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Synthesis of α -Ketoamides by Copper-Catalyzed Reactions of Phenylacetic Acids with N,N-Dialkylformamides

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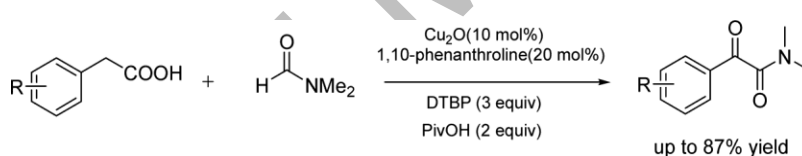
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Abstract

*A new synthetic approach for α -ketoamides was achieved by copper-catalyzed coupling reactions between *N,N*-dialkylformamides and phenylacetic acids. A variety of substrates were well tolerated to give yields 46-87% (17 examples). ¹³C-labeling experiment revealed that the carbonyl group of the products came from the phenylacetic acid.*



KEYWORDS: amides, copper, cross-coupling, oxidation

INTRODUCTION

α -Ketoamides constitute key frameworks in many biologically active agents in natural products such as the immunosuppressive drug rapamycin,^[1] and they could serve as precursors of pharmacologically important structures such as oxazolidinones,^[2] β -lactams,^[2,3] and chiral α -hydroxyamides.^[4] The importance of the α -ketoamide motif

necessitates the development of efficient methods for their preparation. Representative methods for the construction of α -ketoamides include amidation of α -ketoacids and α -ketoacylhalides,^[5] transition-metal-catalyzed double carbonylative amination of aryl halides,^[6] reaction of isocyanide with aromatic acyl chloride or anhydride followed by hydrolysis of the resulting α -ketoimidoyl chloride.^[7] Besides these methods, Cu-catalyzed oxidative approaches have also been reported,^[8] such as cross-coupling reactions between formamide and α -oxocarboxylic acids (path 1, Scheme 1),^[8a,8b] the reactions between aryl acetaldehydes or α -carbonyl aldehyde with amines (path 2, Scheme 1),^[8c,8d] amidation of terminal alkynes with anilines (path 3, Scheme 1)^[8e] and reactions of aryl methyl ketones with amines (path 4, Scheme 1).^[8f, 8g] More recently, Ahmed and co-workers developed an elegant procedure for the construction of α -ketoamides involving highly reactive iminium ions as an intermediate and using DMSO as the oxidant.^[8h] However, this protocol suffered from limited substrate scope in terms of primary amines and was not suitable for the synthesis of *N,N*-dialkyl-substituted ketoamides. Nevertheless, most of these reports are restricted by precursor availability, harsh conditions, multistep processes or utilization of expensive transition-metal catalysts. Therefore, the development of mild, convenient and efficient methods toward α -ketoamides is still in challenging, especially for the synthesis of *N,N*-disubstituted α -ketoamides.

In continuation of our recent work on copper-catalyzed amidation reactions using DMF as an amide source,^[9] herein is reported copper-catalyzed oxidative reactions of the

formation of α -ketoacid from α -arylacetic acids, and followed by the reaction with *N,N*-dialkylformamides to afford α -ketoamides.^[10]

RESULTS AND DISCUSSIONS

Initially, we chose phenylacetic acid **1a** and DMF **2** as model substrates to optimize the reaction conditions under oxygen atmosphere. As shown in Table 1, the control experiment showed that the reaction of phenylacetic acid with DMF failed to give the expected product **3a** in the absence of catalyst (Entry 1, Table 1). Meanwhile, 12% yield of product **3a** was obtained after addition of CuBr and phenanthroline (Entry 2, Table 1). Subsequent studies revealed that Cu₂O was the best copper source to give 42% yield, while other copper salts, such as CuBr, CuCl, CuI, CuSO₄, CuCl₂ and Cu(acac)₂ resulted in much lower yields (Entries 2-8, Table 1). Furthermore, other ligands including bipyridine, TMEDA, DMEDA and *L*-proline were also investigated, but the results were unsatisfactory (Entries 9-12, Table 1). Among different additives, pivalic acid exhibited better results than K₂CO₃, triethylamine, pyridine, TsOH and HOAc (Entries 13-18, Table 1). Then, various oxidants were examined in the model reaction and the results indicated that di-*tert*-butyl peroxide (DTBP) showed to be more beneficial to the reaction than others including TBHP, K₂S₂O₈ and (NH₄)₂S₂O₈ (Entries 19-22, Table 1). The reaction was further improved by increasing the substrate concentration to afford **3a** in 78% yield (Entry 23, Table 1). Decreasing the temperature resulted in lower yield (Entry 24, Table 1). Therefore, the optimized reaction conditions for the model reaction were Cu₂O (10

