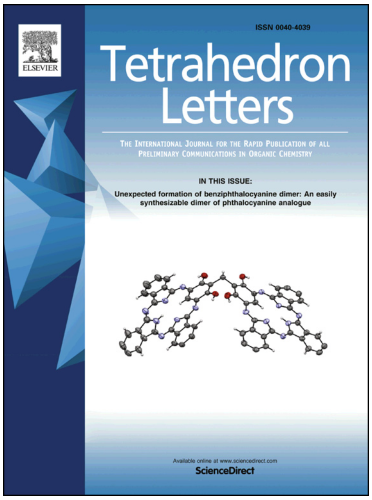

Copper nanoparticles catalyzed economical synthesis of 3-substituted isocoumarins from 2-chlorobenzoic acids/amides and 1,3-diketones

Xiaowen Wang, Chaolong Wu, Youwen Sun, Xiaoquan Yao

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Graphical Abstract

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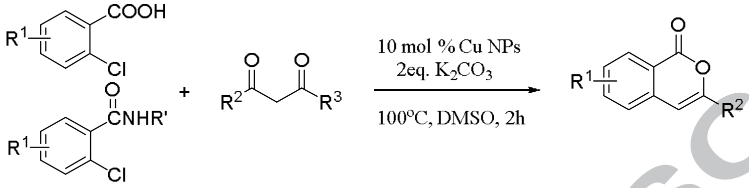

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ABSTRACT

Copper nanoparticles were utilized as a highly efficient catalyst for a facile and economical synthesis of 3-substituted isocoumarins with 2-chlorobenzoic acids and 1,3-diketones as starting materials. The copper nanoparticles catalyst showed highly catalytic activity for the 2-chloro-substituted substrates to afford 3-substituted isocoumarins in good to excellent yields. Further more, good catalytic activity was also observed when 2-chlorobenzoic amides were utilized as substrates instead of the benzoic acids.

Isocoumarins, as an important natural lactone,[1] show a variety of pharmacologyical and biological activities,[2] such as immunomodulatory, antifungal, cytotoxic etc., in which 3-substituted isocoumarins have a great influence on their biological activities respect to other substituted isocoumarins. Moreover, they are important organic synthetic intermediates, especially for biologically heterocylic[3] and carbocyclic compounds.[4] Therefore, the synthesis of 3-substituted isocoumarins has attracted great attention of researchers.

Till now, various approaches for the synthesis of 3-substituted isocoumarins have been reported,[5-8] in which *o*-halobenzoic acid and its derivatives were the very popular starting materials with 1-alkynes or 1,3-diketones together. There are many examples on the transition metal-catalyzed tandem reaction of *o*-halobenzoic acid and 1-alkynes reported to afford 3-substituted isocoumarins.[6,9] However, the methodology is usually nagged by regioselectivities: there are 5-exo and 6-endo cyclization combined products obtained during the domino Sonogashira coupling-intramolecular cyclization process, which restrain its application to a great extent.

Recently, Xi and coworkers[10] reported a domino process of 2-halobenzoic acids and 1,3-diketones for the corresponding 3-substituted isocoumarins with CuI as catalyst, which exhibited high regioselectivity and good to excellent yields were achieved. However, there are some limits on the scope of substrates: 2-chlorobenzoic acids usually give much lower reactivities than 2-iodo and 2-bromo-benzoic acids. On the other hand, Yao[11] et al also reported an approach for the synthesis of 3-substituted isocoumarins with 2-halobenzoic amides and 1,3-diketones as substrates, and the same limit on substrate was observed. Therefore, to develop a facile, efficient and more economical strategy for the synthesis of isocoumarins is still under investigation.

In recent years, much attention has been attracted to the use of nanoparticles as catalysts in organic reactions.[12] Because of their easy preparation and relative stabilities in air, the nanoparticles of coinage metals, such as copper, silver and gold, were widely reported, and there are many excellent examples on their applications as catalysts in organic reactions.[13] Recently, our group also developed some reactions catalyzed by copper nanoparticles, and in most cases, the nanoparticle catalysts show much higher catalytic activities than salts.[14]

Herein, we would like to report a copper nanoparticles catalyzed coupling reaction of 2-halobenzoic acids/amides with 1,3-diketones to 3-substituted isocoumarins. In this approach, 2-chlorobenzoic acids or amide can be utilized efficiently, and good to excellent yields were achieved.

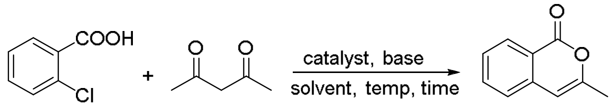
Initially, the reaction of 2-chlorobenzoic acid (**1a**) and pentane-2,4-dione (**2a**) was selected as the prototype to start our investigation for the optimized reaction conditions, and the data were summarized in Table 1.

