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I_2-DMSO mediated oxidative amidation of methyl ketones with anthranils for the synthesis of α-ketoamides†

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An I_2-DMSO mediated oxidative amidation of methyl ketones using anthranils as masked N-nucleophiles has been developed for the direct synthesis of α-ketoamides with high atom-economy. This metal-free process involves reductive N–O bond cleavage of anthranils and oxidative C–N bond formation of methyl ketones under mild conditions. The iodo group and electrophilic formyl group provide multiple possibilities for further functionalization of α-ketoamides.

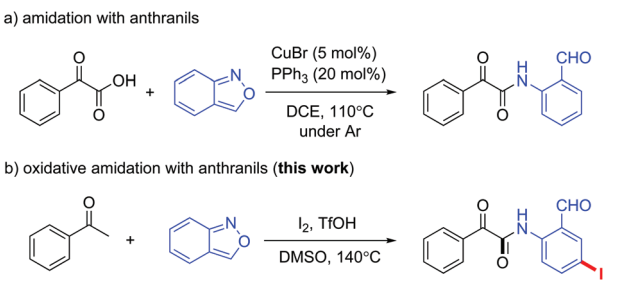
Introduction

α-Ketoamides and their derivatives represent a class of valuable structure motifs which display unique reactivity in biologically natural products and the pharmaceutical industry.[1] Besides, they are important synthetic intermediates and precursors for further functionalization.[2] Consequently, the formation of α-ketoamides has attracted general interest and remained of vital practical significance. A number of traditional synthetic strategies have been applied for the formation of α-ketoamides: (1) the direct amidation of α-ketoaldehydes[3] and α-keto acids;[4] (2) the oxidation of α-hydroxyamides;[5] (3) the oxidative amidation of ethylbenzenes,[6] styrenes,[7] phenylacetylenes,[8] benzylic alcohols,[9] benzaldehydes[10] and acetophenones;[11] and (4) transition-metal catalyzed dicarbonylation of aryl halides.[12]

Compared to employing simple amination agent, the introduction of amino source with multiple functional groups provides more possibilities for further transformation of α-ketoamides. To date, numerous protocols have been established using anthranil as a masked N-nucleophile.[13] The N–O bond of anthranil is unstable and undergoes bond cleavage facilely accompanied with the generation of electrophilic formyl group. However, the formyl group is difficult to introduce and its functional group compatibility remains a challenge. Recently, Zou's group has reported the copper-catalyzed amidation of α-keto acids with anthranils under Ar atmosphere (Scheme 1a).[14] On account of our continued interest in I_2-DMSO mediated reactions,[11b,d] we proposed that methyl ketones might be oxidized to *in situ*-generated phenylglyoxals and captured by anthranils (Scheme 1b). This approach involved N–O bond cleavage and C–N bond formation, providing a novel strategy for the oxidative amidation of acetophenones in the absence of metal catalyst under air conditions. The iodo group might provide more opportunities for further transition-metal catalyzed coupling reactions.[15]

Results and discussion

At the beginning of this study, we used acetophenone (**1a**) and anthranil (**2a**) as model substrates (Table 1). The corresponding product was only obtained in 10% yield in the presence of I_2 in DMSO (Table 1, entry 1). The introduction of Lewis acid caused a slight increase in reaction productivity, giving the best result when TfOH was used as an additive (Table 1, entries 2–6). The reaction temperature was deemed to play a crucial role in the outcome of the yields and the optimal



Scheme 1 Strategies for the synthesis of α-ketoamides.

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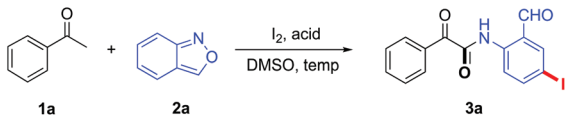
Table 1 Optimization of the standard conditions of **3a**[a]



1a 2a 3a

Entry	Acid (equiv.)	I_2 (equiv.)	Temp. (°C)	Yield[b] (%)
1	None	1.6	120	10
2	TFA (1.0)	1.6	120	13
3	TsOH (1.0)	1.6	120	10
4	TfOH (1.0)	1.6	120	20
5	PhCOOH (1.0)	1.6	120	11
6	$CuBr_2$ (1.0)	1.6	120	13
7	TfOH (1.0)	1.6	110	33
8	TfOH (1.0)	1.6	130	54
9	TfOH (1.0)	1.6	140	60
10	TfOH (1.0)	1.6	150	45
11	TfOH (0.3)	1.6	140	58
12	**TfOH (0.5)**	**1.6**	**140**	**78**
13	TfOH (1.5)	1.6	140	55
14	TfOH (0.5)	0.8	140	33
15	TfOH (0.5)	1.2	140	60
16	TfOH (0.5)	2.0	140	65

