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ARTICLE

Copper(I)-Catalyzed Tandem Synthesis of 4,5-Functionalized Oxazoles from Isocyanoacetate and Aldehydes†

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Oxazoles are among the most important heterocyclic scaffolds in the fields of natural products and medicinal chemistry. Herein is developed a tandem reaction for the synthesis of a diverse array of 4,5-difunctionalized oxazoles utilizing easily-accessible ethyl 2-isocyanoacetate and aldehydes (26 examples, 31–83% yields). This cascade reaction is facilitated by catalytic CuBr and molecular oxygen as the oxidant. The process involves a catalytic cycloaddition oxidative dehydroaromatization mechanism. The broad aldehyde substrate scope, mild reaction conditions, and atom economy make this protocol an attractive alternative to access functionalized oxazoles.

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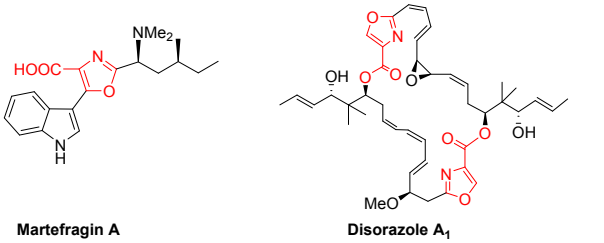
ARTICLE

Introduction

Oxazoles are common five-membered nitrogen-containing heterocycles widely found in natural substances and biologically active compounds.[1] For example, martefragin A, which is isolated from Japanese sea algae *Martensiafragilis*, has potent inhibitory activity against lipid peroxidation,[2] while disorazole A_1 from myxobacterium *Sorangiumcellulosum* was found to show picomolar antitumor activity by interfering with tubulin polymerization dynamics[3] (Figure 1).



Martefragin A **Disorazole A_1**

Figure 1 Examples of oxazole-containing bioactive compounds.

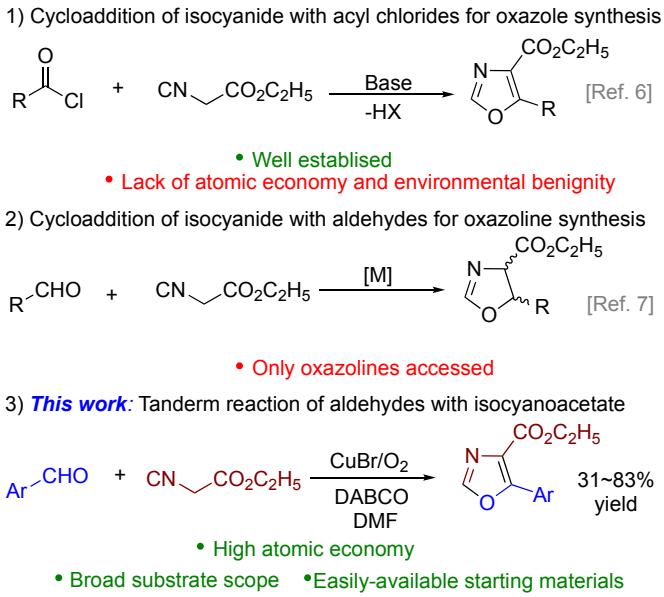


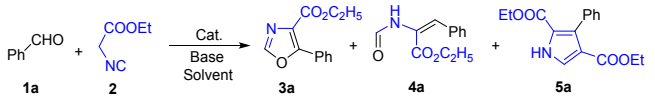
Figure 2 Isocyanoacetate-based protocols for oxazolines and oxazoles synthesis.

