

Unveiling the reaction process of the amine in direct amidation of aromatic ketones in H₂O

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In the classical amidation between aromatic ketones and amines, 2.0 equivalents of amines are necessarily required to gain satisfying yields. The specific role of the amine in the direct amidation already puzzled us for a long time. In this work, we disclosed that the amine acts as both reactant and catalyst.

Specifically, the determination of reaction intermediates revealed the full mechanism, based on which, the introduction of one equivalent base in the amidation is showcased here that a high yield (~95%) can be afforded using only 1.1 equiv. of amine.

Introduction

α -Ketoamides have attracted considerable interest due to their potential ability as versatile synthetic motifs in numerous natural products, biological drug candidates and functional group transformations.^[1,2] Various approaches have been proposed in the synthesis of a diverse array of α -ketoamides from different ketones and amines.^[3–12] Recently, the iodine-driven reaction have emerged as a powerful strategy because of the particularly reactive halogen bond-based systems. In this system, specifically, the drive reagents can be successfully incorporated, resulting from the formation of a highly attractive halogen bond between the iodine of drive reagents and the substrates (e.g., halide atoms).^[13–19] To the best of our knowledge, iodine can significantly reduce activation free energy ($-7.6 < \Delta G_{\ddagger} < -1.8$ kcal mol⁻¹) for reactions involving α,β -unsatu-

rated carbonyls.^[20] However, the mechanism of direct amidation of aromatic aryl ketones remains unclear to date.

In classical amidations with the addition of iodine (I₂), the amine is recognized as the reactant, and I₂ is almost presumed to play the catalytic role.^[8–10] Our previous studies reported the preparation of diverse α -ketoamides under clean and mild conditions from varying substrates including aryl methyl ketones.^[11,12] Currently, there are two issues involved with the direct amidation. Firstly, although I₂ is employed as the catalyst, its loading almost reaches up to the stoichiometric ratio. Secondly, an excess amount (two or more equivalents) of amines are essentially required to afford reasonable conversions/yields. Therefore, it would be of great interest to investigate these two issues, further explaining the mechanism of direct amidation between ketone and amine.

Herein, we report the specific role of amine in the amidation of aromatic aryl ketones through an I₂ assisted green approach in pure water, as shown in Scheme 1. Specifically, the function of I₂ was reexamined as well. By detecting the intermediates formed *in situ* during the reaction, we proposed the possible mechanism in detail. It is anticipated that this work would provide a deeper understanding of the direct amidation process.

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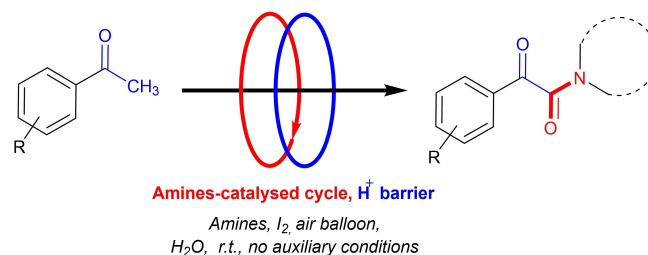
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Scheme 1. This work for amidation of aromatic ketones.

Results and Discussion

Initial investigations for suitable reaction conditions were performed by using acetophenone (**1a**) and morpholine (**1b**) were employed as the model substrates. The specific reaction parameters (solvent, catalyst, gas filled in a balloon, temperatures, reaction times, and the amount of iodine) were examined and summarized in Table 1. Results indicate that the best yield (91%) was obtained using I_2 as the catalyst in water (pH=5.0) with air as the oxidant under room temperature. Interestingly, the stoichiometric loading of I_2 as the catalyst seems to greatly promote the substrate conversions. In addition, the substrates scope of ketones and amines were screened, including different aromatic ketones and various amines (ammonium, primary amine, and secondary amine) (Table 2). All reactions proceeded well with great to excellent yields up to 95%. Furthermore, the electronic effect of substituent groups on the aromatic ring (the ketone moiety) was observed to slightly influence the reaction conversion. With the presence of electron-donating groups, high yields (**2c**, **2t**, **2s**, **3e**, **3f**) are favoured, due to the easier formation of enamine intermediates from electron-rich central-R-C=O. In contrast, the presence of electron-withdrawing groups cause the difficult generation of enamine, resulting in less generation of α -ketoamides (**2b**, **2c**, **2d**, and **2f**).