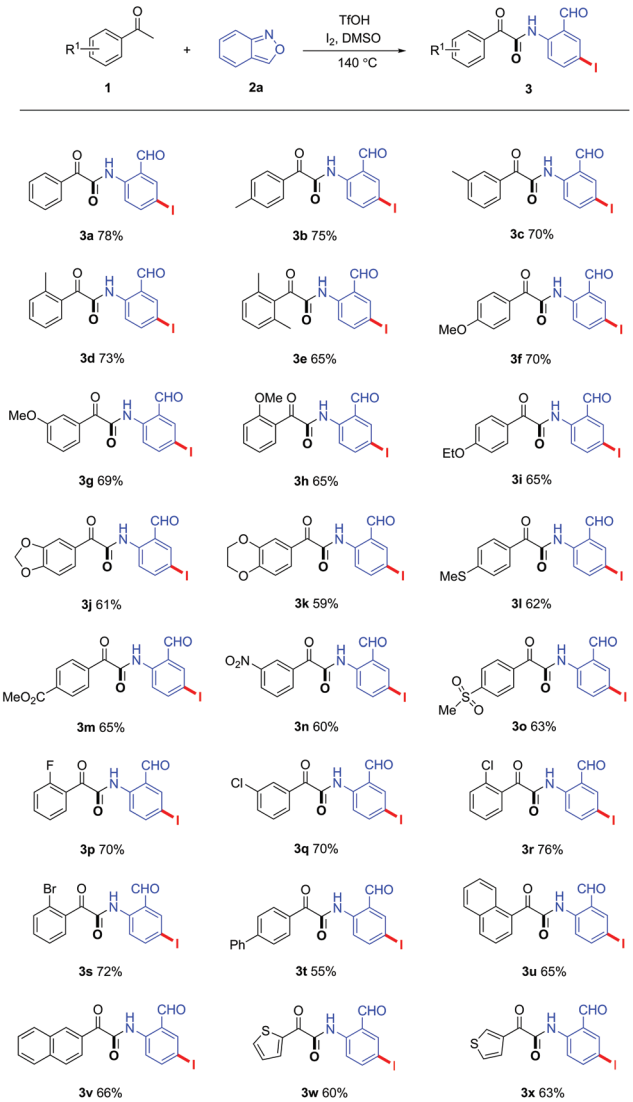
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), and I_2 heated in 2 mL of DMSO. [b] Products were obtained in isolated yields.

temperature was 140 °C (Table 1, entries 7–10). We subsequently investigated the amount of acid from 0.3 to 1.5 equiv. and found that the best result was obtained in the presence of 0.5 equiv. of acid (Table 1, entries 11–13). Further experiments revealed that the optimal equivalent of I_2 was 1.6 equiv. and **3a** was obtained in 78% yield (Table 1, entries 14–16). No side product *via* the Friedel–Crafts reaction was observed in this transformation.[16] Besides, the structure of **3a** was confirmed by X-ray crystallography (see ESI†).

With the optimized reaction conditions in hand, we began to examine the substrate scope for the synthesis of *α*-ketoamide and its derivatives under the optimal conditions (Scheme 2). Methyl ketones containing EDGs (Me, OMe, OEt, 3,4-OCH_2O, 3,4-$O(CH_2)_2O$, SMe, and Ph) and halogen substituents showed relatively high reactivities and transformed to the corresponding products in 55%–78% yields (**3a–3l**, **3p–3t**). Electron-withdrawing groups on the phenyl ring (CO_2Me, NO_2, and SO_2Me) led to slight decreases in the yields (**3m–3o**). Moreover, for naphthyl- and thienyl-substituted methyl ketones, the target compounds were afforded in moderate yields (**3u–3x**). However, aliphatic ketones were not compatible with this transformation (see ESI†).

