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Copper-catalyzed oxidative cyclization of glycine derivatives toward 2-substituted benzoxazoles†

Shan Liu,[a] Zhi-Qiang Zhu, *[a] Zhi-Yu Hu,[a] Juan Tang[b] and En Yuan[c]

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A novel and straightforward intramolecular cyclization of glycine derivatives to 2-substituted benzoxazoles through copper-catalyzed oxidative C–H/O–H cross-coupling was described. A variety of glycine derivatives involving short peptides underwent cross-dehydrogenative-coupling readily to afford diverse 2-substituted benzoxazoles. The synthetic method has the advantages of simple operation, broad substrate scope and mild reaction conditions, thus providing an alternative effective approach for benzoxazole construction.

Introduction

Benzoxazoles are an important class of heterocyclic scaffolds and are frequently found as key structural motifs in a number of biologically active natural products, pharmaceuticals, and functional materials.[1] In particular, 2-substituted benzoxazoles possess a wide range of remarkable biological activities,[2] such as anti-cancer,[3] antitumor,[4] antimicrobial,[5] antibacterial,[6] and antiviral properties.[7] Different substituent groups at the C-2 position of benzoxazole have a significant impact on its bioactivity. Consequently, continuous research interest has been attracted to construct benzoxazoles with various substituents at the C-2 position in the past decades. Classical methods to synthesize 2-substituted benzoxazoles are mainly through the condensation of 2-aminophenols with aldehydes, carboxylic acids or acetyl halides, followed by oxidative cyclization under either acidic or heating conditions.[8] In addition, direct C–H activation and crossing-coupling of benzoxazoles with halides or organoboronic acids by transition-metal catalysis[9] and many other alternative approaches were also developed for the construction of benzoxazole and its derivatives.[10] Despite these notable advances, exploring new and straightforward procedures to synthesize structurally diverse 2-substituted benzoxazoles is still highly desired.

Direct cross-dehydrogenative-coupling (CDC) reactions have been considered as attractive and reliable strategies to produce new chemical bonds since these reactions avoid functional group interconversion and are step- and atom-economical.[11] Great interest has been focussed on direct C–H functionalization of glycine derivatives.[12–14] However, C–heteroatom bond forming *via* dehydrogenative α-C(sp^3)–H functionalization of glycine derivatives remains rare.[14] For example, in 2016, Li and coworkers disclosed a simple and efficient copper-catalyzed phosphorylation of glycine derivatives to α-aminophosphonates *via* C–H/P–H oxidative cross-coupling.[14a] In 2018, Chandrasekharam *et al.* described copper-catalyzed amidation/imidation of glycine derivatives with amides *via* dehydrogenative C–N coupling.[14b] Recently, Huang and coworkers revealed CBr_4-mediated cross-coupling between α-amino carbonyl compounds and alcohols to construct C–O bonds.[15] However, *N*-arylglycine esters could not lead to the desired products at all. Owing to the biological importance of 2-substituted benzoxazoles, and in continuation of our research toward CDC reactions,[16] herein, we describe a simple and efficient intramolecular oxidative cyclization of glycine derivatives to 2-substituted benzoxazoles through copper-catalyzed C–H/O–H cross-coupling at room temperature.

Results and discussion

Our initial study began with ethyl (2-hydroxyphenyl)glycinate **1a** under the catalysis of 5 mol% CuI and 2 eq. of TBHP in MeCN at room temperature (entry 1, Table 1). Gratifyingly, the desired cyclization product **2a** was isolated in 27% yield at room temperature. A variety of metal salts were examined, and the results showed that CuCl is superior to the other catalysts, including CuI, CuBr, $CuCl_2$, $Cu(OAc)_2$, AgOAc and $FeCl_3$, and **2a** was obtained in 53% yield (Table 1, entries 1–7). Other oxi-

[a]*Jiangxi Province Key Laboratory of Synthetic chemistry, School of Chemistry, Biology and Material Science, East China University of Technology, Nanchang 330013, China. E-mail: zhuzq@ecut.edu.cn*
[b]*Ministry of Education Key Laboratory of Functional Small Organic Molecule, Department of Chemistry and chemical engineering, Jiangxi Normal University, Nanchang 330022, China*
[c]*College of Pharmacy, Jiangxi University of Traditional Chinese Medicine, Nanchang, 330004, China*