mol%), 1,10-phenanthroline (20 mol%), DTBP (3.0 equiv), PivOH (2 equiv), DMF(1 mL) at 130 °C for 24h.

Under the optimized reaction conditions, the scope of substituted phenylacetic acids was then investigated. As shown in Table 2, the reactions between phenylacetic acids and DMF proceeded smoothly to give the desired products in moderate to good yields ranging from 52% to 87%. Some substituents such as methyl, methoxyl and halogens could be well tolerated during catalysis. Phenylacetic acids with electron-donating groups seemed to be more beneficial to the reaction than those containing electron-withdrawing groups. For example, *p*-tolylacetic acid gave the corresponding product in 87% yield, while *p*-nitrophenylacetic acid resulted in only 52% yield (Entries 7 and 8, Table 2). Meanwhile, steric hindrance seemed to have fewer effects on the results. For example, phenylacetic acids with methyl group substituted either on *para*, *meta*, or *ortho* position gave similar yields around 85% (Entries 2, 7 and 10, Table 2). Notably, 1-naphthaleneacetic acid could also be reacted well with DMF to give corresponding product in 78% yields (Entry 12, Table 2).

Encouraged by these promising results, *N,N*-diethylformamide could also be applied as substrate instead of DMF for this reaction. As shown in Table 3, moderate yields were obtained in these cases indicating the potential of this protocol for the synthesis of *N*-substituted α -ketoamides (Table 3).

It was reported that DMF could be utilized as a precursor to provide $-\text{CONMe}_2^{[8a]}$ or $-\text{NMe}_2^{[8b]}$ units in the reaction of α -oxocarboxylic acid with DMF. In order to elucidate the possible reaction pathway of this work, several control experiments were carried out as shown in Scheme 2. Firstly, benzaldehyde was used instead of phenylacetic acid under the standard conditions, and desired product 3 couldn't be obtained, which indicated that benzaldehyde is not formed as an intermediate (Scheme 2, eqn (1)). Further evidence of a ^{13}C -labeling experiment unambiguously confirmed that the carbonyl group of the product would come from the phenylacetic acid, rather than DMF (eqn (2), see supporting information for detail), which seemed this reaction might involve a different pathway compared with previous work on copper-catalyzed aerobic decarboxylation of phenylacetic acid by Song et al.^[10] Furthermore, after addition of 2 equiv. of TEMPO to the reaction under standard conditions, the transformation was remarkably suppressed, suggesting that a free *N,N*-dimethylamine radical might be involved in the reaction (Scheme 2, eqn (3)).^[8b,8i,11]

On the basis of these and previously reported results,^[8b,9] a possible reaction pathway was proposed as shown in Scheme 3. Initially, phenylacetic acid is oxidized to 2-oxo-2-phenylacetic acid^[10b], then, 2-oxo-2-phenylacetic acid forms product with *N,N*-dimethylamine radical,^[8b] which is formed through decomposition of DMF under the reaction conditions.^[8i,11] This is different from the work of Reddy and coworkers,^[12] they

showed that amide could be obtained by the decarboxylation of carbamic anhydride formed from the direct coupling of acid with formamide.

CONCLUSIONS

In summary, we have discovered a simple method for the synthesis of α -ketoamides *via* copper-catalyzed coupling of formamides with phenylacetic acids. ^{13}C -labeling experiment confirmed that the carbonyl group of the product came from the phenylacetic acid. This protocol also provides a practical synthetic method for the construction of *N*-substituted α -ketoamides.

