Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 5294

Received 13th April 2021,
Accepted 25th May 2021

DOI: 10.1039/d1ob00715g

rsc.li/obc

A copper iodide-catalyzed coupling reaction of benzofuran-3(2*H*)-ones with amines: an approach to α-ketoamides†

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A CuI-catalyzed coupling reaction of benzofuran-3(2*H*)-ones with amines has been well established for the direct synthesis of α-ketoamides. This process involves C–O bond cleavage and C═O/C–N bond formation. Mechanism studies indicated that this α-ketoamide formation reaction may involve a free radical process.

α-Ketoamides are versatile structural motifs in natural products, biologically relevant molecules, drug candidates and functional materials.[1] Some relevant compounds are displayed in Fig. 1.[2] Consequently, developing novel synthetic methods for the construction of α-ketoamides has attracted considerable attention over the past several decades.[3] Traditionally, the approach to α-ketoamides is based on the amidation of α-oxocarboxylic acids and their derivatives with nitrogen sources.[4] In addition, other synthetic reactions, such as oxidation of α-hydroxyamides and α-aminoamides,[5] transition-metal-catalyzed double carbonylative amination of aryl halides,[6] metal catalyzed or metal free oxidative coupling reactions,[7] and other methods,[8] have been widely used. Although many elegant methods have been developed for the synthesis of α-ketoamides, they suffer from several drawbacks, such as the need for harsh conditions or the use of dangerous reagents. The introduction of multiple functional groups simultaneously allows molecular synthetic versatility and structural diversity.[9] Therefore, the development of more efficient and direct synthetic pathways towards α-ketoamides containing multiple functional groups would be highly desirable.

The development of direct and novel methodologies to install carbon–nitrogen bonds has received continuous attention in organic synthesis.[10] Particularly, the amination of carbonyl compounds has become one of the most powerful and efficient tools in recent years.[10c] In 2001, the group of Loh discovered a copper-catalyzed α-amination of aliphatic aldehydes for the synthesis of α-amino acetals using secondary amines with readily removable protecting groups as a nitrogen source (Scheme 1a).[11] Soon after, a highly efficient α-amination of sterically divergent aldehydes catalyzed by *in situ* generated hypoiodite was described by the same group.[12] In 2012, an oxidative coupling reaction of methyl ketones with primary and secondary amines to synthesize α-ketoamides was established by Wan's group (Scheme 1b).[13] In 2019, Wang developed a catalyst-free oxidative decyanation amidation reaction of β-ketonitriles and primary amines for the synthesis of α-ketoamides (Scheme 1c).[14] Prompted by the above-mentioned considerations, we envisaged that C–N bond formation between benzofuran-3(2*H*)-ones and amines could be achieved *via* α-amination of carbonyl compounds. In an effort to continue our studies of the conversion reaction of carbonyl compounds,[15] herein we disclose a CuI-catalyzed coupling reaction of benzofuran-3(2*H*)-ones with amines for the synthesis of α-ketoamides (Scheme 1d).

At the outset of this investigation, benzofuran-3(2*H*)-one **1a** and morpholine **2a** were selected as the model substrates, $Co(acac)_2$ as the catalyst, TBHP as the oxidant, and EtOAc as the solvent. The mixture was stirred at 70 °C for 12 h. To our delight, the target product **3a** could be isolated in 51% yield (Table 1, entry 1). The structure of the product was confirmed by NMR, HRMS and single-crystal X-ray diffraction.[16] Subsequently, the catalytic activity of various metal catalysts

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†Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectra for products. CCDC 2068416. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob00715g