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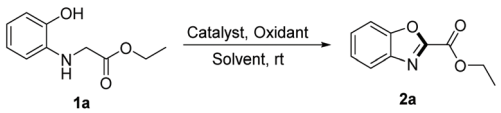
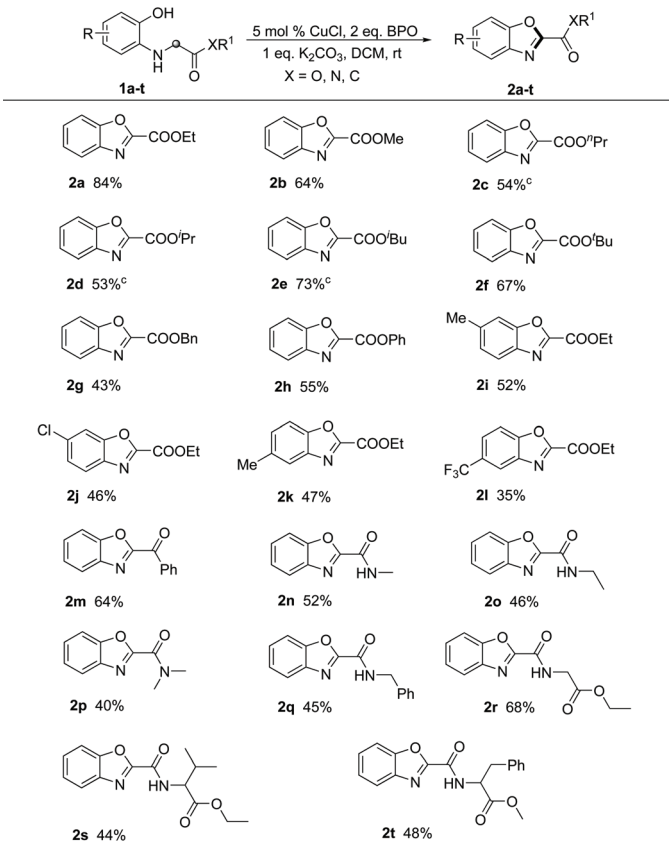
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	CuI	TBHP	MeCN	27
2	CuBr	TBHP	MeCN	20
3	CuCl	TBHP	MeCN	53
4	$CuCl_2$	TBHP	MeCN	10
5	$Cu(OAc)_2$	TBHP	MeCN	26
6	$CoCl_2$	TBHP	MeCN	Trace
7	$FeCl_3$	TBHP	MeCN	30
8	CuCl	DTBP	MeCN	15
9	CuCl	TBPB	MeCN	46
10	CuCl	DCP	MeCN	Trace
11	CuCl	BPO	MeCN	66
12	CuCl	O_2	MeCN	Trace
13	CuCl	BPO	Toluene	35
14	CuCl	BPO	EtOAc	51
15	CuCl	BPO	DCE	40
16	CuCl	BPO	DCM	72
17[c]	—	BPO	DCM	36
18[d]	CuCl	—	DCM	Trace
19[e]	CuCl	BPO	DCM	73
20[f]	CuCl	BPO	DCM	84

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (5 mol%), oxidant (2 equiv.), solvent (2 mL) at room temperature for 2–4 h. [b] Isolated yield. [c] In the absence of a catalyst. [d] No oxidant. [e] Na_2CO_3 (1 eq.) was used. [f] K_2CO_3 (1 eq.) was used.

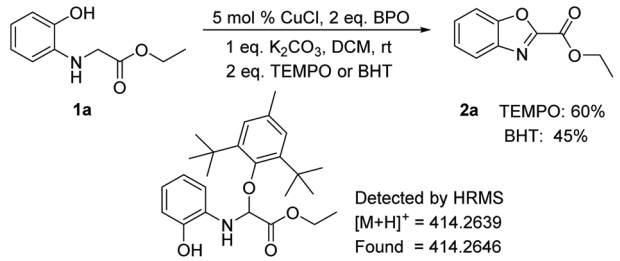
Table 2 Substrate scope for the cyclization reaction[a,b]



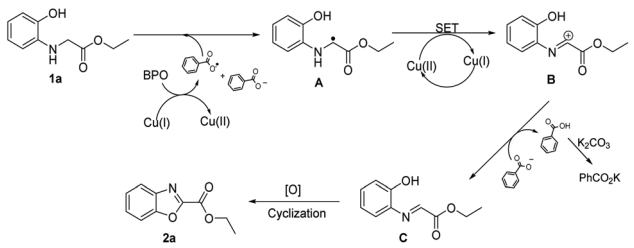
[a] Reaction conditions: **1** (0.2 mmol), CuCl (5 mol%), BPO (2 equiv.), DCM (2 mL) at room temperature for 2–4 h. [b] Isolated yield. [c] AgOAc (5 mol%) was used instead of CuCl.

