SUSTAINABLE CHEMICAL PROCESSES

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Metal-free synthesis of polysubstituted oxazoles via a decarboxylative cyclization from primary α-amino acids

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Abstract

Background: The ubiquitous oxazoles have attracted more and more attention in both industrial and academic fields for decades. This interest arises from the fact that a variety of natural and synthetic compounds which contain the oxazole substructure exhibit significant biological activities and antiviral properties. Although various synthetic methodologies for synthesis of oxazols have been reported, the development of milder and more general procedure to access oxazoles is still desirable.

Results: In this manuscript, a novel method for synthesis of polysubstituted oxazoles was developed from metal-free decarboxylative cyclization of easily available primary α-amino acids with 2-bromoacetophenones.

Conclusions: The method was simple, and this reaction could be carried out smoothly under mild and metal-free conditions. By virtue of this method, various polysubstituted oxazoles were obtained from the primary α-amino acids with moderate yields.

Keywords: Metal-free, Synthesis, Oxazoles, Oxidation, Decarboxylative cyclization, α-amino acids

Background

Oxazoles are a kind of attractive heterocycles not only because of their unique structures and varied applications [1,2] but also they serve as structural elements for a variety of natural products, pharmaceuticals and bioactive compounds [3-5]. For example, the diazonamide and phorboxazole families [6,7], oxazole motif-containing bioactive natural products, exhibit anticancer properties. Moreover, oxazole derivatives can be employed as fluorescent dyes [8], corrosion inhibitors [9] and also as chiral ligands for transition-metal catalysts in asymmetric synthesis [10,11]. Owing to the important applications of oxazole derivatives, various synthetic methodologies for these compounds have been reported. Generally, the procedures for the synthesis of oxazoles include the cyclodehydration of acyclic precursors [12-16], the oxidation of oxazolines [17-19] and the coupling of the prefunctionalized oxazoles with organometallic reagents [20-22]. In light of these applications, the development of milder and more general procedure to access oxazoles is still desirable. To the best of our knowledge, metal-free synthesis of polysubstituted oxazoles is rare although several methods for the synthesis of oxazoles have emerged recently [23-31].

α-Amino acids are readily available, inexpensive and stable starting materials from nature. Therefore, using α-amino acids as the nitrogen-containing motifs to construct heterocycles are very attractive synthetic method. Many reactions about the decarboxylative of α-amino acids have been developed in recent years [32-42]. For example, Fu and our group have reported the synthesis of quinazolinones via a decarboxylative coupling of α-amino acids [43,44]. On the basis of this work, herein we report a new decarboxylative cyclization reaction to construct polysubstituted oxazoles containing the moiety of primary α-amino acids under metal-free conditions.

Results and discussion

Optimization of reaction conditions

Initially, the reaction of phenylglycine (**1a**) with 2-bromoacetophenone (**2a**) was chosen as a model reaction to optimize the reaction conditions. We studied the

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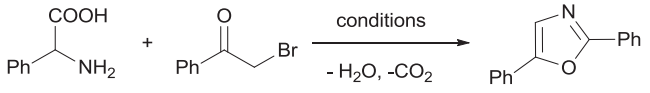
reaction of 0.7 mmol of **1a** and 0.5 mmol of **2a**, with 1 mmol of *tert*-butyl hydroperoxide (TBHP, 70% aqueous solution) as the oxidant and 20 mol% of molecular iodine as the catalyst. The reaction mixture was heated in *N,N*-dimethylacetamide (DMA, 2 mL) under air at 70°C for 5 h. The decarboxylative cyclization product 2,5-diphenyloxazole (**3a**) was obtained with 50% isolated yield (Table 1, entry 1). It was found that catalyst iodine was crucial for this reaction. Only trace amounts of the desired product were observed in the absence of iodine (entry 2). The replacement of catalyst iodine by copper oxide resulted in the decrease of the reaction yield (entry 3). Also, the loading of iodine had an influence on this reaction (entries 4 and 5). For instance, at loadings below or above 20 mol% of iodine, reduced yields were obtained. Besides, the base could affect this reaction. The reaction yield slightly increased when sodium carbonate (0.5 mmol) was added as base. (entry 6) After screening various bases, sodium carbonate proved to be the best base affording **3a** with 54% yield (entries 6–9). Subsequently, different oxidants, such as DTBP, *m*-CPBA, $K_2S_2O_8$, were examined in this reaction. After examination, TBHP gave the highest yield (compared entries 10–12 with entry 6). In addition, we investigated influence of temperature and time on the reaction. Lowering the reaction temperature slightly increased the reaction yield (entry 13). When the reaction was carried out at 25°C for 24 h, a yield of 60% was obtained (entry 14). Finally, the highest yield of 70% was obtained when the reaction was carried out at 25°C for 4 h and then at 60°C for another 4 h, as shown in entry 15 of Table 1.

