
14	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/Cu(NO ₃) ₂ (1:1)/O ₂	65
15	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /NaCl (1:1:1)/O ₂	69
16	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /MgCl ₂ (1:1:1)/O ₂	62
17 ^f	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /LiCl(1:1:1)/O ₂	71
18	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /LiCl (1:1:2)/O ₂	78
19	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /LiCl (1:1:3)/O ₂	84
20	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuCl ₂ /LiCl (1:1:4)/O ₂	82
21	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/LiCl(1:1)/O2	57
22	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/CuSO ₄ /LiCl(1:1:3)/O ₂	63
23	$F_3CSO_3H \cdot SiO_2(0.3 g)$	DDQ/Cu(NO ₃) ₂ /LiCl (1:1:3)/O ₂	81

^aReaction conditions: **1a** (1.0 equiv, 5.0 mmol), **2a** (1.2 equiv), oxidant (1.0 equiv), solvent = dioxane : *n*-propanol (V:V = 2:1, 20.0 mL), reaction temperature (50–70°C), and reaction time (8 h). ^bOne-pot synthesis. ^cDetermined by GC. ^dASR, acidic styrol resin (D001), DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. ^eDDQ (1.0 equiv), O₂ (1.3 MPa). ^fDDQ/CuCl₂/LiCl (1.0 equiv).

oxazoles were not high (Table 1, entries 9, 10, 11, 21). From Table 1, Cu^{2+} is a highly efficient oxidation catalyst (Table 1, entries 12–14), and LiCl is the preferable excitation reagent (Table 1, entries 15–17). It is known that the ratio of $CuCl_2$ to LiCl could affect reaction severely. The yields were the highest when LiCl/CuCl₂ mole ratio was 3(Table 1, entries 19). The action of excitation is not obvious when there is only a small amount of LiCl. However, too much LiCl also was disadvantageous to the reaction, probably because the relative concentration of Cu^{2+} is lower, and Cu^{2+} and O_2 could not contact abundantly (Table 1, entries 17–20). Unexpectedly, the complex catalyst with $CuSO_4/LiCl$ failed to give the ideal yield (Table 1, entries 22).

As a result, the optimal reaction conditions were established as follows: 1.0 equiv (5 mmol) of **1a**, 1.2 equiv of **2a** as reaction substrates, $F_3CSO_3H \cdot SiO_2$ (0.3 g) as cyclization catalyst, 1.0 equiv of DDQ/CuCl₂/LiCl (1:1:3)/O₂ as a complex oxidant, pressure of oxygen (1.3 MPa), reaction

temperature (50–70°C), overall reaction time (8 h), and dioxane : *n*-propanol (V:V = 2:1, 20 mL) as the solvent.

Subsequently, we further investigated the scope of a one-pot synthesis of 2,5-disubstituted oxazoles by using different aldoximes and phenylacetylene as the substrates under the optimal conditions (Scheme 2). The results are summarized in Table 2.

It was found that all of substituted benzaldoxime proceeded smoothly to afford the expected 2,5-diaryl oxazoles (59–91%). Generally, the benzaldoxime-bearing electron-donating group gave poly-substituted oxazoles in higher yields (Table 2, entries 2–5), lower yields were obtained with electron-withdrawing substituents on the benzene ring (Table 2, entries 6–9). Moreover, when fused-ring and heterocyclic aldoximes were chosen as the substrates, the reaction also afforded the corresponding products in high yields (Table 2, entries 10–13). However, aliphatic aldoxime almost failed to yield the desired product (Table 2, entries 14). All compounds obtained were consistent with authentic ones in literature [5,6,13,14].



 $R=C_6H_5,\ 4-CH_3C_6H_4,\ 4-CH_3OC_6H_4,\ 3-CH_3OC_6H_4,\ 4-CIC_6H_4,\ 3-CIC_6H_4,\ 4-O_2NC_6H_4,\ \alpha-Naphthyl,\ \beta-Naphthyl,\ 2-Furan,\ 2-Thiophene,\ n-C_3H_7.$

One-pot synthesis of 2,3-substituted oxazoles.								
Entry	R	Product 3	Entry	R	Product 3			
1	C ₆ H ₅	N 0 9 0 9 0 9 0 9 0 9 0 9 0 9 0 9 0 9 0	8	2-ClC ₆ H ₄	Cl N y ph 3ha (71%), ref.6			
2	4-CH ₃ C ₆ H ₄	H ₃ C N Ph Ph Bba (86%), ref. 6	9	O ₂ N	O ₂ N N N Ph 3ia (59%), ref.13			
3	$4\text{-}CH_3O_6H_4$	H ₃ CO Ph	10	β-Naphthyl	N 0 9ja (83%), ref.6			
4	3-CH ₃ O ₆ H ₄	H ₃ CO Ph 3da (85%), ref. 6	11	α-Naphthyl	N 0 9 3ka (86%), ref.6			
5	2-CH ₃ O ₆ H ₄	OCH ₃ N O 9 Ph 3ea (88%), ref.6	12	2-Furan	0 3la (62%), ref.6			
6	4-ClC ₆ H ₄	N O Ph 3fa (79%), ref.13	13	2-Thiophene	N O S 3ma (67%), ref.6			
7	3-CIC ₆ H	CI Ph 3ga (75%), ref.13	14	<i>n</i> -C ₃ H ₇	n-C ₃ H ₇ N Ph 3na (53%), ref.14			