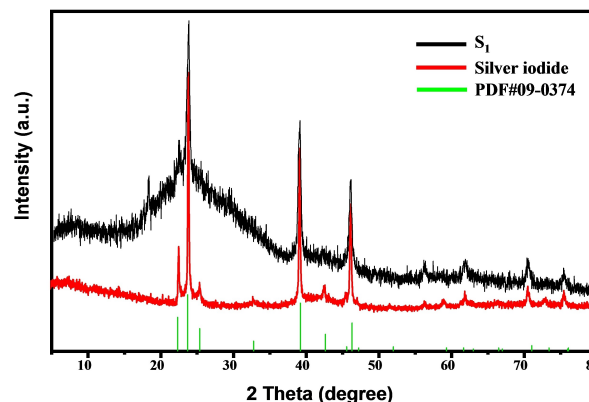


Figure 1. XRD patterns of S1 solid, Silver iodide, Standard PDF#09-0374 card.

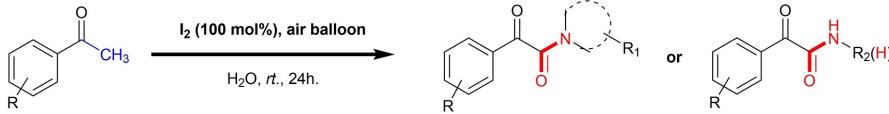
The forms of iodine compounds existed in the reaction solution after α -amidation were detected using murexide indicator and silver nitrate ($AgNO_3$), the results showed that there were basically no iodine left (please see the supporting information), some white precipitate were formed upon the introduction of silver nitrate, the peak in XRD of the white precipitate correlated well with standard sample of AgI (see Figure 1).

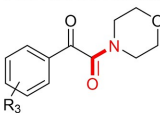
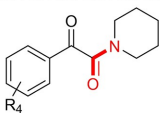
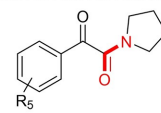
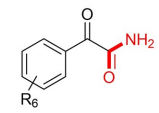
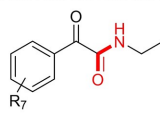
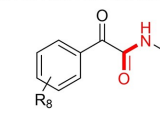
Table 1. Optimization of reaction conditions.^[a]

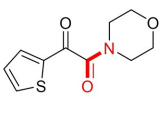
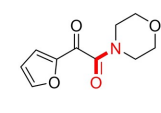
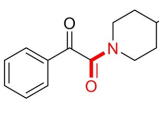
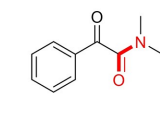
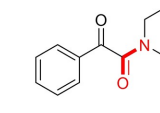
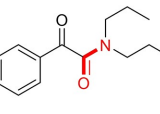
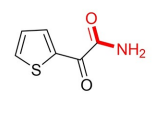
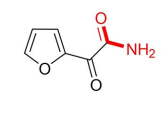
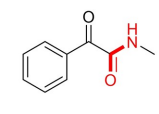
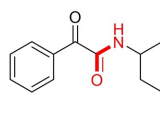
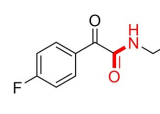
Ent.	Cat.	Solv.	pH	Temp. [°C]	Time [hour]	I_2 [equiv.]	Gas	Y [%]
1	I_2	MeCN	–	rt.	24	1.0	Air	17
2	I_2	MeOH	–	rt.	24	1.0	Air	61
3	I_2	n-Hexane	–	rt.	24	1.0	Air	7
4	HI	H_2O	7.0	rt.	24	1.0	Air	n.d.
5	NaI	H_2O	7.0	rt.	24	1.0	Air	n.d.
6	NaIO	H_2O	7.0	rt.	24	1.0	Air	n.d.
7	NaIO ₃	H_2O	7.0	rt.	24	1.0	Air	n.d.
8	NIS	H_2O	7.0	rt.	24	1.0	Air	17
9	DB	H_2O	7.0	rt.	24	1.0	Air	n.d.
10	CuI	H_2O	7.0	rt.	24	1.0	Air	n.d.
11	I_2	H_2O	3.0	rt.	24	1.0	Air	71
12	I_2	H_2O	5.0	rt.	30	1.0	Air	91
13	I_2	H_2O	5.0	rt.	24	0.5	Air	57
14	I_2	H_2O	5.0	rt.	24	0.8	Air	86
15	I_2	H_2O	5.0	rt.	24	1.0	Air	91
16	I_2	H_2O	5.0	rt.	24	1.2	Air	91
17	I_2	H_2O	5.0	rt.	24	1.5	Air	89
18	I_2	H_2O	5.0	rt.	18	1.0	Air	87
19	I_2	H_2O	5.0	rt.	12	1.0	Air	79
20	I_2	H_2O	5.0	rt.	6	1.0	Air	61
21	I_2	H_2O	5.0	35	24	1.0	Air	75
22	I_2	H_2O	5.0	50	24	1.0	Air	44
23	I_2	H_2O	5.0	75	24	1.0	Air	15
24	I_2	H_2O	7.0	rt.	24	1.0	Air	81
25	I_2	H_2O	9.0	rt.	24	1.0	Air	87
26	I_2	H_2O	5.0	rt.	24	1.0	O ₂	91
27	I_2	H_2O	5.0	rt.	24	1.0	N ₂	n.d.