The scope of the reaction

With the optimized reaction conditions in hand, we investigated the scope of the decarboxylative cyclization reaction (Figure 1). A series of primary α-amino acids were employed as the reaction substrates. Normally, phenylglycine, glycine, alanine, norvaline, valine, isoleucine, leucine and phenylalanine performed well in this reaction to give the corresponding substituted oxazoles with satisfactory yields (**3a**-**3h**). However, when the primary α-amino acids containing active hydrogen on the side chains, such as lysine, arginine and serine, were employed as the start materials, the decarboxylative cyclizations were blocked. Generally, electron-donating substituent (**3b**-**3d**) and the substituent with steric effect (**3e**-**3g**) had negative influence on this reaction. As for 2-bromoacetophenones, the substituent on the aromatic ring had a negative influence on the reaction yield regardless of the electron-donating groups or electron-withdrawing groups on the phenyl ring of R_2 (**3i**-**3p**). It was noted that the decarboxylative cyclization also

Table 1 Optimization of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Oxidant	Base	Temperature (°C)	Yield[b] (%)
1	20% I_2	TBHP	_	70	50
2	_	TBHP	_	70	trace
3	20% CuO	TBHP	_	70	41
4	10% I_2	TBHP	_	70	38
5	30% I_2	TBHP	_	70	49
6	20% I_2	TBHP	Na_2CO_3	70	54
7	20% I_2	TBHP	K_2CO_3	70	52
8	20% I_2	TBHP	*t*-BuOK	70	12
9	20% I_2	TBHP	Et_3N	70	45
10	20% I_2	DTBP	Na_2CO_3	70	49
11	20% I_2	*m*-CPBA	Na_2CO_3	70	27
12	20% I_2	$K_2S_2O_8$	Na_2CO_3	70	30
13	20% I_2	TBHP	Na_2CO_3	60	59
14[c]	20% I_2	TBHP	Na_2CO_3	25	60
15	20% I_2	TBHP	Na_2CO_3	25-60	70

[a] The reaction mixture of 0.7 mmol of phenylglycine, 0.5 mmol of 2-bromoacetophenone, 1 mmol of oxidant and 0.5 mmol of base in 2 mL of DMA was stirred for 5 h with different catalytic loading. [b] Isolated yields based on 2-bromoacetophenone. [c] Reaction time was 24 h. DTBP = di-*tert*-butyl peroxide, *m*-CPBA = m-chloroperoxybenzoic acid.