The prevalence and importance of oxazoles has inspired the development of synthetic methods for their preparation,[4] among which isocyanide-based protocols are particularly attractive, because of their atom- and step-economies. For example, van Leusen's toluenesulfonylmethyl isocyanide (TosMIC) is a versatile reagent that can undergo condensation/cyclization with aldehydes, providing access to mono-substituted oxazoles.[5] Along these lines, ethyl isocyanoacetate has been advanced for the synthesis of oxazole-4-carboxylates through a cyclization with acyl chlorides (Figure 2, eq 1). This reaction releases hydrogen chloride, complicating some applications.[6] Isocyanoacetate can also undergo chemoselective cyclization with aldehydes, which leads to the formation of oxazolines rather than oxazoles (Figure 2, eq 2).[7] From the perspective of green chemistry, we were motivated to combine the oxazoline-formation and aromatization into a cascade process for direct access to oxazoles. Herein, we report the catalytic condensation of aldehydes with isocyanoacetates using a copper catalyst and oxygen as the terminal oxidant (Figure 2, eq 3).

Our investigations were initiated with benzaldehyde (**1a**) and ethyl isocyanoacetate (**2**) as model substrates. Several reactions were carried out to examine the effect of catalyst, base and solvent. We first investigated the effect of catalytic metal complexes, such as $CoCl_2$, $ZnCl_2$, Ag_2CO_3, $SnCl_2$, $FeCl_3$, $(Ph_3P)_2PdCl_2$, $CuCl_2$, $CuBr_2$, CuCl, CuBr, CuI and Cu_2O (Table 1, entries 1–11). Some reactions with these metals formed **4a** as the only product, which arises from the hydrolysis of the condensation intermediate, namely 2-isocyano-3-phenyl acrylate.[8] This observation demonstrates one of the central challenges of this tandem reaction (Table 1, entries 1–3, and 6). The reactions did not proceed using $FeCl_3$ or $(Ph_3P)_2PdCl_2$ as catalyst (Table 1, entries 4–5). Fortunately, some copper complexes could facilitate these transformations. Of note, CuBr outperformed the others, generating **3a** in 56% yield (Table 1, entries 6–11). We then examined the impact of basic additives on this tandem reaction (Table 1, entries 12–19). Bases such as *t*-BuOK and K_2CO_3 exhibited a negative effect on conversion. After examining four organic bases [Et_3N, DMAP (4-*N*,*N*-dimethylaminopyridine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), and DABCO (1,4-diazabicyclo[2.2.2]octane) entries 14–17], DABCO was identified as the most beneficial base, giving 80% yield of the desired product. Examination of different temperatures and solvents led to no improvement on the yield (Table 1, entries 18–22). Reducing the catalyst or base loadings resulted in decreases in the yield (Table 1, entries 23–24). Control experiments were also performed to confirm the significance of the oxygen atmosphere and the Cu(I) catalyst. Only **4a** was formed when the reaction was conducted under a nitrogen atmosphere, suggesting that oxygen is required (Table 1, entry 25). In the absence of CuBr, the reaction exclusively produced **5a** as a result of a [3+2]-cycloaddition between the in situ-generated 2-isocyano-3-phenylacrylate and a second molecule of isocyanoacetate **2**,[9] indicating copper(I) catalyst plays an essential role in the generation of the desired product (Table 1, entry 26). In addition, experiments conducted using

$CuBr_2$ instead of CuBr in presence of DABCO or NEt_3 gave **4a** as the main product. (Table 1, entries 27–28).

Table 1 Optimization of the cyclization of aromatic aldehyde and isocyanoacetate[a]



