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I_2-promoted aerobic oxidative coupling of acetophenes with amines under metal-free conditions: facile access to α-ketoamides†

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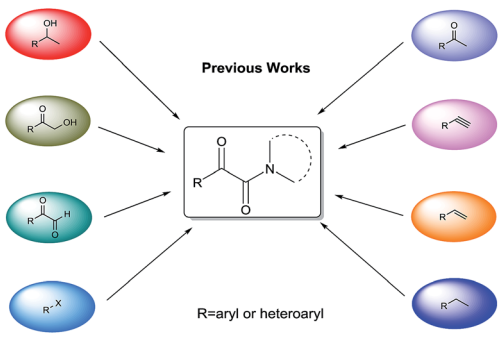
A novel and efficient I_2-promoted oxidative coupling of acetophenes with amines to α-ketoamides is presented, which employs O_2 as an environmentally friendly oxidant under metal-free conditions. Based on a series of control experiments and radical trapping experiments, plausible reaction mechanism was proposed and iminium ion was identified as a significant intermediate in this process. This methodology is a feasible, mild approach to α-ketoamides in good yields.

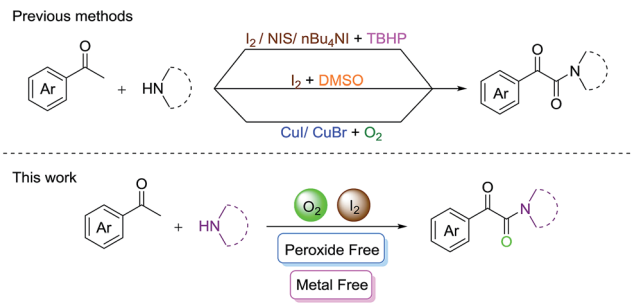
Introduction

α-Ketoamides, a class of pervasive structural moieties of many natural products, marketed pharmaceuticals and versatile synthetic intermediates, possess interesting biological and pharmacological activities and are synthetically useful.[1–5] In addition, α-ketoamides have wide application as precursors for a large number of functional group transformations.[6–9] Consequently, the innovation of the synthesis of α-ketoamides has attracted considerable attention from chemists worldwide.

Traditionally, α-keto acids and α-keto acyl halides were common starting materials to synthesize α-ketoamides through the condensation with amines.[10–12] In the past few years, plenty of modifications and progresses that different reaction conditions and starting materials were developed to generate α-ketoamides smoothly have been reported in this field as shown in Scheme 1. For example, α-ketoamides were synthesized successfully from terminal alkynes, terminal alkenes and ethylarenes in good yields.[13–15] And these powerful compounds were also synthesized from α-keto alcohols or 1-arylethanols by using the domino alcohol oxidation and oxidative cross-dehydrogenative coupling reaction sequence.[16,17] Moreover, α-ketoamides could be prepared by oxidative coupling of isocyanides and aldehydes,[18,19] oxidative double carbonylation reactions of halogen benzene,[20] metal-catalyzed oxidation of ynamides[21] and cross-dehydrogenative coupling of α-ketoaldehydes with amines.[22–24] Acetophenones are prevalent and commercially available starting materials to α-ketoamides in a variety of reaction conditions.[25] However, most of these methods employed toxic transition metal salts as oxidation catalysts or utilized harsh peroxides as strong oxidants. Recently, Qazi and his co-workers reported an I_2-promoted C–H (sp^3) functionalization approach from acetophenones to α-



Scheme 1 A variety of starting materials to α-ketoamides.



Scheme 2 Iodine-promoted aerobic oxidative coupling process.

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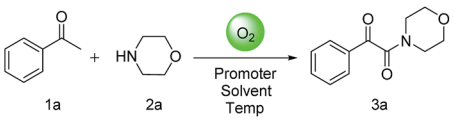
ketoamides using DMSO as oxidant.[25i] Molecular oxygen, the abundant, green and mild oxygen source in organic synthesis, has been regarded as an ideal oxidant.[26] In this work, we developed a mild I_2-promoted oxidative coupling of acetophenones with amines to α-ketoamides especially using O_2 as the environment-friendly oxidant (Scheme 2).