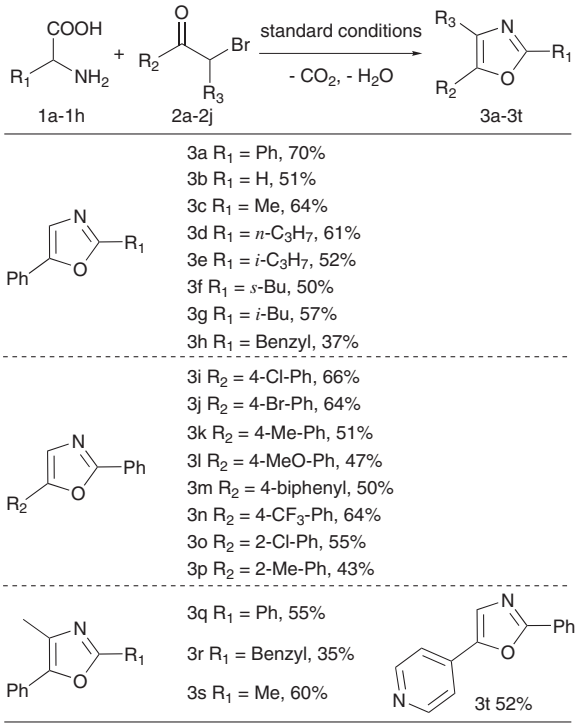


Figure 1 The scope of the reaction. Standard conditions: 0.7 mmol of amino acids (**1a**-**1h**), 0.5 mmol of **2a**-**2j**, 0.1 mmol of I_2, 1 mmol of TBHP, 2 mL of DMA, were stirred at 25°C for 4 h then slowly raised to 60°C for 4 h. Catalysts amount and isolated yields were based on **2**.

proceeded smoothly to give the corresponding products with moderate yields when 2-bromopropiophenone was employed as the reaction substrate (**3q**-**3s**). When a heterocycle compound, 2-bromo-1-(pyridin-4-yl)ethanone, was chosen as the reaction substrate, the reaction also afforded the corresponding product in 52% yield (**3t**).

Research of the reaction mechanism

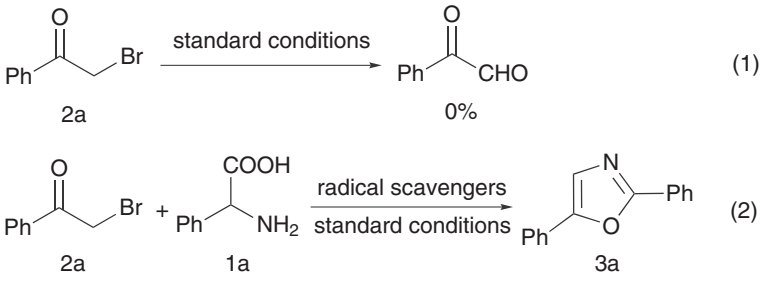
To explore the reaction process, several control experiments were carried out (Scheme 1, see details of control experiments in Additional file 1). Firstly, when 2-bromoacetophenone was employed as substrate alone under reaction condition, no benzoylformaldehyde was obtained (eq. 1). This implied that benzoylformaldehyde was not the reaction intermediate. On the other hand, when radical scavengers, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 1,4-benzoquinone or acrylonitrile, were added to the reaction system respectively, the yield of **3a** was sharply reduced from 70% to less than 15% (eq. 2). This indicated that the reaction should undergo a radical pathway.

Based on the results described above and previous reports [27,28,45,46], a plausible mechanism for this decarboxylative cyclization was proposed as follows (Scheme 2). Initially, compound **A**, formed by the substitution reaction of **1a** with **2a**, which can be transformed following two pathways: (a) I^+, generated by the oxidation of iodine, could oxidize **A** to radical intermediate **B**, which eliminates one molecular of CO_2 to generate radical **C**, which is further oxidized to imine **D** or its isomer **E**. Subsequently, **F** is obtained by intramolecular nucleophilic addition of **E**. Finally, the desired product (**3a**) is given by deprotonation and oxidation of **F**; (b) **G** is formed from the oxidation of **A**. Then **3a** is obtained through **H, I, J, K** following a process similar to path a.