[a] Conditions: **1a** (0.1 mmol), **1b** (0.2 mmol), I_2 (100 mol%) and water (1 ml), air balloon(1 atm), reaction time 24 h, rt., room temperature, n.d., not found. Yields was determined by HPLC analysis, and the yields in brackets were isolated ones.

Table 2. Results of amidation of aromatic aryl ketones with varying amines.



 2a , 91% <i>p</i> -NO ₂ : 2b , 71% <i>p</i> -Me: 2c , 95% <i>p</i> -F: 2d , 88% <i>p</i> -Cl: 2e , 75% <i>p</i> -Br: 2f , 76% <i>m</i> -OMe: 2g , 81% <i>m</i> -Br: 2h , 65% <i>o</i> -Br: 2i , 58% <i>o</i> -Me: 2j , 79%	 2n , 89% <i>p</i> -Me: 2s , 83% <i>p</i> -NO ₂ : 2u , 67% <i>p</i> -Br: 2w , 77% <i>m</i> -Me: 2y , 76% <i>m</i> -Br: 2z , 57% <i>o</i> -Me: 2ab , 70%	 2o , 85% <i>p</i> -NO ₂ : 2v , 65% <i>p</i> -Br: 2x , 75% <i>p</i> -Me: 2t , 86%	 3i , 92% <i>p</i> -Me: 3l , 85% <i>p</i> -F: 3j , 79% <i>m</i> -OMe: 3k , 74% <i>m</i> -Me: 3m , 75% <i>o</i> -Me: 3n , 70%	 3c , 79% <i>p</i> -F: 3g , 79% <i>p</i> -Me: 3f , 81%	 3b , 77% <i>p</i> -Me: 3e , 82%
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 2k , 88%	 2l , 71%	 2r , 80%	 2p , 83%	 2q , 75%	
 2m , 87%	 3o , 88%	 3p , 70%	 3a , 87%	 3d , 76%	 3h , 67%

Conditions: aromatic aryl ketones (0.1 mmol), varying amines (0.2 mmol), I₂ (100 mol%) and water (1 mL), air balloon (1 atm), reaction time 24 h, *rt.*, room temperature. Yields were determined by HPLC analysis, and the yields in brackets were isolated ones. series 2 were label to amine moiety: secondary amine, series 3 were label to amine moiety: primary amine, ammonium.

Particularly, two equivalents of amines were required in our approach to achieve acceptable conversions. However, less than 2 equivalent gave rise to unsatisfied yields. After the reaction, a more acidic solution was obtained (see Figure 2). Moreover, we proved that all I₂ was completely converted into I⁻, evidencing the non-catalytic role of I₂. Therefore, these