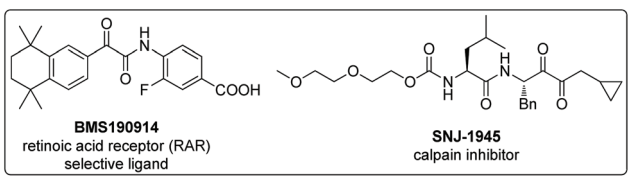
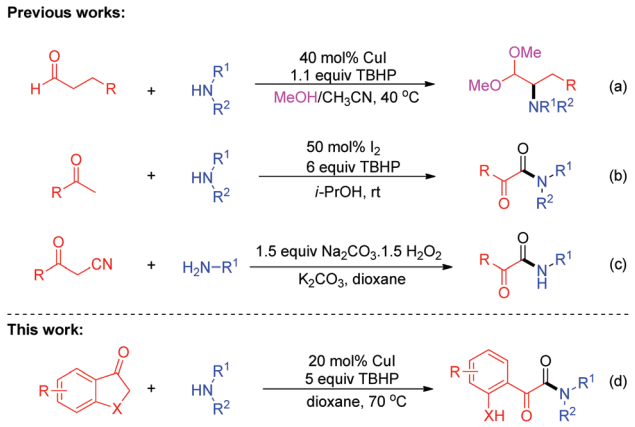
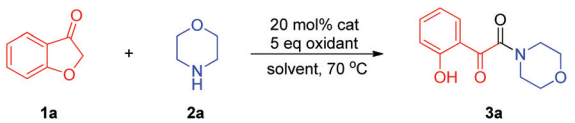


Fig. 1 Biological molecules containing the α-ketoamide moiety.



Scheme 1 Amination of carbonyl compounds.

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

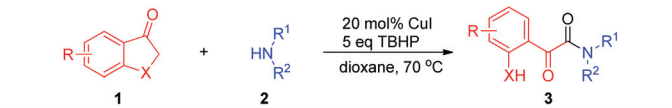
Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$Co(acac)_2$	TBHP	EtOAc	51
2	$FeCl_3$	TBHP	EtOAc	31
3	$Pd(OAc)_2$	TBHP	EtOAc	20
4	$Mn(OAc)_2{\cdot}4H_2O$	TBHP	EtOAc	18
5	CuCl	TBHP	EtOAc	61
6	CuBr	TBHP	EtOAc	64
7	$CuBr_2$	TBHP	EtOAc	54
8	CuI	TBHP	EtOAc	75
9	$Cu(OTf)_2$	TBHP	EtOAc	54
10	$Cu(OAc)_2$	TBHP	EtOAc	39
11	CuI	TBHP	CH_3CN	69
12	CuI	TBHP	DCE	77
13	CuI	TBHP	Dioxane	88
14	CuI	TBHP	Toluene	82
15	CuI	TBHP	THF	65
16	I_2	TBHP	Dioxane	81
17	TBAI	TBHP	Dioxane	65
18	NaI	TBHP	Dioxane	76
19	CuI	DTBP	Dioxane	83
20	CuI	H_2O_2	Dioxane	85
21	CuI	CHP	Dioxane	70
22	CuI	$K_2S_2O_8$	Dioxane	25
23	CuI	O_2	Dioxane	62
24	CuI	Air	Dioxane	50
25		TBHP	Dioxane	<5
26	CuI		Dioxane	48

[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (1.2 mmol, 4.0 equiv.), catalyst (0.06 mmol, 20 mol%), oxidant (1.5 mmol, 5.0 equiv.) and solvent (2.0 mL) in a test tube at 70 °C for 12 h. [b] Isolated yields. TBHP = *tert*-butyl hydroperoxide (70% in water). DTBP = di-*tert*-butyl peroxide. CHP = cumene hydroperoxide.