When **1a** (0.2 mmol) and 2 equiv of **2a** were treated with 10 mol % of Cu NPs[15] in 1.5 mL of DMSO at 100 °C with 2 equiv of K_2CO_3 as the base under nitrogen for 2 h, **3a** was achieved in 92% yield (entry 1, Table 1). Some copper salts, such as CuI, $Cu(OAc)_2$, and $CuSO_4$ were then examined, and only *ca.* 55% yields were observed (entries 2-4). On the other hand, a blanket reaction was carried out in the absence of Cu NPs catalyst, and no reaction occurred (entry 5). Increasing or decreasing the loading of the catalyst were all led to worse yields (entries 6 and 7), and higher or lower temperature could result in the same thing (entries 8 and 9).

Different solvents, such as DMF, toluene, MeCN, 1,4-dioxane and DCE, were then evaluated in the reaction, and DMSO was found as the best of choices (entry 1 *vs.* 10-14). Some other bases, such as Na_2CO_3, K_3PO_4, NaOH, KOH and *i*-Pr_2NEt, were also screened. It was found that the expected product was obtained only in moderated yields in the presence of inorganic bases except K_2CO_3 (entries 15-18 *vs.* entry 1), while *i*-Pr_2NEt inhibited the reaction at all (entry 19). Further more, a base-free condition was also tried, and no reaction occurred (entry 20). On the other hand, shortening or extending the reaction time could not improve the yields either (entries 21, 22).

Thus, the optimal conditions involved the following parameters: 10 mol % of Cu NPs and 2 equiv of K_2CO_3 in 1.5mL of DMSO at 100 °C under nitrogen.

Table 1. The reaction of 2-chlorobenzoic acid and pentane-2,4-dione [a]



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

Entry	Catalyst	Solvent	Base	Temp (°C)	Time (h)	Yield [b] (%)
1	Cu NPs	DMSO	K_2CO_3	100	2	92
2	CuI	DMSO	K_2CO_3	100	2	56
3	$Cu(OAc)_2$	DMSO	K_2CO_3	100	2	55
4	$CuSO_4$	DMSO	K_2CO_3	100	2	58
5	—	DMSO	K_2CO_3	100	2	N.D.
6[c]	Cu NPs	DMSO	K_2CO_3	100	2	81
7[d]	Cu NPs	DMSO	K_2CO_3	100	2	77
8	Cu NPs	DMSO	K_2CO_3	90	2	82
9	Cu NPs	DMSO	K_2CO_3	110	2	80
10	Cu NPs	DMF	K_2CO_3	100	2	84
11	Cu NPs	Toluene	K_2CO_3	100	2	N.D.
12	Cu NPs	MeCN	K_2CO_3	100	2	29
13	Cu NPs	1,4-dioxane	K_2CO_3	100	2	8
14	Cu NPs	DCE	K_2CO_3	100	2	N.D.
15	Cu NPs	DMSO	Na_2CO_3	100	2	40
16	Cu NPs	DMSO	K_3PO_4	100	2	65
17	Cu NPs	DMSO	NaOH	100	2	62
18	Cu NPs	DMSO	KOH	100	2	70
19	Cu NPs	DMSO	*i*-Pr_2NEt	100	2	N.D.
20	Cu NPs	DMSO	—	100	2	N.D.
21	Cu NPs	DMSO	K_2CO_3	100	1	73
22	Cu NPs	DMSO	K_2CO_3	100	4	84

[a] The reaction was performed with **1a** (0.2 mmol), **2a** (0.4 mmol), Cu NPs (0.02 mmol), and base (0.4 mmol) in solvent (1.5 mL) under N_2.

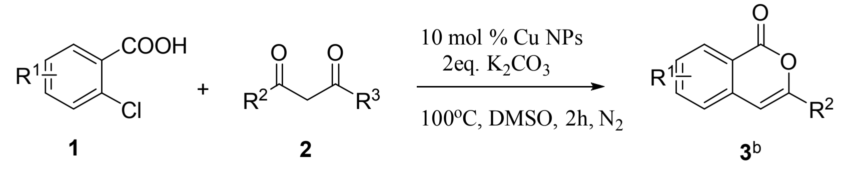
[b] Isolated yields; N.D. = no reaction.

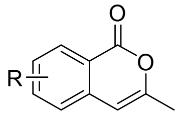
[c] Cu NPs (0.0 1mmol).

