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Synthesis of 2-oxo-acetamidines via copper-catalyzed oxidative crosscoupling of α -amino ketone compounds with amines

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ABSTRACT

A general and efficient method for the synthesis of 2-oxo-acetamidines via copper-catalyzed oxidative cross-coupling of amines with α -amino ketone compounds was achieved. In this reaction, the C–N bond of α -amino ketone is broken and new C–N and C=N bonds are constructed in one single transformation. This reaction system has a broad substrate scope and provides a facile pathway for the synthesis of 2-oxo-acetamidines.

As an important means of constructing carbon carbon bonds and carbon heteroatom bonds, the oxidative crosscoupling reaction through the functionalization of C-H bonds makes it possible to directly synthesize complex compounds from simple raw materials, and plays an irreplaceable role in organic synthesis, medicinal chemistry and synthesis of natural products.[1-5] The α -amino carbonyl structure subunits exists widely in natural products, biomolecules, constituting the core structures of a large variety of medicines.[6-11] It's also treated as a kind of important intermediate in organic synthesis because of activity of its carbonyl and amino groups, [12-16] some significant progress has been achieved in past decades for the functionalization of α -C-H of α -amino carbonyl compounds when different nucleophiles are employed to form C-S, C-P, C-N, C-O bonds. [17-19] For examples: Huang's group described an easy and efficient methods to synthetize 2-oxo-aceta-midines in good yields, however, it was shown that only secondary amines can be applied in this system.[20] Lately, our group reported a copper-catalyzed system which constructs C-N bond and C=N bond between the α -amino ketones and anilines to synthetize 2-oxo-acetamidines in excellent yields. However, long reaction time is required. [21]

Acetamid ine and its substituted products have important applications in natural products, medicinal chemistry and functional materials. They are also important organic synthesis intermediates. [22-26] The synthesis of 2-oxo-acetamid ines has been a longstanding hot topic due to their high activity of carbonyl groups.

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[27-28] However, most traditional methods for the synthesis of 2-oxo-acetamidines require long times, harsh conditions, low selectivity, but yield totally unsatisfactory. Therefore, it is necessary to develop a new catalytic method for the synthesis of 2-oxo-acetamidines.

For continuing interest in this area, we decided to explore a valuable catalytic system and to explore the possibility of the C-N bond formation at the methylene in α -amino ketones. After series of trials, a catalytic system for the reaction between primary amines and α -amino ketones leading to 2-oxo-acetamidines was found, which was Cu(OAc)₂·H₂O combined with DCP (bis(1-methyl-1-phenylethyl) peroxide) under a nitrogen atmosphere. Herein we report that the oxidative cross-coupling of α -amino carbonyl compounds with primary amines can be accomplished to afford 2-oxo-acetamidines in moderate to good yields using Cu(OAc)₂·H₂O/DCP system, in which the carbon nitrogen double bond and carbon nitrogen single bond can be successfully constructed at the same time.

2. Result and discussion

We began our investigation by using 4-methyl-N-(2-oxo-2-phenylethyl)benzenesulfonamide (1a) and aniline (2a) as the raw materials (Table 1). At first, we explored the reactivity of this reaction under the conditions of $Cu(OAc)_2 \cdot H_2O$ (10 mol%) TBHP (tert-Butyl hydroperoxide) (1 equiv.), DCE (1,2-dichloroethane) (2 mL) under N₂ atmosphere at 80°C for 24 h. Fortunately, we obtained the expected product **3a** with an isolated yield of 35% (entry 1). Then, We proceeded to screen metal salt catalyst, such as Pd(OAc)₂, Co(OAc)₂, AgOAc, and other

Scheme 1



different types of copper catalysts, and results found that $Cu(OAc)_2 \cdot H_2O$ was still the optimal catalyst (entries 2-8). Base also has an impact on the reaction, so we chose three bases (NaOH, NaOAc and Et₃N) as the representatives (entries 9-11). When NaOAc (1 equiv.) was added to the reaction, the yield of product **3a** increased to 38%. Screening

of different oxidants (such as TBHP, $K_2S_2O_8$, DCP and DTBP (bis(tert-butyl) peroxide)) showed that DCP was the best, up to 50% yield was obtained (entries 12-14). Moreover, when EtOAc was used as the solvent instead of DCE, the yield of **3a** was increased to 60% from 50%, but results of DMF and MeCN were not ideal (entries 15-17). When the reaction was carried out

under air atmosphere, the yield was slightly reduced to 56% (entry 18). Increasing or lowering the temperature could not increase the yield, so 80° C was also the best choice (entries 19 and 20). When 3 equivalent of DCP was used as the oxidant, the yield increased to 83%, and the reaction time could be shortened to 1 h from 24 h. As a result, it was meaningless to

Entry	Catalyst	Oxidant	Solvent	Base	Yield ^b (%)
1	Cu(OAc) ₂ .H ₂ O	TBHP ^c	DCE		35
2	$Pd(OAc)_2$	TBHP	DCE		24

further increase the amount of DCP (entries 21-23). In summary, the optimal reaction conditions are **1a** (0.3 mmol), **2a** (1.2 mmol, 4 equiv.), $Cu(OAc)_2 \cdot H_2O$ (10 mol%), DCP(0.9 mmol, 3 equiv.), EtOAc 2mL under a nitrogen atmosphere for 1h to afford the desired product within 85% yield.