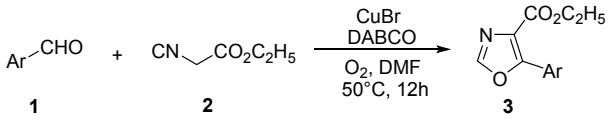
1a 2 3a 4a 5a

Entry	Catalyst	Base	Yield (%) [j]		
			3a	**4a**	**5a**
1	$CoCl_2$	-	-	45	-
2	$ZnCl_2$	-	-	28	-
3	Ag_2CO_3	-	trace	35	trace
4	$FeCl_3$	-	-	-	-
5	$PdCl_2(PPh_3)_2$	-	-	-	-
6	$CuCl_2$	-	trace	43	-
7	$CuBr_2$	-	27	36	-
8	CuCl	-	10	20	trace
9	CuBr	-	56	28	trace
10	CuI	-	trace	27	-
11	Cu_2O	-	10	24	trace
12	CuBr	*t*-BuOK	trace	trace	-
13	CuBr	K_2CO_3	trace	40	trace
14	CuBr	Et_3N	40	32	trace
15	CuBr	DMAP	35	39	trace
16	CuBr	DABCO	80	trace	trace
17	CuBr	DBU	42	36	trace
18[b]	CuBr	DABCO	56	38	trace
19[c]	CuBr	DABCO	68	15	trace
20[d]	CuBr	DABCO	38	40	trace
21[e]	CuBr	DABCO	35	45	trace
22[f]	CuBr	DABCO	trace	35	trace
23[g]	CuBr	DABCO	52	trace	trace
24[h]	CuBr	DABCO	46	trace	trace
25[i]	CuBr	DABCO	trace	30	trace
26	-	DABCO	0	trace	35
27	$CuBr_2$	DABCO	35	57	trace
28	$CuBr_2$	Et_3N	29	63	trace

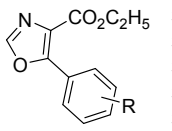
[a]Reaction conditions: **1a** (1 mmol), **2** (1 mmol), base (0.5 mmol), catalyst (0.25 mmol), dry DMF (2 mL), O_2 balloon, 50 °C, 12 h, unless otherwise stated; [b]30 °C; [c]100 °C; [d]Dry dimethyl sulfoxide (2 mL); [e]Dry *N*-methyl-2-pyrrolidone (2 mL); [f]Dry acetonitrile (2 mL); [g]DABCO (0.25 mmol); [h]CuBr (0.125 mmol); [i]N_2 balloon; [j]Isolated yields.

With the optimized reaction conditions established (entry 16), a variety of aromatic aldehydes were examined (Table 2). Benzaldehydes containing electron-donating groups (2-Me, 3-Me, 4-Me, 4-Et, 4-OMe) reacted smoothly with isocycanoacetatete to provide the corresponding oxazoles in 46–65% yield (Table 2, **3b–3f**). Halogenated benzaldehydes bearing 4-Cl, 2-Cl, 2,4-Cl_2, 4-F, 2-F and 4-Br were also tolerated in this protocol, producing the desired products in 61–83% yields (Table 2, **3g–3l**). When aldehydes carrying strong electron-withdrawing groups, such as 4-NO_2, 4-CN, 4-CF_3, and 2-CO_2H, were utilized, the desired products were obtained in 58–77% yield (Table 2, **3m–3q**). π–Extended 2-naphthaldehyde and biphenyl-4-carbaldehyde underwent this transformation under the standard conditions to give the corresponding oxazoles **3r** and **3s** with 73% and 56% yields, respectively (Table 2). A series of heterocyclic aldehydes, such as quinoline-4-carbaldehyde, thiophene-2-carbaldehyde, 2-furaldehyde, thiazole-2-carbaldehyde, 1*H*-pyrrole-2-carbaldehyde, nicotinaldehyde and isonicotinaldehyde, were all accommodated with this protocol providing target oxazoles in 31–63% yield (Table 2, **3t–3z**). The esters in these 5-heterocycle-substituted oxazoles can be converted to the medicinally relevant acids or amides by known methods.[10] Unfortunately, propanal and pivalaldehyde reacted with **2** under the standard conditions producing the hydrolyzed intermediate analogous to **4a**, indicating aliphatic aldehydes are not viable under the optimized conditions.

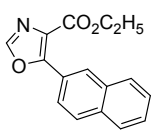
Table 2 The cyclization reaction of aromatic aldehydes with isocyanoacetate[a,b]



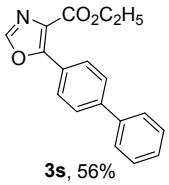
1 2 3



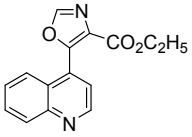
3a, R=H, 80%
3b, R=2-CH_3, 46%
3c, R=3-CH_3, 55%
3d, R=4-CH_3, 61%
3e, R=4-CH_2CH_3, 58%
3f, R=4-OCH_3, 65%
3g, R=4-Cl, 83%
3h, R=2-Cl, 61%
3i, R=2,4-Cl, 71%
3j, R=4-F, 78%
3k, R=2-F, 63%
3l, R=4-Br, 74%
3m, R=3-NO_2, 58%
3n, R=4-NO_2, 61%
3o, R=4-CN, 77%
3p, R=4-CF_3, 66%
3q, R=2-COOH, 67%



