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ARTICLE TYPE

Copper-Catalyzed Oxidative Cyclization of Arylamides and β-Diketones: New Synthesis of 2,4,5-Trisubstituted Oxazoles

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A novel copper catalyzed approach to oxazoles via enamide intermediates was developed from benzamides and β-diketones. The successive condensation and cyclization reactions afforded various 2,4,5-trisubstituted oxazoles in good yields.

Substituted oxazoles are an important class of heterocycles that are ubiquitous in biologically active molecules, including natural products, agrochemicals and pharmaceutical drugs.[1] A large number of oxazole-containing natural products have been isolated from marine invertebrates and microorganisms.[2] Moreover, many synthetic trisubstituted oxazoles have been evaluated to show activity against diabetes, breast cancer and pancreatic cancer.[3] (Figure 1) Consequently, great effort has been paid on the development of efficient synthetic methods to access substituted oxazoles, and most of the existed methods are using ketone derivatives as the starting materials.[4] Traditionally, a range of highly substituted and complex oxazoles are prepared via cyclodehydration of α-acylaminoketones, esters, or amides (the Robison-Gabriel oxazole synthesis,).[5] Nevertheless, this method requires the use of highly functionalized diketone substrates (Scheme 1, a). Additionally, catalytic decomposition of α-diazocarbonyl compounds in nitriles,[6] photolysis and pyrolysis of N-acylisoozalones[7] can provide alternative procedures for the preparation of functionalized oxazole derivatives. Transition metals such as copper,[8] rhodium,[9] ruthenium[10] and gold[11] are successfully used as the cyclization catalysts to afford various substituted oxzoles.

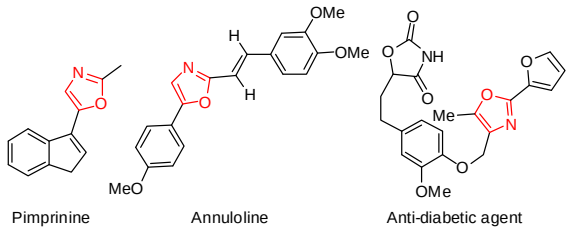
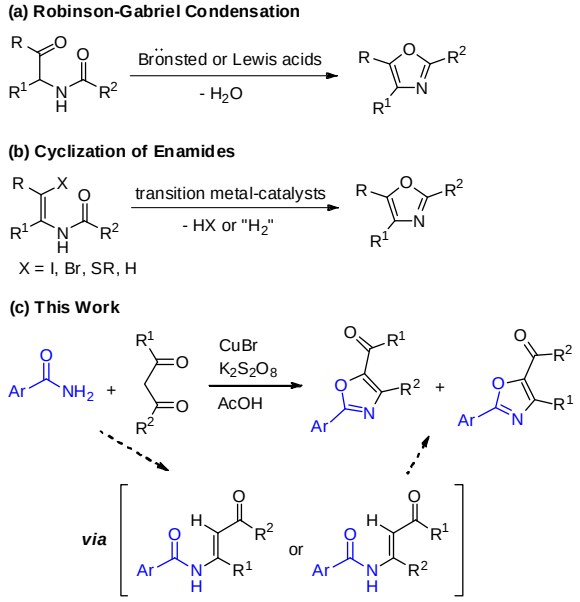


Figure 1. Selected oxazole-containing drugs

In recent years, enamides bearing β-vinylic C-heteroatom bonds are proved to be versatile cyclization precursors to construct the oxazole ring (Scheme 1, b).[12] The groups of Buchwald and Stahl reported copper-mediated oxidative cyclization of enamides to 2,5-disubstituted oxazoles via vinylic C-H functionalization.[13] This method provided a more direct approach to substituted oxzoles by avoiding the substrate functionalization. However, some highly functionalized enamide precursors require several steps to prepare. Therefore, the in situ formation of enamides from readily available starting materials such as β-diketones is highly desirable for one pot construction of oxazoles. There are only few reports on multi-substituted oxazole synthesis from β-diketones and arylamides or benzyl amines.[14] Moreover, a leaving group need to be introduced into the α-position of β-diketones. Efficient method to prepare multi-substituted oxazoles in one pot from β-diketones without leaving substituents is highly desirable. Herein, we report an efficient copper-catalyzed oxidative cyclization strategy from readily available benzamides and β-diketones (via enamide intermediate), providing the 2,4,5-trisubstituted oxazoles in good yields (Scheme 1, c).[15] In the whole process, the acyl functional group is retained and located selectively at the ortho position of the oxygen atom.[16]