Experimental

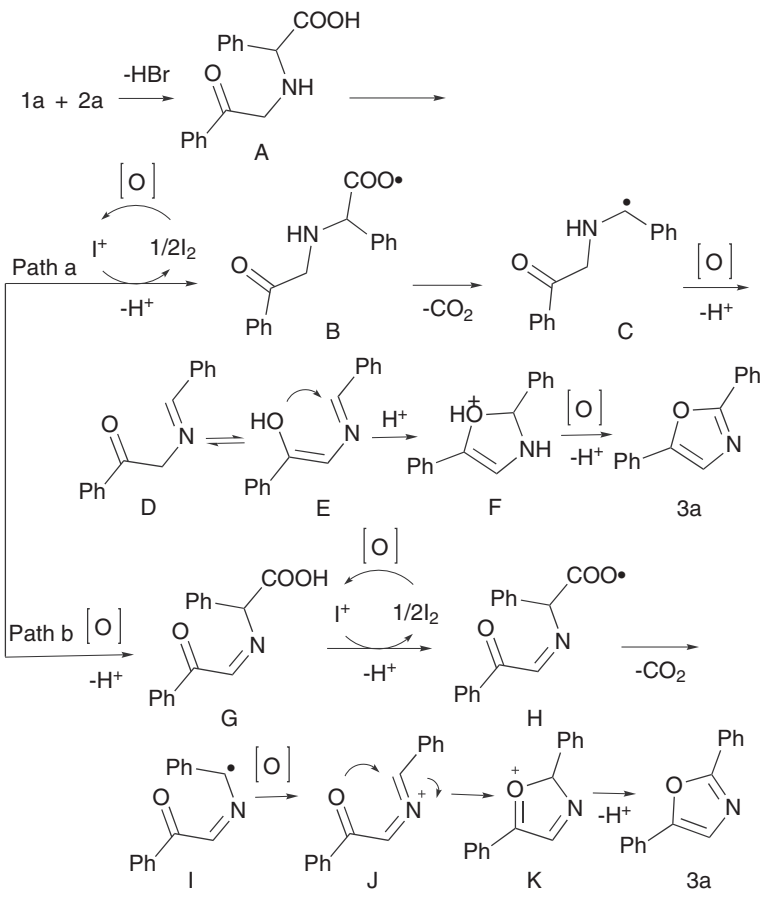
Instruments

Infrared samples were recorded on a Perkin-Elmer 2000 FTIR spectrometer and all IR data were given in cm^{-1}. NMR spectra were recorded on Brucker AVANCE 300 NMR spectrometer. The chemical shifts (δ) and coupling



radical scavengers	yield
TEMPO	<15
1,4-benzoquinone	<5
acrylonitrile	<5

Scheme 1 Control experiments.



Scheme 2 Plausible mechanism.

constants (*J*) were expressed in ppm and Hz respectively. HRMS was recorded on a Micromass UK LTD GCT spectrometer. Melting points were determined on a Beijing Tech Instrument Co., LTD X-6 melting point apparatus and are uncorrected. Unless otherwise indicated, all compounds and reagents were purchased from commercial suppliers and used without further purification.

General procedure for the synthesis of polysubstituted oxazoles

1a (105.8 mg, 0.7 mmol), **2a** (99.5 mg, 0.5 mmol), I_2 (50.8 mg, 0.2 mmol), DMA (2 mL) and TBHP (70% aqueous solution, 1 mmol) were placed in a tube (10 mL) and sealed with a thin film. Then the reaction mixture was stirred at 25°C for 4 h, heated up to 60°C and stirred at this temperature for another 4 h. After that, the resulting mixture was cooled to the room temperature, diluted with water, extracted with ethyl acetate. The organic phase was washed with saturation sodium chloride solution, dried and filtrated. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column separation (petroleum ether:ethyl acetate = 10:1) to give **3a** (154.7 mg, 70%) as light yellow solid, mp = 70–72°C.

Other oxazoles were prepared via similar procedures, for details of their characterization data and NMR spectra, see Additional file 1.

Conclusions

In summary, a new metal-free decarboxylative cyclization of available primary α-amino acids with 2-bromoacetophenones was developed for the synthesis of polysubstituted oxazoles. A series of oxazoles can be obtained with moderate yields under mild conditions. It is attractive for chemists and chemical industries because oxazoles are useful synthetic intermediates for bioactive compounds.

Additional file

Additional file 1: Control experiments, characterization data and NMR spectra for the products.

Abbreviations
TBHP: *tert*-butyl hydroperoxide; DMA: *N,N*-dimethylacetamide; DTBP: di-*tert*-butyl peroxide; *m*-CPBA: *m*-chloroperoxybenzoic acid.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
In this research YL designed experimental procedures and carried out the experimental work. YL, FG and ZZ prepared this manuscript. ZW, who is corresponding author for this manuscript, evaluated the progress of the study. All authors read and approved the final manuscript.

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