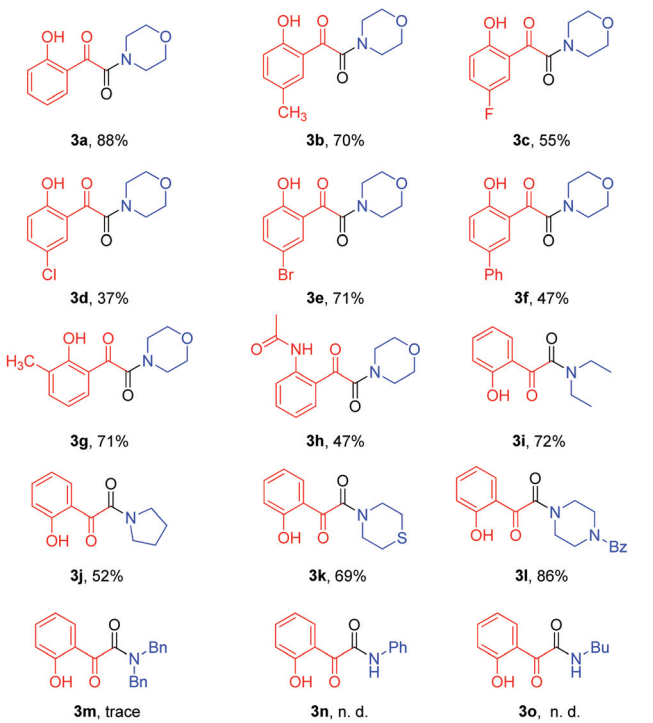
was examined. To our delight, common metal catalysts, including $FeCl_3$, $Pd(OAc)_2$, $Mn(OAc)_2{\cdot}4H_2O$ and CuCl, could promote this α-ketoamide formation reaction and CuCl demonstrated the highest reactivity to give **3a** in 61% yield (entries 2–5). Further screening of other copper catalysts revealed that CuI was the optimal catalyst, providing the expected product **3a** in 75% yield (entries 5–10). A short survey of solvents demonstrated that dioxide was better than EtOAc, CH_3CN, DCE, toluene and THF (entries 11–15). As CuI provided superior yields to other copper salts, we doubted whether iodide is involved in the catalytic cycle. Successively, we examined several iodine reagents and found that they could also give the target product smoothly compared with CuI (entries 16–18). Meanwhile, the effect of different oxidants was also investigated and the result suggested that TBHP is still the best choice (entries 19–24). Moreover, a control experiment suggested that a copper catalyst and oxidant were essential for this transformation (entries 25 and 26).

With the optimized reaction conditions in hand, the generality and limitation of the protocol were examined with respect to both benzofuran-3(2*H*)-ones and amines as shown in Table 2. Firstly, the substrate scope of benzofuran-3(2*H*)-ones was explored and we found that all reactions proceeded smoothly to give the corresponding products (**3a–3g**) in moderate to good yields under the optimized conditions. Halogen atoms, such as F, Cl and Br, did not affect the reactivity of the substrates (**3c–3e**) and created opportunities for further derivatization. When different groups were present at the C7 posi-

Table 2 Scope of substrates[a]



1 2 3

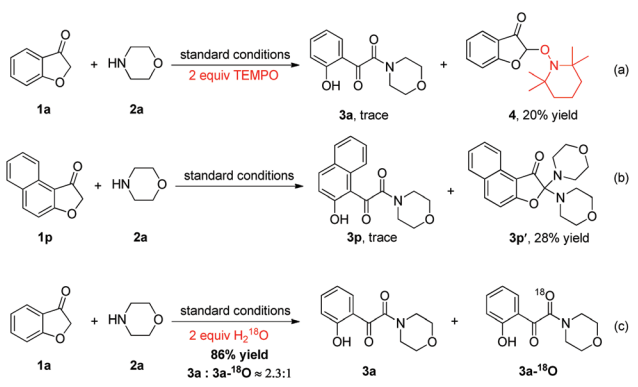


[a] Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (1.2 mmol, 4.0 equiv.), CuI (0.06 mmol, 20 mol%), TBHP (70% in water, 1.5 mmol, 5.0 equiv.) and dioxane (2 mL) at 70 °C for 12 h in a sealed tube.