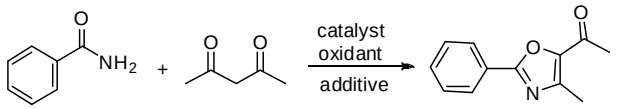


Scheme 1. Various procedures for multi-substituted oxazole synthesis

In the first experiment we examined the reaction between benzamide (**1a**) and pentane-2,4-dione (**2a**) in toluene using molecular oxygen as the oxidant. As shown in Table 1, four

different copper salts were screened using p-toluenesulfonic acid (TsOH) as the acidic additive. Among the catalysts investigated, CuBr showed the best efficiency (entries 1-4). Various oxidants were investigated instead of oxygen using CuBr as the catalyst (entries 5-8). Among the various oxidants screened, $K_2S_2O_8$ showed the best activity and its use improved the reaction yield to 24% (entry 7). The choice of acidic additive is very important, and the product **3a** could be obtained in 46% yield when acetic acid was used (entry 10). Slightly higher yield was obtained when the reaction was carried out in $Cl_2CHCHCl_2$ (entry 14). The reaction yield increased from 51% to 64% when the ratio of **1a**:**2a** changed to 2:1 (entry 15). The desired product could be obtained in 82% yield when the reaction temperature increased from 120 °C to 140 °C (entry 16). Compared with $CuBr_2$, CuBr showed better efficiency (entry 16 and 17).

Table 1. Optimization of the reaction conditions[a]



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

Entry	Catalyst	Oxidant	Additive	Solvent	Yield [%][b]
1	$Cu(OAc)_2$	O_2	TsOH	toluene	8
2	$CuSO_4$	O_2	TsOH	toluene	7
3	$CuBr_2$	O_2	TsOH	toluene	11
4	CuBr	O_2	TsOH	toluene	12
5	CuBr	DDQ	TsOH	toluene	trace
6	CuBr	TBHP	TsOH	toluene	5
7	CuBr	$K_2S_2O_8$	TsOH	toluene	24
8	CuBr	Dess-Martin	TsOH	toluene	7
9	CuBr	$K_2S_2O_8$	CF_3COOH	toluene	11
10	CuBr	$K_2S_2O_8$	CH_3COOH	toluene	46
11	CuBr	$K_2S_2O_8$	PivOH	toluene	32
12	CuBr	$K_2S_2O_8$	CH_3COOH	DMF	10
13	CuBr	$K_2S_2O_8$	CH_3COOH	1,4-dioxane	44
14	CuBr	$K_2S_2O_8$	CH_3COOH	$Cl_2CHCHCl_2$	51
15[c]	CuBr	$K_2S_2O_8$	CH_3COOH	$Cl_2CHCHCl_2$	64
16[c,d]	CuBr	$K_2S_2O_8$	CH_3COOH	$Cl_2CHCHCl_2$	82
17[c,d]	$CuBr_2$	$K_2S_2O_8$	CH_3COOH	$Cl_2CHCHCl_2$	70

[a] Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (20 mol%), oxidant (2.0 equiv.), additive (2.0 equiv.), solvent (0.4 mL), 120 °C, 36 h under argon (under oxygen for entries 1-4). [b] GC yield based on **1a**. [c] **1a** (0.4 mmol), **2a** (0.2 mmol), yield based on **2a**. [d] At 140 °C.

The scope of this reaction was studied under the optimized conditions (Table 2). Arylamides with electron-donating group at the para position smoothly coupled with pentane-2,4-dione (**2a**) to give the heterocyclic products in high yields (entries 1-4). When halogen substituents presented at the para position of amides, the corresponding products were obtained in fairly good yields (entries 5-7). For example, 68% yield of **3g** which could be converted to other useful compounds easily was obtained when an active bromo substituent existed. Strong electron-withdrawing substituent significantly decreased the reaction yield. For example, when 4-nitrobenzamide (**1h**) was used in the reaction, the desired product **3h** was observed in only 38% yield (entry 8). Similar yield was observed when the methyl substituent shifted from para to meta position (entries 2 and 9).

