

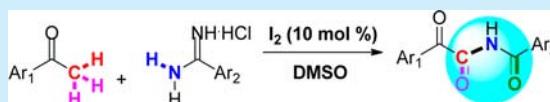
I<sub>2</sub>-Catalyzed Oxidative Cross-Coupling of Methyl Ketones and Benzamidines Hydrochloride: A Facile Access to  $\alpha$ -Ketoimides

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## S Supporting Information

**ABSTRACT:** An iodine-catalyzed oxidative cross-coupling of C–H/N–H has been demonstrated. This simple and efficient approach constructed  $\alpha$ -ketoimides in good to excellent yields from methyl ketones and benzamidines hydrochloride under metal-free and peroxide-free conditions. This synthetic strategy was achieved via an in situ iodination-based oxidative coupling pathway.

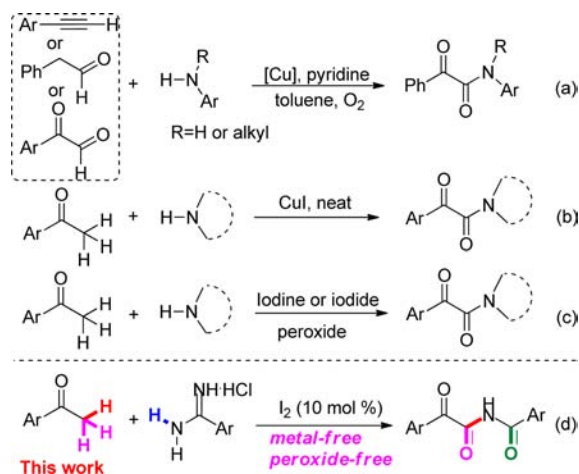


In recent years, direct oxidative C–H bond functionalization, especially a  $sp^3$  C–H bond toward the formation of C–C and C–heteroatom bonds, is one of the most attractive and powerful strategies in organic synthesis.<sup>1,2</sup> Direct C–H bond oxidative amidation through C–H/N–H oxidative cross-coupling has always been a fascinating topic<sup>3</sup> since nitrogen-containing compounds include imides,  $\alpha$ -ketoamides, and  $\alpha$ -ketoimides that are potentially valuable synthetic building blocks for the preparation of various heterocyclic ring systems of biological interest.<sup>4</sup> Significantly, Jiao and co-workers presented a novel Cu-catalyzed C–H bond oxidative amidation via oxidative coupling of aryl acetaldehydes or  $\alpha$ -carbonyl aldehydes or phenylacetylenes with anilines (Scheme 1a).<sup>5a–c</sup> Recently, Cu-catalyzed direct oxidative coupling between aryl methyl ketones and amines under ambient conditions for the attainment of  $sp^3$  C–H bond oxidative amidation have been developed by Ji (Scheme 1b).<sup>6</sup> Moreover, iodine or iodide combination of peroxide synergistic promoted  $sp^3$  C–H bond oxidative amidation via the oxidative coupling of methyl

ketones with amines has been established by Prabhu,<sup>7a</sup> Wan,<sup>7b</sup> and Wang<sup>7c</sup> (Scheme 1c). However, these recent advances were focused on the oxidative coupling of RH with N–H of amines to construct  $\alpha$ -ketoamides. Directly employing amide compound oxidative cross-coupling with a C–H bond has not previously been reported to build  $\alpha$ -ketoimides, due to the predominant limitations presented by very weak nucleophilicity especially of the free N–H of amides. Therefore, in order to develop a simple and practical strategy for the synthesis of  $\alpha$ -ketoimides, discoveries of new N–H reagents instead of amides as nucleophiles are desperately needed. To the best of our knowledge, the free N–H of benzamidines hydrochloride has not yet been directly utilized as a nucleophile reagent for the oxidative coupling with methyl ketones for construction of a novel  $\alpha$ -ketoimides skeleton. In view of this, herein the first known example of an iodine-catalyzed protocol to access  $\alpha$ -ketoimides via a C–H/N–H oxidative cross-coupling is reported from methyl ketones and benzamidines hydrochloride (Scheme 1d).