Results and discussion

At the outset of our investigation, we concentrated on the optimization of reaction conditions by using the model reaction between acetophenone **1a** and morpholine **2a** to screen various parameters. The results were summarized in Table 1. As listed, when the model reaction was carried out under different promoters at 50 °C, iodine exhibited the highest reactivity with 36% yield of desired product **3a** isolated (Table 1, entry 5). The effect of TBAI, TBAB, KI and NaI was relatively inefficient to this reaction (Table 1, entries 1–5). Therefore, iodine was determined as the ideal promoter and we screened subsequently various temperatures (Table 1, entries 6–11). To our delight, the impact of temperature on this reaction was very significant: as the temperature raised to 90 °C, the yield of the desired product **3a** increased to 91% (Table 1, entry 10). Meanwhile, lower and further higher temperature could not make it better. When the model reaction was performed in different solvents such as DCE, toluene, THF, DMF, ACN, 63–87% yields of product **3a** was obtained (Table 1, entries 12–16), representing the results that 1,4-dioxane was the best solvent choice. Next, we screened various concentrations of I_2 (Table 1, entry 17–21): when the model reaction was carried out without iodine (Table 1, entry 17), no desired product **3a** was observed, indicating that iodine plays an essential role in this oxidative coupling process. Moreover, reducing the equivalents of I_2 did simultaneously decrease the yields of the desired product **3a** (Table 1, entries 18–20). However, 2.5 equivalents of I_2 made no obvious improvement on the yield (Table 1, entry 21). Thus, the optimized reaction condition was determined as **1a** (1.0 mmol) with **2a** (5.0 mmol) in the presence of 2.0 mmol I_2 in 4.0 mL 1,4-dioxane at 90 °C under O_2 balloon protected for 16 h.

With the optimized reaction conditions in hands, we next investigated the scope and limitations of this reaction (Table 2). Initially, acetophenones bearing different substituents were examined with morpholine and results demonstrated that substrates bearing either electron-withdrawing or electron-donating groups were tolerated and produced the corresponding products with moderate to excellent yields (Table 2, **3a–3h**). Besides, the position of these substituents had no conspicuous

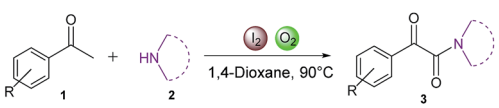
Table 1 Optimization studies of reaction conditions[a]

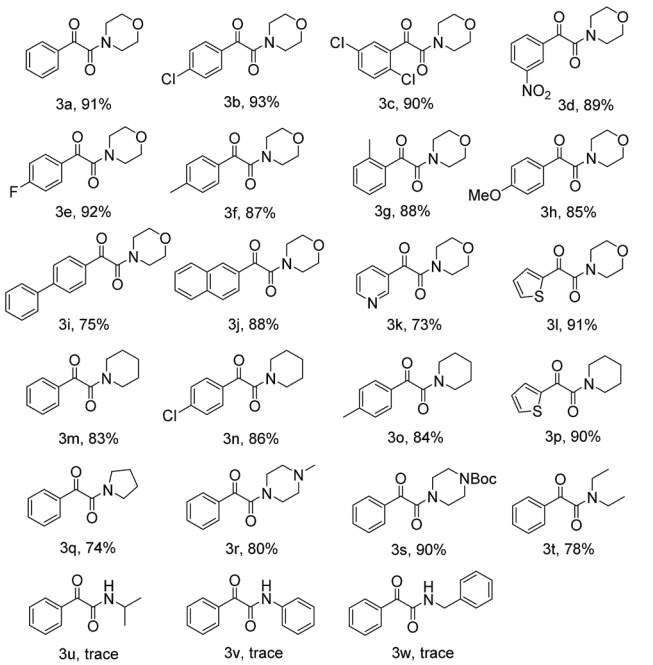


Entry	Promoter	Solvent	Temp (°C)	Yield[b] (%)
1	TBAI	Dioxane	50	<5
2	TBAB	Dioxane	50	Nr[c]
3	KI	Dioxane	50	<5
4	NaI	Dioxane	50	<5
5	I_2	Dioxane	50	36
6	I_2	Dioxane	30	20
7	I_2	Dioxane	60	39
8	I_2	Dioxane	70	47
9	I_2	Dioxane	80	64
10	I_2	Dioxane	90	91
11	I_2	Dioxane	100	90
12	I_2	DCE	90	72
13	I_2	Toluene	90	66
14	I_2	THF	90	70
15	I_2	DMF	90	87
16	I_2	ACN	90	63
17	—	Dioxane	90	Nr
18	I_2	Dioxane	90	16[d]
19	I_2	Dioxane	90	60[e]
20	I_2	Dioxane	90	83[f]
21	I_2	Dioxane	90	90[g]

[a] Reaction conditions: 1.0 mmol acetophenone **1a**, 5.0 mmol morpholine **2a** and 2.0 mmol promoters in 4.0 mL solvent with O_2 balloon protected were heated for 16 h. [b] Yields of the isolated product. [c] No reaction. [d] 0.5 mmol I_2. [e] 1.0 mmol I_2. [f] 1.5 mmol I_2. [g] 2.5 mmol I_2.