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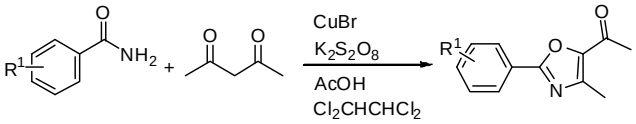
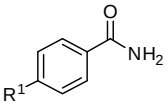
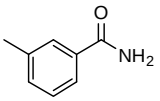
Table 2. Reaction of pentane-2,4-dione (**2a**) with various aromatic amides[a]



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

Entry	Arylamides		Product	Yield [%][b]
				
1	R^1 = H	**1a**	**3a**	83
2	R^1 = CH_3	**1b**	**3b**	81
3	R^1 = OCH_3	**1c**	**3c**	82
4	R^1 = *tert*-butyl	**1d**	**3d**	84
5	R^1 = F	**1e**	**3e**	75
6	R^1 = Cl	**1f**	**3f**	70
7	R^1 = Br	**1g**	**3g**	68
8	R^1 = NO_2	**1h**	**3h**	38
9		**1i**	**3i**	80

[a] Conditions: **1** (0.4 mmol), **2a** (0.2 mmol), CuBr (20 mol%), $K_2S_2O_8$ (0.4 mmol), AcOH (0.4 mmol), $Cl_2CHCHCl_2$ (0.4 mL), 140 °C, 36 h under Argon. [b] Isolated yield based on **2a**.

The scope of the reaction with β-diketones is outlined in Table 3. 1,3-Diphenylpropane-1,3-dione (**2b**) reacted with benzamide to give (2,4-diphenyloxazol-5-yl)(phenyl)methanone (**3j**) in 81% yield (entry 1). Besides symmetrical β-diketones, various unsymmetrical β-diketones were also employed in the oxidative cyclization reaction, providing the corresponding products in moderate to good yields (entries 2-9). For regioselectivity of the unsymmetrical β-diketones, the steric hindrance is a key factor. In all cases, 5-acyl substituted oxazoles were the major products. When 1-(naphthalen-1-yl)butane-1,3-dione (**2h**) was used, the 5-acyl substituted oxazole **3p** was obtained almost as the sole product (entry 7). Furthermore, extension of this reaction to heteroaryl β-diketones proved to be successful (entry 8). It is important to point out that changing the substituting position on the aromatic ring of 1-phenylbutane-1,3-dione (**2c**) greatly influenced the reaction yields of the corresponding products (entries 6 and 9). Unfortunately, no desired product was observed when β-diketone was replaced by ethyl acetoacetate.

A series of control experiments were designed to investigate the reaction mechanism (Scheme 2). When the reaction of **1a** with **2a** was stopped after 2 h, **4a** and **3a** were obtained in 8% and 9% yields, respectively (Scheme 2, a). The starting materials could be smoothly converted into the desired product **3a** with

extension of time whereas no significant change was observed for intermediate **4a** (Scheme 2, b). The isolated **4a** could be further transformed into **3a** in 80% yield under the standard reaction conditions (Scheme 2, c). These results suggested that enamide might be the key intermediate during the formation of oxazoles. Only trace amounts of **3a** and **4a** were observed when two equiv of TEMPO was added to the reaction mixture (Scheme 2, d). This means that a radical process was possibly involved in this transformation. Based on these competition experiments and related literatures,[13] a possible mechanism to illustrate this reaction is presented in Scheme 3. Condensation of **1a** with **2a** yields an enamide intermediate **4a** which can be further converted into a radical cation **A** in the presence of Cu(II) and Cu(I) is released and oxidized into Cu(II). The cyclization of **A** generates intermediate **B**. Subsequent oxidation of the intermediate **B** by Cu(II) provides the product **3a** and releases Cu(I) which can be re-oxidized to participate the next catalytic cycle.