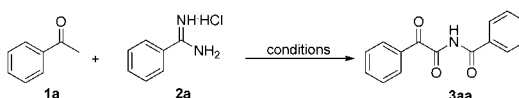
Initially, an optimized iodine-catalyzed oxidative cross-coupling of aromatic methyl ketone (1a) with benzamidine hydrochloride (2a) was examined in DMSO. To our delight, the reaction of acetophenone (1a, 1.0 mmol) and benzamidine hydrochloride (2a, 2.0 mmol) with I<sub>2</sub> (1.6 mmol) could afford the desired oxidative coupling product in 87% yield at 100 °C in DMSO (Table 1, entry 1). The structure of the product was unambiguously confirmed by X-ray crystallography analysis (see Supporting Information). Encouraged by the results, subsequent studies indicated that decreases in the equivalents of 2a did not afford any changes in the yield (Table 1, entries 2–4). Next, various temperatures were scanned to improve the yield, and 130 °C was determined as optimum for the oxidative coupling reaction (Table 1, entries 5–9). To our surprise, the reaction performed smoothly even with decreases in the equivalents of I<sub>2</sub> to 10 mmol % (Table 1, entries 10–13). However, the reaction was found unable to proceed in the

**Scheme 1. Oxidative Cross-Coupling Reactions Between C–H and N–H**



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Table 1. Optimization of Reaction Conditions<sup>a</sup>


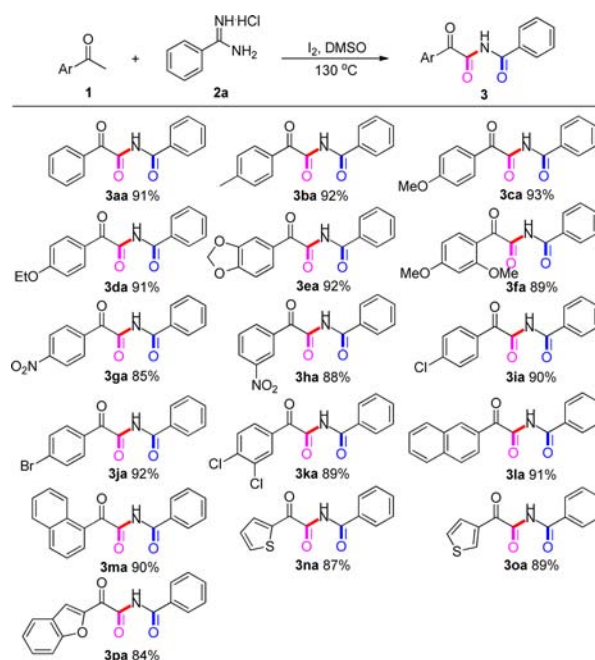
entry	I <sub>2</sub> (equiv)	2a (equiv)	temp (°C)	yield (%) <sup>b</sup>
1	1.6	2.0	100	87
2	1.6	1.5	100	87
3	1.6	1.2	100	87
4	1.6	1.0	100	87
5	1.6	1.0	60	29
6	1.6	1.0	80	78
7	1.6	1.0	90	82
8	1.6	1.0	110	88
9	1.6	1.0	130	90
10	1.0	1.0	130	91
11	0.5	1.0	130	90
12	0.3	1.0	130	91
13	0.1	1.0	130	91
14		1.0	130	0

<sup>a</sup>Reaction conditions: **1a** (1.0 mmol), **2a**, and I<sub>2</sub>, heated in 3 mL of DMSO within 3 h. <sup>b</sup>Isolated yield.

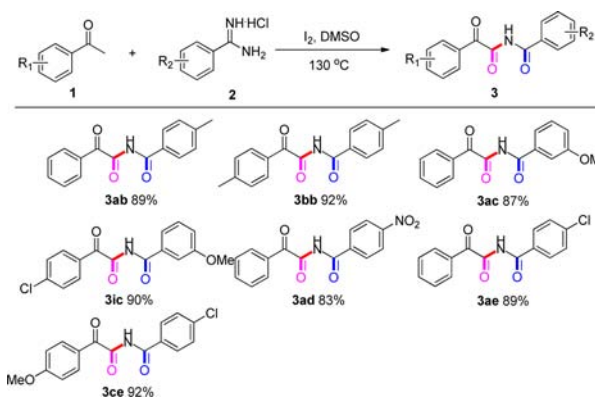
absence of I<sub>2</sub> (Table 1, entry 14), which indicated that iodine was an important mediator in this transformation. After several experimental optimizations, the optimized conditions were determined as **1a** (1.0 mmol) with **2a** (1.0 mmol) in the presence of I<sub>2</sub> (0.1 mmol) in DMSO at 130 °C to afford the desired product in 91% yield (Table 1, entry 13).