Table 2 Scope of oxidative coupling of acetophenones with amines[a]

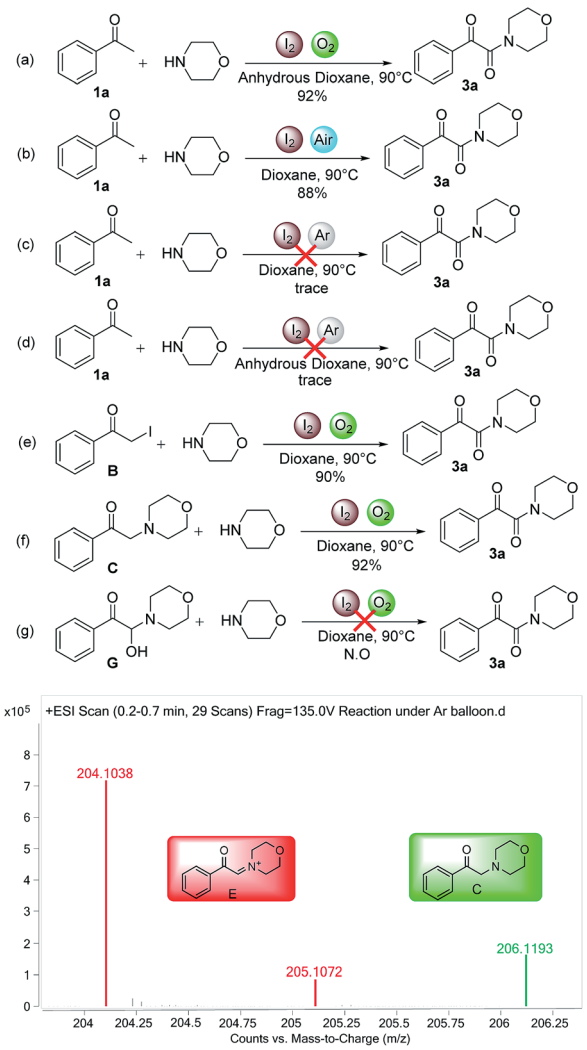




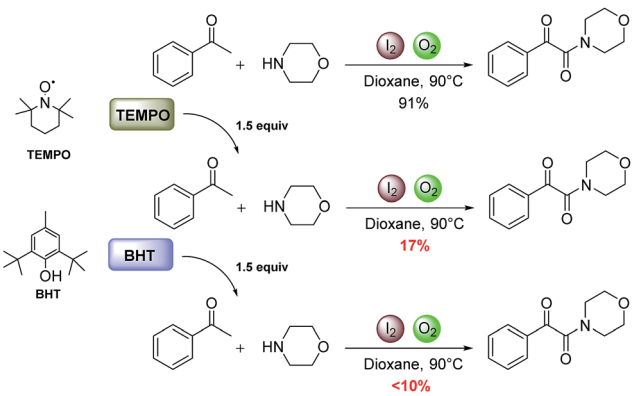
[a] Reaction conditions: **1** (1.0 mmol), **2** (5.0 mmol) and 2.0 mmol I_2 in 4.0 mL 1,4-dioxane were heated at 90 °C under O_2 balloon protected for 16 h. Yields given for isolated products after chromatography.

impact on the efficiency of the reaction. Notably, 4-phenylacetophenone and 2-acetylnaphthalene were suitable to this optimized reaction conditions, producing the desired products in 75% and 88% yields (Table 2, **3i** and **3j**). Moreover, 3-acetylpyridine and 2-acetylthiophene could also be transformed to the corresponding products in 73% and 91% yields showing that heteroaryl ketones were feasible in this reaction (Table 2, **3k** and **3l**). Subsequently, substituted acetophenones and 2-acetylthiophene could also couple with piperidine to produce corresponding products (Table 2, **3m–3p**). Then we carried out this reaction with a series of secondary amines such as tetrahydropyrrole, 1-methylpiperazine, *tert*-butyl 1-piperazinecarboxylate and diethylamine, 74–90% yields of corresponding products were obtained respectively (Table 2, **3q–3t**). In order to further expand the scope of this methodology, we next applied this process to a series of primary amines (Table 2, **3u–3w**). However, the reaction between acetophenone and primary amines failed to produce desired products in an ideal yield, implying that primary amines were not feasible in optimized reaction conditions for the synthesis of α-ketoamides.