[d] Cu NPs (0.03 mmol).

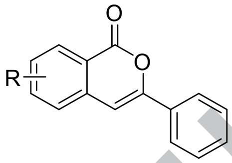
With the optimized reaction conditions, various substituted 2-chlorobenzoic acids and 1,3-diketones were explored.[16] The results were listed in Table 2. As can be seen, 2-chlorobenzoic acids with 3-CH_3, 4-CH_3, 6-CH_3, 4-OCH_3 , and 4-F groups reacted with pentane-2,4-dione (**2a**) to give the products **3b-3f** in moderate to excellent yields while 2,4-dichlorobenzoic acid gave the product **3g** in a low yield. Then, 1,3-diphenylpropane-1,3-dione (**2b**) was used to react with the 2-chlorobenzioc acids instead of **2a**, and the corresponding products **3h-3l** were formed in good to excellent yields. When heptane-3,5-dione (**2c**) was examined, the desired products **3m-3r** were achieved in 41-87% yields. From these results above, it demonstrated that electron-donating substitutes on 2-chlorobenzoic acids seemed to be favored to the reaction compared with electron-withdrawing groups (**3m-3p** *vs.* **3q-3r**). Subsequently, an unsymmetrical 1,3-diketone, 6-methylheptane-2,4-dione (**2d**), was utilized in the reaction. It can be seen that only the mixture of two isomeric products were obtained in all of four examples with good combined yields. The 3-isopropylisocoumarins were obtained as the major products.

Table 2. The reaction of 2-chlorobenzoic acids and 1,3-diketones [a]

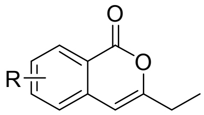


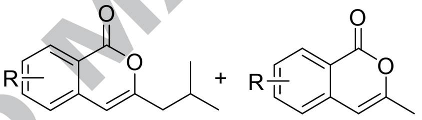


R = H, **3a**, 92%
R = 3-CH$_3$, **3b**, 85%
R = 4-CH$_3$, **3c**, 61%
R = 6-CH$_3$, **3d**, 55%[c]
R = 4-OCH$_3$, **3e,** 81%[c]
R = 4-F, **3f**, 59% [c]
R = 4-Cl, **3g**, 18%[c]



R = H, **3h**, 95%
R = 3-CH$_3$, **3i**, 78%
R = 4-CH$_3$, **3j**, 95%
R = 6-CH$_3$, **3k**, 78%
R = 4-OCH$_3$, **3l,** 94%





R = H, **3m**, 82%
R = 3-CH$_3$, **3n**, 82%
R = 4-CH$_3$, **3o**, 87%
R = 6-CH3, **3p**, 82%
R = 4-F, **3q** 41%[c]
R = 4-Cl, **3r**, 43%[c]

R = H, **3s+3a** (1.43:1), 90%[c, d]
R = 3-CH$_3$, **3t+3b** (1.53:1), 83%[c, d]
R = 4-CH$_3$, **3u+3c** (1.45:1), 83%[c, d]
R = 4-F, **3v+3f** (1.50:1), 30%[c, d]

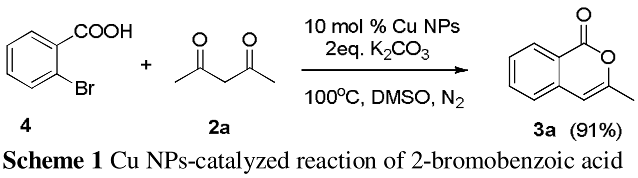
[a] Reaction conditions: nitrogen atmosphere, **1** (0.2mmol), **2** (2 equiv), copper nanoparticles (10 mol %), K$_2$CO$_3$ (2 equiv), DMSO (1.5mL), stirred at 100 °C under N$_2$.

[b] Isolated yields.

[c] Reaction performed in 8 h.

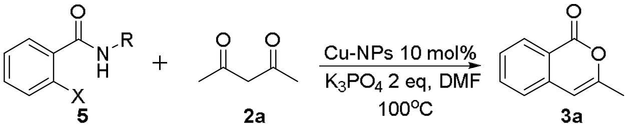
[d] Combined yield.

In order to detect the adaptability of the Cu NPs catalyst, 2-bromobenzoic acid was tested in the reaction under the optimized conditions, and the desired products were isolated in an excellent yield (Scheme 1). Obviously, Cu NPs catalyst shows almost same catalytic activities on both 2-bromo and 2-cholo benzoic acid substrates.



Scheme 1 Cu NPs-catalyzed reaction of 2-bromobenzoic acid (**4**) and pentane-2,4- dione (**2a**).