To test the substrate generality of this I<sub>2</sub>-catalyzed oxidative coupling reaction, a series of substituted aryl methyl ketones were investigated under the optimized reaction conditions. To our satisfaction, the results indicated that aryl methyl ketones bearing diverse functional groups and substitution patterns afforded the desired products in good to excellent yields (84–93%) as shown in Scheme 2. The electron neutral (4-H, 4-Me), electron-donating (4-OMe, 4-OEt, 2,4-(OMe)<sub>2</sub>, 3,4-OCH<sub>2</sub>O), and electron-deficient (3-NO<sub>2</sub>, 4-NO<sub>2</sub>) groups that were attached to the phenyl rings of the aryl methyl ketones exhibited excellent reactivity (85%–93%, **3aa–ha**). The electronic and steric nature of the aromatic methyl ketones was seen to have little influence on the reaction efficiency, and all of the corresponding products were obtained in good to excellent yields. In addition, the scope of the substrates was further extended to various halogenated (4-Br, 4-Cl, 3,4-Cl<sub>2</sub>) substrates (89%–92%, **3ia–ka**), which could be used as an intermediate to synthesize more complex compounds. Meanwhile, sterically hindered 2-acetylnaphthalene **1l** and 1-acetylnaphthalene **1m** also furnished the desired products **3la** and **3ma** smoothly in 91% and 90% yields, respectively. The heteroaryl methyl ketones, such as thiophenyl and benzofuryl, were found compatible under the optimal conditions and provided oxidative coupling products in good yields (84–89%, **3na–pa**).

The scope of the study was extended to substituted benzamidines hydrochloride. The results are subsequently displayed in Scheme 3. Various substituted benzamidines hydrochloride were found compatible in the reaction. Electron neutral (4-CH<sub>3</sub>), electron-deficient (4-NO<sub>2</sub>), and electron-rich (3-OMe) groups on the phenyl rings of benzamidines hydrochloride were compatible and provided the corresponding products in good to excellent yields (83–92%, **3ab–ad**).

Scheme 2. Scope of Aryl Methyl Ketones and Benzamidine Hydrochloride<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol), and I<sub>2</sub> (0.1 mmol) in DMSO (3 mL) at 130 °C for 3 h. <sup>b</sup>Isolated yield.

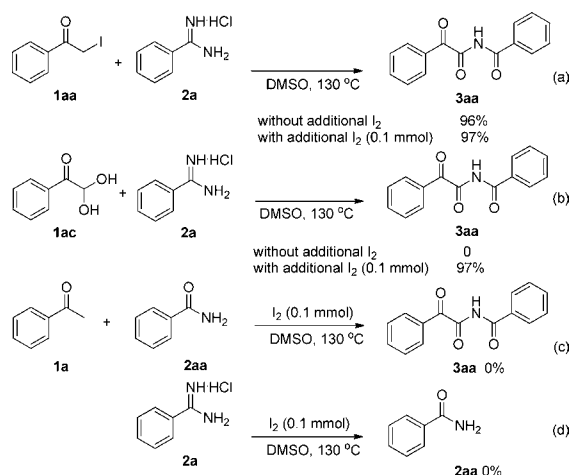
Scheme 3. Scope of Aryl Methyl Ketones and Benzamidines Hydrochloride<sup>a,b</sup>

<sup>a</sup>Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), I<sub>2</sub> (0.1 mmol) in DMSO (3 mL) at 130 °C for 3 h. <sup>b</sup>Isolated yield.

Halogen-substituted benzamidine hydrochloride (4-Cl) also afforded the desired products in good to excellent yields (89–92%, **3ae–ce**).