For the purpose of investigating the mechanism of this reaction and gaining insight into the significant role of molecular oxygen in this process, a series of control experiments were carried out as shown in Schemes 3 and 4. In the experiment (a), anhydrous 1,4-dioxane replaced the general solvent of the model reaction and the excellent yield of the desired product **3a** was obtained, ruling out the indispensable effect of water. In the experiment (b), reaction was performed under air atmosphere instead of pure oxygen. Interestingly, the yield of product **3a** decreased only a little to 88% but the reaction time extended to 23 h to complete, acetophenone **1a** could also be transformed to corresponding α-ketoamide **3a** smoothly. The further investigation of experiment (c) was carried out under comparatively inert environment of argon. Notably, the yield of desired product **3a** was terribly poor but two types of prominent by-products were highly detected by ESI-MS analysis: 2-morpholino-1-phenylethanone (compound **C**) and the iminium ion (compound **E**) as shown in Scheme 3, demonstrating the essential role of molecular oxygen in this oxidative coupling process. Moreover, LC-ESI-MS analysis performed in the course of the reaction (6 h) between acetophenone **1a** and morpholine **2a** under the optimized conditions, the results fully demonstrate that both iminium ion and 2-morpholino-1-phenylethanone were significant intermediates and reaction triggers with generation of iminium ion followed by conversion to desired product (shown in ESI†). Next, when compound **B** and compound **C** were performed in the same reaction conditions, comparable yields of **3a** was observed as shown in experiment (e) and (f). In the experiment (g), no corresponding product was observed, proving non participation of hydroxyl compound **G** in this process. To further understand the reaction mechanism, radical trapping experiments were conducted. Radical scavenger such as TEMPO and BHT was added to the reaction. In this case, the formation of product **3a** was hindered badly (Scheme 4), which suggests that the oxidative coupling process undergoes through radical intermediates.[23,25a]

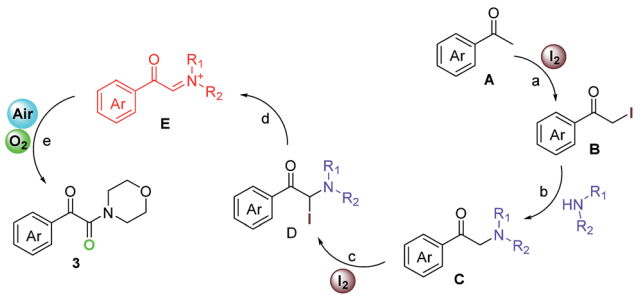


Scheme 3 A series of control experiments and highly detected signal in experiment c and d (ESI).



Scheme 4 Radical trapping experiments.

Based on these exploring experiments above, plausible reaction mechanism was proposed as shown in Scheme 5. In the step a, compound **B** was produced from the iodination of



Scheme 5 Plausible reaction mechanism of the aerobic oxidative coupling of acetophenes with amines to α-ketoamides.

arylmethylketone **A**. Nucleophilic substitution of amine to compound **B** generates α-aminoketone **C** in step b. Obviously secondary amines performed better in this step than primary amines because of theirs better nucleophilicity. Besides, 2.0 equivalents concentration of iodine was necessary in this reaction, which reveals that the process of further iodination of α-aminoketone **C** and iodo-α-aminoketone **D** was generated in the step c. Subsequently, as an important intermediate iminium ion was formation from ionization of **D** in step d. Finally, under O_2 and the high temperature (90 °C) environment, iminium ion was transformed to the desired product α-ketoamides **3** in the step e, where the generation of α-ketoamides went through the aerobic oxidation of iminium ion intermediate.[27]

Conclusions

In summary, we have developed a convenient, moderate and efficient approach to α-ketoamides through I_2-promoted sp^3 C–H bond aerobic oxidative coupling process using commercial available starting materials with secondary amines. The reaction was carried out not only under metal-free and peroxide free conditions, but also employed O_2 as the green oxidant effectively and air atmosphere were also feasible. What's more, plausible mechanism was proposed after a series of control experiments and iminium ion was proved to be an importantly functional intermediate in this reaction. Further studies on the applications of this strategy will be reported in due course.

Acknowledgements

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