EXPERIMENTAL SECTION

Typical procedure for the synthesis of *N,N*-dimethyl-substituted α -ketoamides (3a) and *N,N*-diethyl-substituted α -ketoamide (5a) Cu_2O (0.05 mmol), PivOH (1.0 mmol), 1,10-phenanthroline (0.1 mmol), DTBP (1.5 mmol), phenylacetic acid (0.5 mmol), and DMF (1 mL) or DME (1 mL) were added into a Schlenk tube (25 mL) equipped with a magnetic stirrer bar. The Schlenk tube was then closed and the resulting mixture was stirred at 130 °C for 24 h. After cooling down to room temperature, the mixture was filtered with celite, and the filtrate was washed with water and dried over Na_2SO_4 . The residue was directly purified by silica gel column chromatography with petroleum ether/EtOAc (10:1 to 4:1) to give α -ketoamides.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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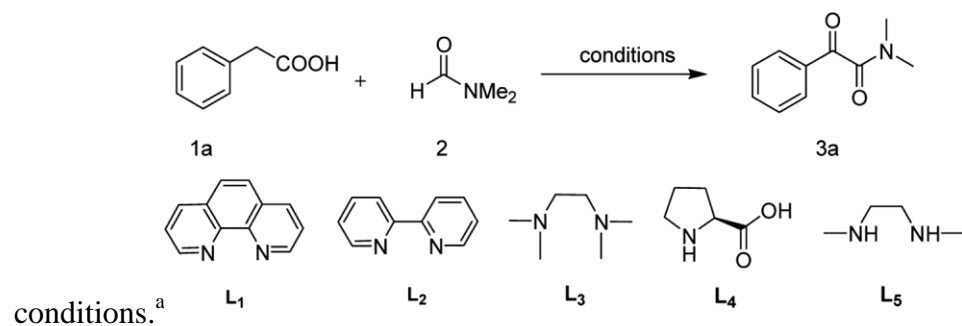
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Table 1. Selected results from the optimization of the reaction



Entry	Catalyst	Oxidant	Ligand	Additive	Yield ^b [%]
1	—	O ₂	—	—	NR
2	CuBr	O ₂	L ₁	—	12
3	CuCl	O ₂	L ₁	—	10
4	CuI	O ₂	L ₁	—	trace
5	Cu ₂ O	O ₂	L ₁	—	42
6	CuSO ₄	O ₂	L ₁	—	trace
7	CuCl ₂	O ₂	L ₁	—	trace
8	Cu(acac) ₂	O ₂	L ₁	—	16
9	Cu ₂ O	O ₂	L ₂	—	21
10	Cu ₂ O	O ₂	L ₃	—	13
11	Cu ₂ O	O ₂	L ₄	—	39
12	Cu ₂ O	O ₂	L ₅	—	trace
13	Cu ₂ O	O ₂	L ₁	K ₂ CO ₃	NR
14	Cu ₂ O	O ₂	L ₁	Et ₃ N	23

15	Cu ₂ O	O ₂	L ₁	Py	41
16	Cu ₂ O	O ₂	L ₁	TsOH	26
17	Cu ₂ O	O ₂	L ₁	HOAc	24
18	Cu ₂ O	O ₂	L ₁	PivOH	58
19	Cu ₂ O	DTBP	L ₁	PivOH	67
20	Cu ₂ O	TBHP	L ₁	PivOH	40
21	Cu ₂ O	(NH ₄) ₂ S ₂ O ₈	L ₁	PivOH	NR
22	Cu ₂ O	K ₂ S ₂ O ₈	L ₁	PivOH	NR
23 ^c	Cu ₂ O	DTBP	L ₁	PivOH	78
24 ^d	Cu ₂ O	DTBP	L ₁	PivOH	62

^a Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol%), oxidant (1.5 mmol), ligand (20 mol%), additive (1.0 mmol), DMF (2 mL), 130 °C, 24h, O₂.

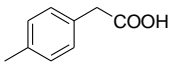
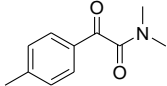
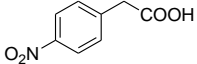
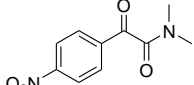
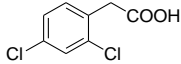
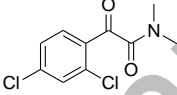
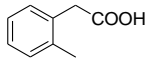
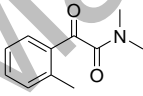
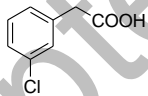
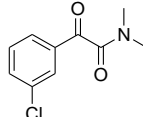
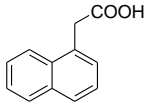
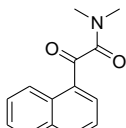
^b Isolated yields.