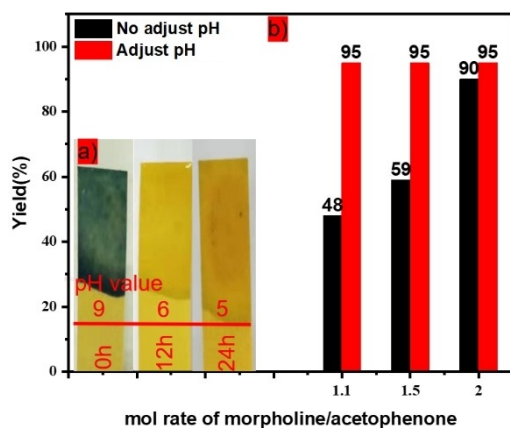
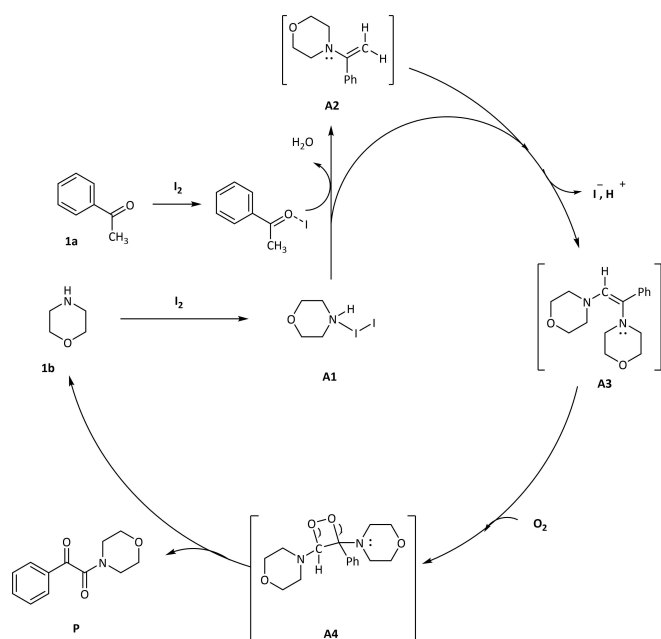


Figure 2. a) Profiles of pH at different reaction time and b) yields obtained proceeding to adjust/non-adjust the pH.

results provoke us to further explore the specific roles of amine and I₂.

Based on the above results and some relevant publications,^[9,10,18,21–23] a plausible mechanism was proposed, as shown in Scheme 2. Notably, the intermediate characterization would be useful to understand the possible reaction mechanism. So we performed the direct analysis of reaction intermediates using HPLC-MS at the reaction half-life (12 h). The corresponding results obtained from the model reaction between acetophenone and morpholine with the addition of I₂ were listed in Table 3. Based on these results, we successfully captured and proposed the specific structures of the intermediate species (A1, A2, A3, A4 (A1 calculated *m/z* for [M+H]⁺, C₄H₉NOI₂, 341.9293, observed 341.8761; A2 calculated *m/z* for [M-H]⁻, C₁₂H₁₅NO, 188.1081, observed, 188.0906); A3 calculated *m/z* for [M-H]⁻, C₁₆H₂₂N₂O₂, 273.1609, observed, 273.1500)) and; A4 calculated *m/z* for [M+H]⁺, C₁₆H₂₂N₂O₄, 307.1731, observed, 307.1795). Substrates (1a, I₂ (1a calculated *m/z* for [M+H]⁺, C₈H₈O, 121.0648, observed 121.0597; I₂ calculated *m/z* for [M+H]⁺, I₂, 254.8162, observed 254.8098; The product P, calculated *m/z* for [M+H]⁺, C₁₂H₁₃NO₃, 220.0969, observed 220.0971. All the intermediates mentioned in maintext were confirmed.

Clearly, it is seen that no intermediate species were generated *in situ* in absence of morpholine or I₂ (see entries 2, 3



Scheme 2. Insights of the mechanism of I_2 promoted amidation of aromatic ketones (take acetophenone and morpholine for the example).

Table 3. Control reactions and the results.

Entry	Reaction parameters	Compounds
1	1a, 1b, H_2O , <i>rt.</i> , Air balloon	1a
2	I_2 , 1a, H_2O , <i>rt.</i> , Air balloon	I_2 , 1a
3	I_2 , 1b, H_2O , <i>rt.</i> , Air balloon	I_2 , 10
4	I_2 , 1a, 1b, H_2O , <i>rt.</i> , N_2 balloon	I_2 , 1a, A1, A2, 13
5	I_2 , 1a, 1b, H_2O , <i>rt.</i> , Air or O_2 balloon	I_2 , 1a, P, A1, A2, 13, A4

Conditions: reactions were proceeded under *rt.*, in H_2O , acetophenone, 0.1 mmol, morpholine, 0.2 mmol, I_2 , 100 mol%, H_2O , 1 ml, compounds were determined by HPLC-MS; reaction time 12 h; MS Scan 100–600 m/z.

in Table 3), indicating that the reactions would not occur in absence of either amine or I_2 . Only both morpholine and I_2 present in the reaction system (sealed with N_2 balloon) can initiate the formation of three intermediates A1, A2 and A3.