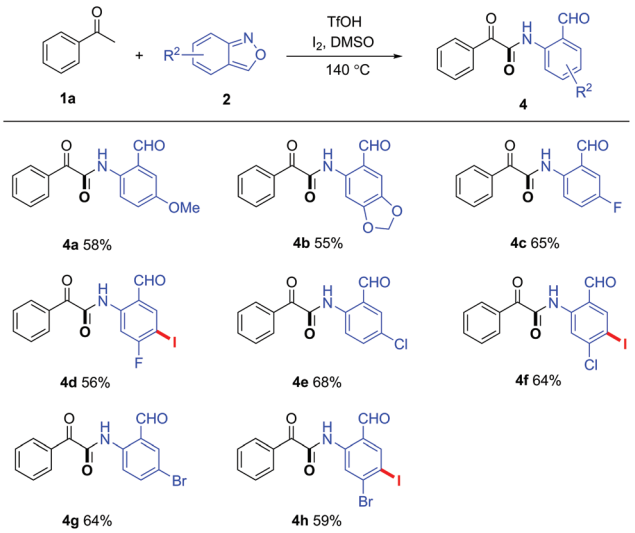
The reactions were further extended to investigate the scope of anthranil derivatives and various C4/C5-substituted benzoisoxazole substrates with electron donating groups or halogen groups proved to be feasible for constructing α-ketoamides (Scheme 3), giving the corresponding products (**4a–4h**) in 55%–68% yields.

To obtain a deep understanding of the mechanism for the synthesis of **3a**, a series of control experiments were carried out (Scheme 4). Acetophenone (**1a**) could be transformed to phenylglyoxal (**1ab**) and its corresponding hydrated species

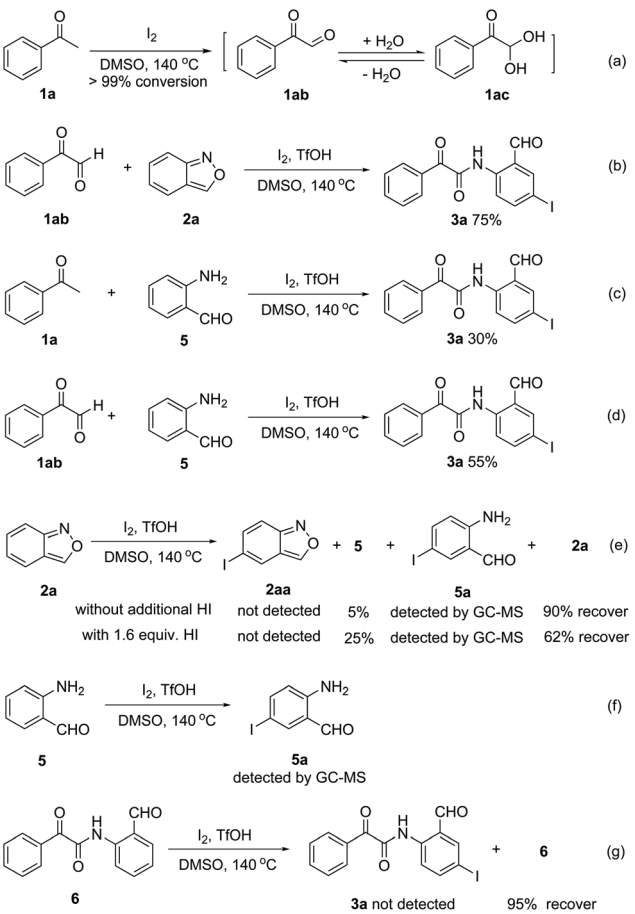


Scheme 2 Substrate scope of methyl ketones. Reaction conditions: 0.5 mmol scale. Isolated yields.

(**1ac**) under the I_2-DMSO mediated reaction (Scheme 4a). By replacing acetophenone (**1a**) with phenylglyoxal (**1ab**) to react with anthranil (**2a**), the corresponding product **3a** was obtained in 75% yield, indicating that phenylglyoxal (**1ab**) might be a possible intermediate (Scheme 4b). When using 2-aminobenzaldehyde (**5**) to react with **1a** and **1ab**, **3a** was obtained in 30% and 55% yields, respectively (Scheme 4c and d). This result revealed that **5** might be a possible intermediate, which was formed through N–O bond cleavage of anthranil. We subsequently used anthranil to react under standard conditions. However, 2-aminobenzaldehyde (**5**) and 2-amino-5-iodobenzaldehyde (**5a**) were detected instead of 5-iodobenzoisoxazole (**2aa**). With the addition of 1.6 equiv. HI, **5** was obtained in a 25% yield which further verified that anthranil (**2a**) was reduced by HI and transformed to intermediate **5** (Scheme 4e). Besides, we used 2-aminobenzaldehyde (**5**) as a substrate to react under standard conditions, 2-amino-5-iodo-



Scheme 3 Substrate scope of anthranils. Reaction conditions: 0.5 mmol scale. Isolated yields.