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Table 1Optimization of the reaction conditions ^a





3	Co(OAc) ₂ .H ₂ O	TBHP	DCE		32			
4	AgOAc	TBHP	DCE		6			
5	Cu(acac) ₂	TBHP	DCE		27			
6	Cu_2O	TBHP	DCE		12			
7	$Cu_2(OH)_2(NO_3)_2$	TBHP	DCE		11			
8	$Cu_2(OH)_2CO_3$	TBHP	DCE		18			
9	Cu(OAc)2.H2O	TBHP	DCE	NaOH	31			
10	Cu(OAc)2.H2O	TBHP	DCE	NaOAc	38			
11	Cu(OAc)2.H2O	TBHP	DCE	Et ₃ N	36			
12	Cu(OAc)2.H2O	$K_2S_2O_8$	DCE	NaOAc	9			
13	Cu(OAc)2.H2O	DCP	DCE	NaOAc	50			
14	Cu(OAc)2.H2O	DTBP	DCE	NaOAc	36			
15	Cu(OAc) ₂ .H ₂ O	DCP	EtOAc	NaOAc	60			
16	Cu(OAc) ₂ .H ₂ O	DCP	DMF	NaOAc	33			
17	Cu(OAc)2.H2O	DCP	MeCN	NaOAc	47			
18 ^d	Cu(OAc)2.H2O	DCP	EtOAc	NaOAc	56			
19 ^e	Cu(OAc) ₂ .H ₂ O	DCP	EtOAc	NaOAc	41			
20^{f}	Cu(OAc)2.H2O	DCP	EtOAc	NaOAc	59			
21	Cu(OAc) ₂ .H ₂ O	DCP ^g	EtOAc	NaOAc	83			
22	Cu(OAc)2.H2O	DCP ^h	EtOAc	NaOAc	82			
23 ⁱ	Cu(OAc)2.H2O	DCP ^g	EtOAc	NaOAc	85			
^a Reaction conditions: 1a (0.3 mmol), 2a (1.2 mmol), [cat] 10 mol%, [O] 1 equiv, base								

Reaction condutions: 1a (0.5mmo)), 2a (1.2mmo)), [cat] 10mo)%, [O] 1equiv. base 1equiv. and solvent (2mL) under a nitrogen atmosphere at 80 °C for 24 h unless otherwise noted.

Isolated yield.

70% in aqueous. under an airatmosphere.

at 90 °C.

[O] 4equiv. for 1h.

^a Reaction conditions: **1** (0.3mmol), **2a** (1.2mmol), Cu(OAc)₂H₂O (10mol%), DCP (0.9 mmol) and NaOAc (0.3mmol) in EtOAc (2mL) under a nitrogen atmosphere at 80 °C for 1h ^b Isolated yield.

Based on the optimal reaction conditions, we began to explore the effect of substituents on this oxidative cross -coupling reaction (Table 2). At first, we designed different substrates 1 to react with aniline by changing the group R^1 attached to the carbonyl group. Different substrates with -Me, -Br and -OMe groups on the aromatic ring were all well-tolerated, and the corresponding products were obtained in moderate to good yields. And election-withdrawing groups were superior to election-donating groups. In addition, positions of substituents on benzene rings also show different influence to the reaction. The y ield of *para*-methyl group is 63% and *ortho*-methyl group is 77%.

Table 3

Variation of sulfamido groups^{a,b}



^a Reaction conditions: 1 (0.3mmol), 2a (1.2mmol), Cu(OAc)₂:H₂O (10mol%), DCP (0.9 mmol) and NaOAc (0.3mmol) in EtOAc (2mL) under a nitrogen atmosphere at 80 °C for 1h Isolated yield

Next we tested the effect of the different sulfonamide groups by changing group R^2 , including 2-tolyl, 4-methoxyphenyl, 4-bromophenyl, 4-trifluoromethylphenyl and ethyl (Table 3). When these substrates were chosen to react with aniline, the

at 60 °C .

^g [O] 3equiv.

yields of product **3a** were between 60-93%. In addition, we found that electron withdrawing groups (such as -Br, $-CF_3$) on the aromatic ring were superior to electron donating groups (such as -Me, -OMe).