Under the experimental conditions in Entry 5, four compounds/intermediates were detected, including A1, A2, 13, A4. Additionally, the reaction was initially run under conditions in entry 4 after 1 h, in which three intermediates A1, 12 and 13 were measured. Subsequently, the reaction solution was filled with O_2 /air through a balloon. After another 11 h, surprisingly, four compounds/intermediates were detected as those collected in entry 5. Therefore, the introduction of O_2 /air triggered the generation of another one more intermediates of A4 and P product. A comparison of these captured intermediates between Entry 4 and Entry 1 confirmed that I_2 is prerequisite to initiate the reaction, as well as morpholine. However, all I_2 was consumed during the reaction, concluding that I_2 acted as both

the oxidant and the coupling reagent, rather than as the catalyst that was conventionally considered for a long period. As shown in Scheme 2, a two morpholine-ring structured intermediate 13 was formed, which immediately transformed into the final target product P through A4 species after eliminating one morpholine moiety. In addition to the role of reactant, morpholine was also verified to play the catalytic role for the first time.^[22]

A weak acidic solution was obtained once the reaction was completed, inferring the release of H^+ during the reaction. Indeed, the morpholine would be directly neutralized at the starting of the reaction. However, morpholine cations were presumed to lose the reactive activity, which cannot further react with an aromatic ketone or late with A2. So only the deprotonation of morpholine cation could open an opportunity to lower the amount of morpholine. To further prove this concept, we repeated the reaction in the presence of NaOH (1.0 equiv.) as the additional

Base to maintain system pH about 7 or used buffer which pH was 7. As expected, our results demonstrated that the additional one equivalent base (NaOH) successfully released free morpholine, resulting in a lower loading of morpholine (1.1 equivalent) affording a high yield of 95% (Figure 2). These results also confirmed that one equiv. of amine was inevitably requisite to neutralized the H^+ released in the classical amidation. However, when we added more NaOH or used more high pH value buffer, the product yield was bad. This might be the reason there was a reaction equilibrium between OH^- and iodine molecules. Too much OH^- would reduce the concentration of iodine in the reaction system, making the reaction equilibrium unfavorable the amidation reaction proceeds.^[24]

Conclusions

In summary, we have, for the first time, discovered the specific role of the amine in the amidation of aromatic ketones that has been commonly considered as the reactant for decades. In our studies, we observed that I_2 was completely consumed during the reaction, indicating its role as both the oxidant and the coupling reagent. Using the captured intermediates, we successfully elucidated the possible mechanism for the direct amidation between amine and ketones. Due to the release of H^+ in the reaction system, at least 2 equiv. amine was required. Furthermore, with the addition of 1.0 equiv. of NaOH, we achieved a high yield (~95%) of amidation using only 1.1 equiv. of amine substrate. We believe that these new findings and deep insights into the classical amidation will provide a better understanding of the mechanism and a further rational extension of the amidation approach to other challenging catalytic conversions.

Experimental Section

Methods

All chemicals were economically available and purchased from Aladdin (Shanghai, China), and were used without any further purifications. All chemicals were of analytical grade. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in DMSO or CDCl_3 depending on their dissolution. All chemical shifts (δ) were quoted in parts per million (ppm) and reported relative to an internal tetramethylsilane (TMS, δ 0.00) standard. The yield of products was measured with a SHIMADZU HPLC instrument equipped with a Wonda Sil C18-WR 5 μm column. HPLC-MS spectra were recorded on a Shimadzu liquid chromatography/mass spectrometry ion-trap time-of-flight (LCMS-IT-TOF) instrument.

X-ray diffraction (XRD) patterns were collected from 5° to 80° with a step of 0.02 on a Bruker D 8 Advance diffractometer with Cu $K\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$) and a Lynxeye one-dimensional detector.

Synthesis of α -Ketoamides

A mixture of Aryl methyl ketone 0.1 mmol, amine or aqueous ammonia 0.2 mmol, iodine 0.1 mmol 25 mg was charged in a 25 ml double mouth round-bottom flask filled with 1 ml water, air was flushed into a balloon and sealed along with the flask, stirred at room temperature for 24 hours. Then, the reaction mixture was extracted with ethyl acetate 3 times, each time with 50 ml. The organic layers were separated and combined together, and washed with brine solution, dried over anhydrous MgSO_4 and filtrated with a pad of cotton. Ethyl acetate was removed under vacuum, the residues were collected and purified by chromatography to afford pure products.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: amidation reaction · aromatic ketones · α -ketoamide · reaction mechanism · NMR spectroscopy

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