dants were evaluated in the reaction (Table 1, entries 8–12), and BPO (benzoyl peroxide) gave the best yield of **2a**. Upon further screening of various solvents, it was found that DCM was the best choice, resulting in the formation of the desired cyclization product **2a** in 72% yield (Table 1, entries 13–16). In the absence of a catalyst, a significantly diminished yield of product **2a** was observed (Table 1, entry 17). Only a trace amount of product **2a** was detected without the use of BPO (Table 1, entry 18). Further screening results revealed that the yield of **2a** was improved to 73% and 84% when Na_2CO_3 and K_2CO_3 were added into the reaction, respectively (Table 1, entries 19 and 20). After exploring different parameters, the optimal conditions are **1a** (0.2 mmol), CuCl (5 mol%) and BPO (2 equiv.) in DCM (2 mL) at room temperature for 2 h.

With the optimal reaction conditions in hand, various glycine derivatives **1** were investigated in this oxidative cyclization, and the results are shown in Table 2. Initially, steric variations in R^1 of glycine derivatives **1** were examined under the standard conditions. A number of substituents in the ester moiety, such as methyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, benzyl and phenyl, were found to be suitable for this transformation, delivering the corresponding cyclization products **2a–h** in moderate to good yields. Due to the relatively low yields of products **2c–e** obtained under the standard conditions, we further screened several transition-metal catalysts. To our surprise, the yields of **2c–e** were improved efficiently by silver catalysis; for example, the yield of **2e** increased from 59% to 73% when AgOAc was used as a catalyst (Table 2). Glycine derivatives **1i** and **1j** bearing either electron-rich or electron-deficient substituents at the *para*-position of the amido unit on the benzene rings underwent the oxidative cyclization reaction readily to generate the desired products **2i** and **2j** in moderate yields. When the substituents were located at the *para*-position of the hydroxyl group on the benzene rings, the reaction proceeded well to give the desired products **2k** and **2l**. However, with a very strong electron-withdrawing group like nitro on the benzene ring, only a trace amount of the cyclization product was detected by LC-MS analysis. The experimental results indicated that electron-rich groups on the aryl rings of glycine esters worked more efficiently as compared to their counterparts with electron-deficient groups. Interestingly, α-amino ketone **1m** was found to be a suitable substrate, affording the desired product **2m** in a good yield. In addition to glycine esters, a series of glycine amides were also tested under the current conditions and the experimental results revealed that a range of glycine amides including methyl, ethyl, benzyl, and *N*,*N*-dimethyl amides were also able to furnish the corresponding cyclization products **2n–q** in moderate yields. Moreover, a variety of short peptides **1r–1u** were also found to be efficient for the oxidative cyclization, providing the



Scheme 1 Control experiments.



Scheme 2 Proposed mechanism.

corresponding products **2r–2u** with satisfactory yields. To demonstrate the practicability of this methodology, (2-hydroxyphenyl)glycine ester **1a** (6 mmol, 1.17 g) was reacted on a gram scale and the desired 2-substituted benzoxazole **2a** was isolated in 61% yield.

To gain insight into the mechanism of this transformation, several control experiments were conducted (Scheme 1). When the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the reaction, the yield of **2a** was partially suppressed (Scheme 1). Note that high-resolution mass spectrometry revealed that a trace of the adduct of BHT was generated. This result implies that the reaction may proceed through a radical pathway. On the basis of the above experimental results and previous reports,[14,15] a possible mechanism of this conversion is proposed as follows (Scheme 2). Initially, the reaction commences with the Cu(I)-assisted cleavage of BPO to produce the benzoxy radical and Cu(II). Then, the corresponding α-amino acid ester **1a** undergoes hydrogen atom abstraction by the benzoxy radical to generate alkyl radical intermediate **A**, which can be likely converted into iminium ion **B** through a single electron transfer (SET) assisted by Cu(II). Immediately, iminium ion **B** can convert into imine intermediate **C** under basic conditions. Finally, intramolecular oxidative cyclization occurs to give the desired product **2a**.

Conclusions

In conclusion, we have described a simple and direct intramolecular oxidative cyclization reaction of glycine esters through copper-catalyzed C–H bond functionalization. A broad range of glycine derivatives involving short peptides underwent the dehydrogenative coupling cyclization readily, producing the desired 2-substituted benzoxazoles *via* C–O bond formation. The synthetic protocol has potential to be used for the construction of natural products and bioactive molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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