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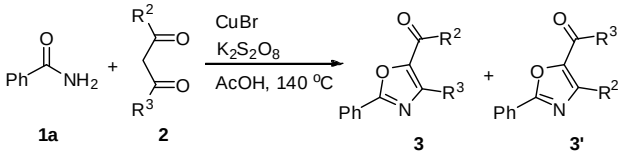
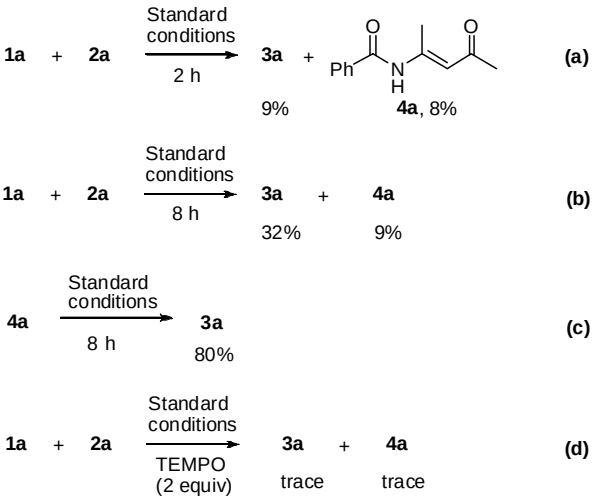
Table 3. Reactions of 1a with various β-diketones[a]

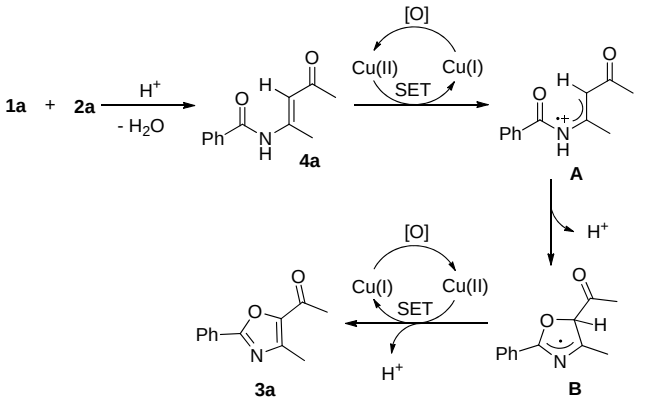


Entry	Ketone	Product	Yield [%][b]
1[c]	**2b**: $R^2 = R^3 = Ph$	**3j**	81
2	**2c**: $R^2 = Ph$, $R^3 = CH_3$	**3k:3k' (3:1)**	82
3	**2d**: $R^2 = 4\text{-Me-}C_6H_5$, $R^3 = CH_3$	**3l:3l' (4:1)**	81
4	**2e**: $R^2 = 4\text{-MeO-}C_6H_5$, $R^3 = CH_3$	**3m:3m'(4:1)**	76
5	**2f**: $R^2 = 4\text{-F-}C_6H_5$, $R^3 = CH_3$	**3n:3n' (3:1)**	66
6	**2g**: $R^2 = 4\text{-Cl-}C_6H_5$, $R^3 = CH_3$	**3o:3o' (4:1)**	73
7	**2h**: R^2 = 1-naphthyl, $R^3 = CH_3$	**3p:3p' (80:1)**	75
8	**2i**: R^2 = 2-thienyl, $R^3 = CH_3$	**3q:3q' (8:1)**	77
9	**2j**: $R^2 = 2\text{-Cl-}C_6H_5$, $R^3 = CH_3$	**3r: 3r' (4:1)**	50

[a] Conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CuBr (20 mol%), $K_2S_2O_8$ (2.0 equiv.), AcOH (2.0 equiv.), $Cl_2CHCHCl_2$ (0.4 mL), 140 °C, 36 h under Argon. [b] Isolated yield based on **2**. [c] 48 h.



Scheme 2. Control experiments



Scheme 3. Proposed mechanism

Conclusions

In conclusion, we have developed a novel approach for the synthesis of oxazoles using CuBr as the catalyst. Readily available β-diketones and primary arylamides were used as the starting materials. 5-Acyl substituted oxazoles were obtained as the sole products in all cases. Halogen substituted benzamides also could be employed for this kind of transformation. This strategy affords an efficient approach for the synthesis of biologically active oxazoles with acyl substituents from readily available starting materials with cheap and low toxic copper catalyst. The generality and synthetic applications of this methodology are under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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