 Table 2

 One-not synthesis of 2 5-substituted oxazoles ^{a,b,c}

^aReaction conditions: 1a (1.0 equiv, 5.0 mmol), 2a (1.2 equiv), oxidant (1.0 equiv), and reaction time (8 h). ^bOne-pot synthesis. ^cIsolated yield.

EXPERIMENTAL

On the basis of our experimental results and previous reports, we propose the following possible mechanism (Scheme 3).

"IR (Perkin-Elmer, 2000 FTIR)" is reworded to "IR (Perkin-Elmer, 2000 FTIR, Tianjin China)", ¹H and ¹³C NMR spectra were recorded on a "Bruker AC-300 FT spectrometer" is reworded to "Bruker AC-300 FT spectrometer (Switzerland)" using TMS as internal standard. The chemical shifts (δ) and coupling constants (*J*) were expressed in ppm and Hz,respectively. HRMS was recorded on a "MS-GC (HP5890 (II)/HP 5972, EI) spectrometer" is reworded to "MS-GC (HP5890 (II)/HP 5972, EI) spectrometer (Hewlett-Packard, USA)". TLC was purchased from "Anhui Liangchen Silicon Material Co., Ltd.," is reworded to "Anhui Liangchen Silicon Material Co., Ltd. (Hefei, China)," and all material were from Aldrich (Shanghai, China) and used directly as received.

General procedure for the synthesis of 2,5-substituted oxazoles. The mixture of substituted benzaldoximes (1.0



equiv, 5.0 mmol), $F_3CSO_3H\cdot SiO_2$ (0.3 g), and toluene (5 mL) was stirred for 0.5 h at 50°C. Then, phenylacetylene was added dropwise to the mixture. After the reaction mixture was stirred for 3.5 h at 70°C, the mixture of DDQ (1.0 equiv), CuCl₂·2H₂O (1.0 equiv), LiCl·H₂O (3.0 equiv), and dioxane:*n*-propanol (V:V=2:1, 20 mL) was added to the reactor. The reaction was sequentially stirred for 4 h at 60°C under reaction pressure of oxygen (1.3 MPa). After the reaction, the mixture was extracted with CH₂Cl₂ and separated, the organic phase was washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The pure products were obtained by flash chromatography on silica gel eluting with petroleum ether/EtOAc (1:6, V: V) and identified by IR, ¹H, ¹³C NMR and HRMS.

2-(Furan-2-yl)-5-phenyl-oxazole (3la). White solid, mp: 57–61°C.; IR: 1662, 1585, 756 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.78–7.67 (m, 2H), 7.54–7.51 (s, 1H), 7.44–7.35 (m, 3H), 7,34–7.43 (m, 1H), 7.07–7.04 (d, *J*=1.4 Hz, 1H), 6.54–6.52 (d, *J*=1.2 Hz, 1H).; ¹³C NMR (75 MHz, CDCl₃) δ 153.41,

150.87, 133.32, 128.94, 128.47, 128.28, 127.98, 127.81, 127.65, 124.18, 123.36.; HRMS Calcd $C_{13}H_9NO_2~(M^{+}):$ 211.0633, found: 211.0639.

2-(Thiophen-2-yl)-5-phenyl-oxazole (3ma). White solid. mp: 62–65°C.; IR: 1648, 1586, 1247 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ : 7.74–7.71 (dd, J=8.0, 1.8 Hz, 1H), 7.69– 7.51 (dd, J=2.7, 1.2 Hz, 2H), 7.49–7.45 (m, 3H), 7.42–7.38 (d, J=5.1 Hz, 1H), 7.35–7.32 (d, J=5.1 Hz, 1H), 7.14–7.11 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 157.72, 151.31, 130.51, 129.37, 129.04, 127.59, 127.13, 126.46, 124.72, 123.23, 120.81.; HRMS: Calcd for C₁₃H₉NOS (M⁺): 227.2115, found: 227.1892.

In summary, we have developed a novel tandem one-pot synthetic method for preparation of 2,5-substituted oxazoles from substituted benzaldoximes and phenylacetylene. In contrast to the synthetic methods reported for oxazoles, it is featured as accessible raw materials and as a high-efficiency catalytic oxidation. Therefore, this method is a useful complement to the existing methods for the synthesis of the 2,5-disubstituted oxazoles. Acknowledgments. We appreciate the Natural Science Fund of Anhui Province Education Office (KJ2011z050), the Natural Science Foundation of China (20771004/B0101), and the Anhui Key Laboratory of Advanced Building Materials.

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