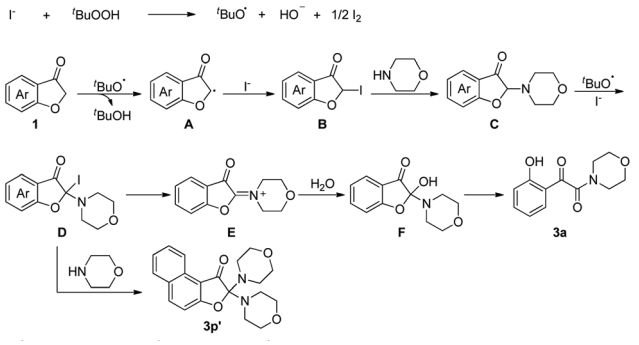
tion, such as 7-CH_3, the reaction could equally proceed well with good yields (**3g**). To our delight, 1-acetylindolin-3-one was compatible with the reaction conditions, and reacted smoothly with **2a** to furnish the corresponding product **3h** in 47% yield. We next evaluated the scope of amines for this coupling reaction. Differently substituted secondary amines displayed no obvious detrimental effect on the reaction efficiency and afforded the desired products **3i–3l** in moderate to good yields. When we used other amines as the substrate under the standard conditions, such as dibenzylamine, aniline or butylamine, unfortunately, it was observed that the reaction did not take place (**3m–3o**).

To shed light on the reaction mechanism of this transformation, control experiments were performed, as shown in Scheme 2. As expected, the addition of the well-known radical-trapping reagent TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) suppressed the reaction and radical adduct **4** was separated in 20% yield, which indicated that the carbon radical intermediate of benzofuran-3(2*H*)-one at the C2 position may be involved in this transformation (Scheme 2a).[17] Based on the result of screening several iodine reagents (Table 1), the iodine anion is the key to the catalytic cycle, not the copper catalyst. Furthermore, when using naphtho[2,1-*b*]furan-1(2*H*)-one as the substrate, the desired target product **3p** was not obtained, but compound **3p′** was separated in 28% yield (Scheme 2b). This result revealed that the iodo intermediate further undergoes a nucleophilic substitution reaction with the amine. When an ^{18}O-labeled reaction was carried out, both **3a** and **3a**-^{18}O were obtained and the ratio was approximately 2.3 : 1, which suggested that nucleophilic attack of a water molecule may be involved in the catalytic cycle (Scheme 2c).

Based on the above experiments and previous studies in the literature,[13,17] we formulated a plausible mechanism for this transformation leading to α-ketoamides, as depicted in Scheme 3. Initially, TBHP decomposes to the *tert*-butoxyl radical and a hydroxyl anion in the presence of I^-.[13,18] Subsequently, hydrogen atoms were abstracted from benzofuran-3(2*H*)-one **1** by the *tert*-butoxyl radical to provide carbon radical **A**,[17] which undergoes iodination to form intermediate **B**.[19] Then nucleophilic substitution of the amine to **B** yields



Scheme 2 Preliminary mechanism studies.



Scheme 3 Proposed reaction mechanism.

intermediate **C**, which undergoes further iodination producing intermediate **D**. Ionization of **D** generates iminium-type intermediate **E**, followed by nucleophilic attack by H_2O to give intermediate **F**. Finally, C–O bond cleavage affords the desired **3a**. In addition, nucleophilic substitution of the amine to intermediate **D** could also form **3p′**.[20]

Conclusions

In summary, we have implemented a CuI-catalyzed coupling reaction of benzofuran-3(2*H*)-ones with amines that allows efficient synthesis of diverse α-ketoamide derivatives. This process involves C–O bond cleavage and C=O/C–N bond formation. Mechanism studies indicated that this α-ketoamide formation reaction may involve a free radical process. Our method utilizes easily available starting materials and offers operational simplicity as well as functional group tolerance. Further explorations of the synthetic utility of this transformation are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (21702176, 21801214), the Natural Science Foundation of Henan (202300410016) and the funding of the Henan Province University Student Innovation Program (S202011071006).

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