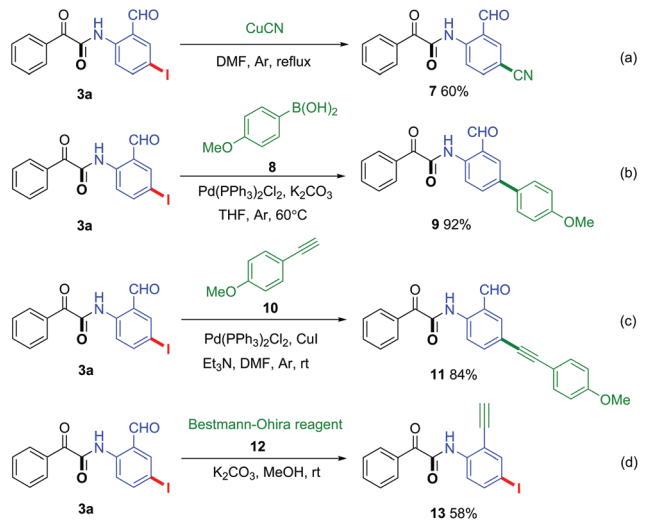


Scheme 4 Control experiments.

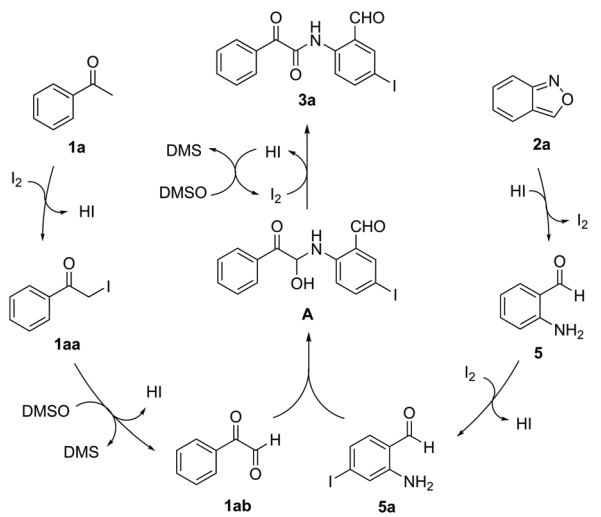
benzaldehyde (**5a**) was detected by GC-MS (Scheme 4f). However, α-ketoamide (**6**) was recovered in a 95% yield under the standard conditions (Scheme 4g). These results revealed that the iodination reaction occurred after ring-opening of anthranil (**2a**).

Further synthetic transformations of α-ketoamides were also explored to investigate the applicability of this reaction (Scheme 5). The iodo group of **3a** could be substituted by the cyano group in DMF, giving the corresponding product **7** in 60% yield (Scheme 5a). Besides, **3a** was able to undergo a transition-metal catalyzed coupling reactions, such as Suzuki–Miyaura coupling and Sonogashira coupling. These reactions gave the desired products **9** and **11** in relatively high yields (Scheme 5b and c). The formyl group of **3a** could undergo Seyferth–Gilbert Homologation and transform to the terminal alkyne compound **13** (Scheme 5d).

Based on the control experiments and previous studies, we disclose a possible mechanism for the synthesis of **3a** (Scheme 6).[17] Initially, acetophenone (**1a**) reacts with I_2 to



Scheme 5 Synthetic applications.



Scheme 6 Proposed mechanism.

afford α-iodo ketone (**1aa**). After Kornblum oxidation, **1aa** can be transformed into phenylglyoxal (**1ab**) with the release of HI. At the same time, anthranil (**2a**) is reduced by HI to obtain 2-aminobenzaldehyde (**5**) which further reacts with I_2 giving intermediate **5a**. The intermediate **1ab** is attacked by **5a** to get intermediate **A**. Intermediate **A** is oxidized by I_2 to form the desired product **3a**.

Conclusions

In summary, we have developed a novel and efficient strategy for enriching the synthesis of α-ketoamides using commercially available anthranils as masked N-nucleophiles. This metal-free process involves oxidative amidation of methyl ketones and reductive N–O bond cleavage of anthranils under air conditions. The synthetic approach has great tolerance for functional groups and high atom-efficiency, which means it has potential for practical applications. Further synthetic applications of this process are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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