^c DMF (1 mL).

^d The temperature is 110 °C.

Table 2. Reaction of phenylacetic acids with

Entry	Readant	Product	Yield ^b (%)
1			78
	1a	3a	
2			82
	1b	3b	
3			80
	1c	3c	
4			67
	1d	3d	
5			75
	1e	3e	
6			70

	1f	3f	
7			87
	1g	3g	
8			52
	1h	3h	
9			61
	1i	3i	
10			83
	1j	3j	
11			70
	1k	3k	
12			78
	1l	3l	

^a Reaction conditions: phenylacetic acids 0.5 mmol, DMF 1 mL, Cu₂O 10 mol%, Phen 20 mol%, PivOH 1.0 mmol, DTBP 1.5mmol, at 130 °C for 24 h.

^b Isolated yields.

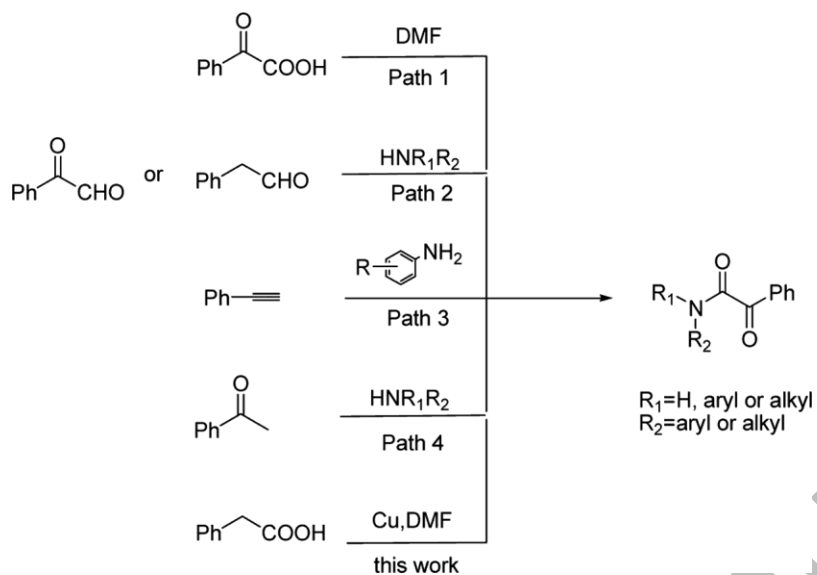
Table 3. Reaction of phenylacetic acids with

Entry	Readant	Product	Yield ^b (%)
1			57
	1a	5a	
2			46
	1d	5d	
3			47
	1e	5e	
4			64
	1g	5g	
5			61
	1j	5j	

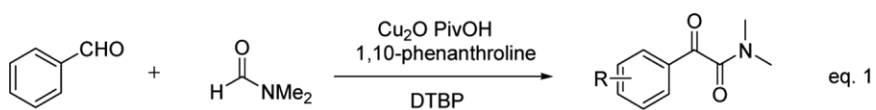
^a Reaction conditions: phenylacetic acids 0.5 mmol, DEF 1 mL, Cu₂O 10 mol%, Phen 20 mol%, PivOH 1.0 mmol, DTBP 1.5mmol, at 130 °C for 24 h.

^b Isolated yield.

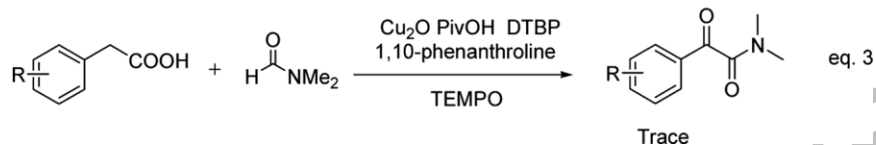
Scheme 1. Methods for the copper-catalyzed preparation of α -ketoamides



Scheme 2. Exploring the reaction pathway of formation of α -ketoamides.



No Reaction



Trace

Scheme 3. Proposed pathway for the synthesis of α -ketoamides.