Table 4

Variation of anilines^{a,b}



^a Reaction conditions: **1a** (0.3 mmol), **2**(1.2 mmol), Cu(OAc)₂H₂O (10 mol%), DCP (0.9 mmol) and NaOAc (0.3 mmol) in EtOAc (2 mL) under a nitrogen atmosphere at 80 °C for 1 h unless otherwise noted. ^b Isolated yield

^c Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **2** (0.6 mmol) Cu(OAc)₂ H₂O (10mol%), DCP (0.9 mmol) and NaOAc (0.3 mmol) in EtOAc (2mL) under a nitrogen atmosphere at 80 °C for 1h

40% methylamine in aqueous

Finally, we chose different amine compounds to explore their reactivity. Aromatic amines, including 4-tolyl, 2-tolyl, 4methoxyphenyl, 4-fluorophenyl, and 4-chlorophenyl, were all well-tolerated (Table 4), and electron withdrawing groups (-F, -Cl) on the aromatic ring were superior to electron donating groups (-Me, -OMe). Unfortunately, when pyridin-2-amine was used as the substrate, the reaction could not happen. Moreover, we chose two types of amines as reaction substrates to find out their reactivity with α -amino ketones **1a**. When aniline and methylamine reactions with α -amino ketones **1a**, the desired product with different R₃ and R₄ was obtained in 27% yield. However, when combination of aniline and morpholine was used, the desired product was obtained in a yield of 11%.

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Scheme 2 control experiment



To study the mechanism of this reaction, we designed the following control experiments (Scheme 2). When the reaction was carried out without copper catalyst, the target product cannot be detected (reaction 1). Similarly, when the reaction was carried out in the absence of DCP, no target product was formed (reaction 3). The results of these two experiments showed that copper catalyst and DCP were both necessary for the reaction. However, when reaction carried out in the absense of base, targ et product was provided with a yield in 77% (reaction 2). Then, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction under the standard conditions and the desired product was obtained in 81% yield, which showed that the reaction was not a radical process (reaction 4). Moreover, 2-oxo-2-phenylacetaldehyde was detected by GC-MS when the reaction was carried out in the absence of aniline (reaction 5). We then designed the reaction of aniline and 2-oxo-2-phenylacetaldehyde, and the desired product was obtained in 79% yield (reaction 6). The results of reaction 5 and 6 led us to believe that the aldehyde **4** was an intermediate of the reaction.

Based on experimental results, a plausible mechanism for this reaction is proposed in Scheme 3. At first, α -amino ketone **1a** coordinated with copper catalyst and base to form an active intermediate **5** and hydrogen atoms on amino and

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methylene were activated in the meanwhile and then oxidized to intermediate **6** in the presence of DCP.[29-32] Then, the intermediate **6** was hydrolyzed by H_2O to afford the intermediate **4**, which then reacted with aniline to form imine **7**.[33-34] Finally, the activated copper complex **8** formed when imine **7** coordinated with copper catalyst. The desired product **3a** was obtained when **8** was attacked by aniline.

Scheme 3 plausible mechanism



3. Conclusion

In summary, we have developed a general methods for synthesis 2-oxo-aceta midines via α -amino carbonyl compounds and amines. This novel protocol has some attractive features: Firstly, a variety of substrates scope can be adapted in the system with a moderate to excellent yield; then, stable starting materials are used in this system; finally, a short reaction time is required. Importantly, this new protocal provides another process to synthetise the 2-oxo-acetamidines and makes the α -amino carbonyl compounds more valuable with some unique chemical activity.

4. Experimental

A nitrogen-dried round-bottomed flask was charged with **1a** (86.7mg, 0.3 mmol), aniline **2a** (111.6 mg, 1.2mmol), $Cu(OAc)_2 \cdot H_2O$ (6 mg, 0.03 mmol), DCP (81 mg, 0.3 mmol) in ethyl acetate (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80°C for 1h. The reaction mixture was washed with saturated NaCl aqueous when reaction finished. The aqueous phase was reextracted with ethyl acetate (3×10mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=8:1, V/V) to afford **3a** as a yellow solid in yield of 85%.

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Acknowledgement

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Appendix A. Supplementary data

Appendix sections are coded under \appendix.

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Graphical Abstract

Synthesis of 2-oxo-acetamidines via copper-catalyzed oxidative cross-coupling of α -amino ketone compounds with amines

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This work:

$$R_{1} \xrightarrow{N} R_{2} = aryl R_{2} = aryl or alkyl$$

$$R_{1} \xrightarrow{N} R_{2} = aryl or alkyl$$

3.stable raw material and broad scope

Highlights

R₃=aryl or alkyl R₄=aryl or alkyl

Synthesis of 2-oxo-acetamidines via copper-catalyzed oxidative cross-coupling of α-amino ketone compounds with amines

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SCP W

- High total yield up to 99%
- · Short time required
- · Stable raw material and broad scope

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