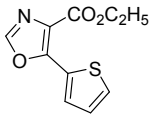
3r, 73%



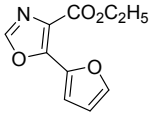
3s, 56%



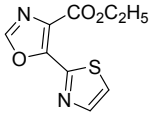
3t, 63%



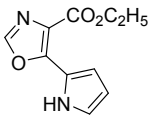
3u, 55%



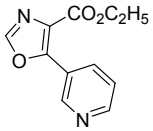
3v, 31%



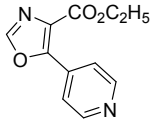
3w, 62%



3x, 45%



3y, 46%

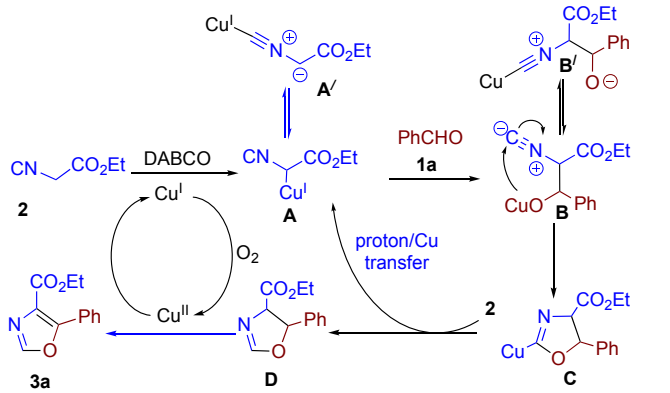


3z, 42%

[a]Reaction conditions: **1** (1 mmol), **2** (1 mmol), DABCO (0.5 mmol), CuBr (0.25 mmol), dry DMF (2 mL), O_2 balloon, 50 °C, 12 h; [b]Isolated yield.

Based on literature reports[11,12] and relevant experimental results (Table 1, entries 25–26), we propose a plausible catalytic cycle for this tandem reaction (Scheme 1). The Cu(I) complex binds to the isocyanide carbon, acidifying the protons alpha to the carbonyl group. Deprotonation of the alpha C–H by DABCO results in the formation of complex **A**′. The Cu(I)-isocyanide complex **A′** undergoes an aldol-type condensation with benzaldehyde **1a** to generate an alkoxide intermediate **B**. Intermediate **B** subsequently undergoes an intramolecular cyclization to form the Cu(I)-substituted oxazoline complex (**C**). Protonolysis of **C** by isocyanoacetate **2** forms the oxazoline intermediate **D** with the regeneration of the copper intermediate **A** and (or) **A**′. Molecular oxygen oxidizes copper(I) to

copper(II), to initiate the oxidative dehydrorogenation and aromatization of oxazoline **D** to afford the oxazole product (**3**). Consistent with this proposal, the independently prepared oxazoline **D** (from **1g** and **2**)[7d] was smoothly transformed to the final product **3g** under the standard conditions (95% yield).



Scheme 1 Proposed reaction mechanism

Conclusions

In summary, oxazoles are important heterocycles in synthetic and medicinal chemistry. A Cu(I)-catalyzed construction of oxazoles is established via the reaction of isocyanoacetates with aldehydes under an oxygen atmosphere. The reaction involves a cascade sequence of cycloaddition and oxidative dehydrogenation/aromatization, both promoted by a commercially available copper catalyst (CuBr). The high atom- and step-economy, the inexpensive catalyst and the operational simplicity render this approach practical for the synthesis of functionalized oxazoles.

Author contributions

YW performed the optimization of the reaction and the substrate scope. Product characterization were performed by YW and JW with help from HM and HZ. The first draft was written by YL. All authors contributed to revising the draft. The research was directed by YL with the help of PJW.

Conflicts of interest

There are no conflicts to declare.

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