To gain some insight into the mechanism of the reaction, a series of control experiments were performed (Scheme 4). The reaction of  $\alpha$ -iodo acetophenone **1aa** with benzamidine hydrochloride **2a** was found successful, and the product **3aa** was obtained in excellent yields both with I<sub>2</sub> (10 mol %) and without I<sub>2</sub> (Scheme 4a). In the presence of additional iodine, hydrated hemiacetal **1ac** could react with **2a** and afford the oxidative coupling product **3aa** in 97% yield (Scheme 4b). These results clearly confirmed the intermediacy of phenacyl iodine **1aa** and phenylglyoxal **1ac** in the transformation. However, the reaction was found unable to proceed smoothly in the absence of I<sub>2</sub> (Scheme 4b), which emphasized the crucial

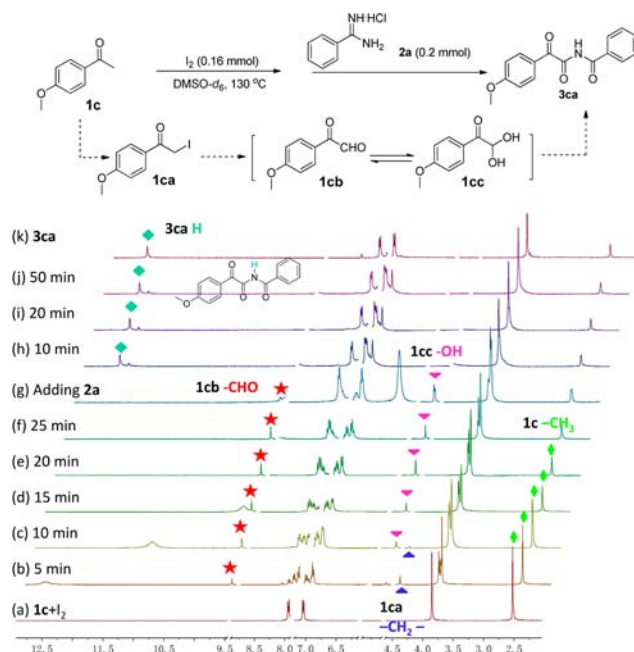
## Scheme 4. Control Experiments



role of iodine in the subsequent domino process. Moreover, the universality and mechanism of the reaction was further examined through the reaction of acetophenone **1a** and benzamide **2aa** in the presence of  $I_2$  (10 mol %) in DMSO. However, the target product **3aa** could not be obtained under optimum condition (Scheme 4c). Furthermore, it was found that **2a** could not produce **2aa** under the standard conditions (Scheme 4d). The results suggested that benzamidine hydrochloride may be reacted with acetophenone first and then underwent hydrolysis to obtain the target product.

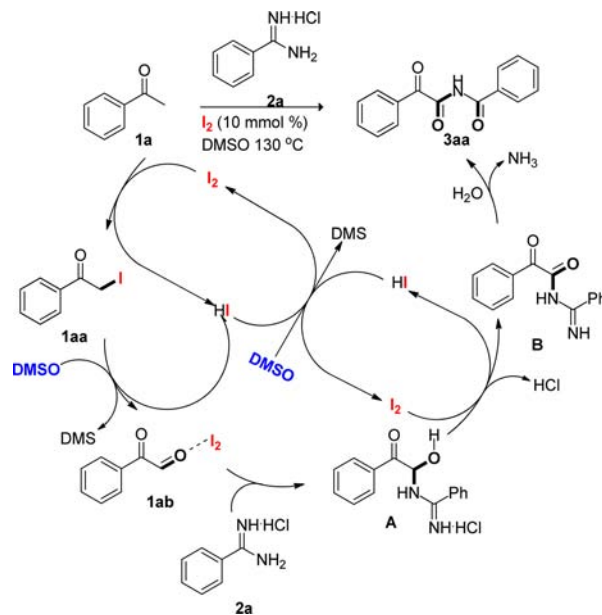
We also monitored the reaction of **1c** (0.10 mmol) and **2a** (0.20 mmol) with  $I_2$  (0.16 mmol) in  $DMSO-d_6$  by  $^1H$  NMR spectroscopy to further investigate the reaction process. Based on previous reports,<sup>8</sup> the signal at 4.53 ppm was assigned to the  $-CH_2-$  group of  $\alpha$ -iodo aryl methyl ketone **1ca** at 5–10 min. In addition, the signals at 9.54 and 5.66 ppm were assigned to the phenylglyoxal aldehyde group (**1cb**) and the hemiacetal group (**1cc**), respectively. With the consumption of **1c**, the intermediate **1cb** and **1cc** appeared and the concentration subsequently increased over time. The signals at 3.83 and 3.85 ppm were assigned to the  $-OCH_3$  group of the phenylglyoxal (**1cb**) or hydrated hemiacetal (**1cc**) and the  $-OCH_3$  group of *N*-(2-(4-methoxyphenyl)-2-oxoacetyl)benzamide (**3ca**), respectively. With the addition of **2a**, the characteristic peaks of **1ca** and **1cc** were seen to disappear immediately. Meanwhile, by comparison with an authentic sample, the characteristic peaks of **3ca** was seen to appear ( $N-H$  at  $\delta = 12.32$ ). As shown in Figure 1, the reaction was achieved in 75 min with high conversion. These results demonstrated that phenacyl iodine (**1ca**) and phenylglyoxal (**1cb**) were important intermediates in the whole transformation.