The successful utilization of the Cu NPs catalyst in the reaction of 2-cholobenzoic acids and 1,3-diketones encouraged us to explore its catalytic ability in the coupling reaction of 2-chlorobenzoic amides and 1,3-diketones. Under similar conditions (10 mol % of Cu NPs, 2 equiv of K$_3$PO$_4$ in DMF at 100 °C under nitrogen), several kinds of amides were utilized to react with pentane-2,4-dione (**2a**), and the results were summarized in Scheme 2.



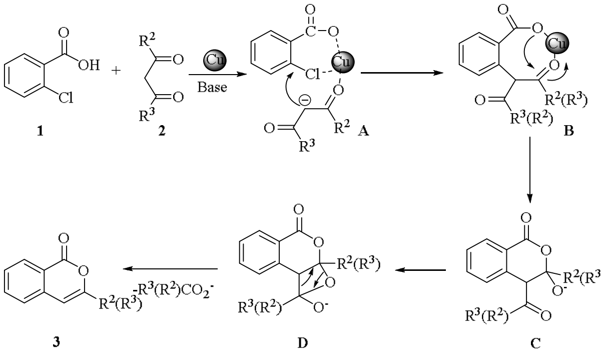
5a, X = Br, R = Ph, 91% of **3a**
5b, X = Cl, R = Ph, 84% of **3a**
5c, X = Br, R = *p*-Br-C$_6$H$_4$, 92% of **3a**
5d, X = Cl, R = *p*-Br-C$_6$H$_4$, 89% of **3a**

Scheme 2 Cu NPs-catalyzed reaction of 2-halobenzoic amide (**5**) and pentane-2,4- dione (**2a**).

It can be seen from Scheme 2, the Cu NPs catalyst showed excellent catalytic activity to both 2-bromo- and 2-chloro-substituted benzoic amide in the coupling reaction. It is also worthy to mention that all of the reactions finished in 0.5 h.

When 2-bromo-N-phenylbenzamide (**5a**) was used, the reaction time was even shortened to 15 min.

A plausible mechanism was also proposed for the reaction of 2-cholobenzoic acids and 1,3-diketones: Initially, the intermediate **A** was formed through the substrate **1** and **2** in the presence of base, and give the intermediate **B** by the Hurtley reaction.[10, 17] The higher catalytic activity of Cu NPs for the coupling reaction might be due to a multi-center synergistic effect occurred on the surface of Cu NPs.[18] The carbonyl group of 1,3-diketone was then attacked by the carboxylate anion to give **C** as intermediate**.** The alkoxy anion of **C** would activate another keto moiety to generate intermediate **D** with a four-member ring; and then, through the bond-breaking of the C-O bond and C-C bond, the product **3** was achieved finally.[10]



Scheme 3 Proposed reaction mechanism for the reaction of 2-cholobenzoic acids and 1,3-diketones.

In conclusion, an efficient and economical strategy has been demonstrated for the synthesis of 3-substituted isocoumarins under Cu NPs catalyzed process of 2-chlorobenzioc acids and 1,3-diketones. In addition, the Cu Nps catalyst shows good catalytic activities to the reaction of 2-chlorobenzoic amides and 1,3-diketones. The detailed mechanism, the effect of particle size and particle support as well as the scope of the reaction are currently under further investigations.

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16. **Typical procedure for copper nanoparticles catalyzed sunthsis of 3-substituted isocoumarins from 2-chlorobenzoic acids and pentane-2,4-dione (entry 2, Table 1)**: 2-chlorobenzoic acids (**1a,** 0.2 mmol), pentane-2,4-dione (**2a**, 2eq), Cu NPs (1.3 mg, 10 mol%), K_2CO_3 (2.0 equiv) and 1.5 mL of DMSO were added into a 5-mL sealed tube under N_2. The mixture was stirred at 100°C for 2 hour. The reaction mixture was then purified by flash column chromatography on silica gel (hexanes/EtOAc 15:1). Compound **3a** was obtained in >92% of yield. **3-methyl-1H-isochromen-1-one (3a)**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 6.26 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 163.0, 154.6, 137.7, 134.8, 129.5, 127.6, 124.9, 120.0, 103.6, 19.7 (ref. 10a). The characterization data for all of products were also provided in SI, ^{1}H & ^{13}C NMR Spectrum were also attached.
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- A facile and economical catalytic synthesis of 3-substituted isocoumarins was achieved.
- 2-Chloro-benzoic acids/amides were utilized as starting materials with 1,3-diketones.
- Copper nanoparticle catalyst shows highly catalytic activity for the 2-chloro-substituted substrates.