According to the aforementioned information and based on previous reports,<sup>9</sup> a proposed mechanism for this  $I_2$ -catalyzed C–H/ $N-H$  oxidative cross-coupling is outlined in Scheme 5. Initially, the substrate acetophenone **1a** reacted with  $I_2$  to afford the intermediate  $\alpha$ -iodo acetophenone **1aa**, which converted into phenylglyoxal **1ab** and released HI after a subsequent Kornblum oxidation. The aldehyde group of phenylglyoxal **1ab** was activated by regenerated Lewis acid  $I_2$ . Then, benzamidine hydrochloride **2a** attacked the activated aldehyde group of phenylglyoxal **1ab** to give the intermediate **A**, which was followed by further rapid oxidation by  $I_2$  to afford intermediate **B**.<sup>5c,10</sup> Hydrolysis could then be undertaken to provide the desired product **3aa**.



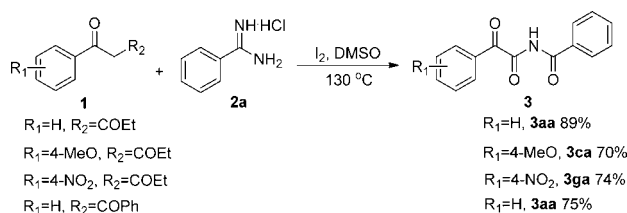
**Figure 1.** Reaction process of **1a** (0.10 mmol), **2a** (0.20 mmol), and  $I_2$  (0.16 mmol) at 130 °C was monitored by  $^1H$  NMR spectroscopy (400 MHz,  $DMSO-d_6$ ,  $298 \pm 0.5$  K).

## Scheme 5. Proposed Mechanism



Fortunately, some active methylene groups of 1,3-diketo compounds could react with benzamidines hydrochloride and give desired products in good to excellent yields when we tried to further expand the substrate. Various substituted ethyl 3-oxo-3-phenylpropanoate and 1,3-diphenylpropane-1,3-dione were found compatible in the reaction, as shown in Scheme 6. The related mechanism is shown in the Supporting Information.

In summary, a molecular iodine-catalyzed  $sp^3$  C–H bond oxidative amidation has been described for the construction of  $\alpha$ -ketoimides through the oxidative coupling of aryl methyl ketones and benzamidine hydrochloride derivatives. This method has provided a new strategy for  $sp^3$  C–H bond

**Scheme 6. Scope of Various Substituted Ethyl 3-Oxo-3-phenylpropanoate and 1,3-Diphenylpropane-1,3-dione<sup>a,b</sup>**

<sup>a</sup>Reaction conditions: **1** (1.0 mmol), **2a** (1.0 mmol),  $I_2$  (0.1 mmol) in DMSO (3 mL) at 130 °C for 3 h. <sup>b</sup>Isolated yield.

oxidative amidation. Furthermore, investigation of the mechanism suggested that the reaction could have occurred through a self-sequenced iodination/Kornblum oxidation/amidation/oxidation cascade reaction. Further studies on the applications of this strategy will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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