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A novel approach for the one-pot preparation of α-ketoamides by anodic oxidation†

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The direct oxidative synthesis of α-ketoamides *via* anodic oxidation was developed by using dioxygen as a reactant under mild conditions. This methodology has a broad substrate scope (aromatic amines, aliphatic amines and ammonium acetate) and opens up an interesting and attractive avenue for the synthesis of α-ketoamide derivatives.

The α-ketoamides are important synthetic intermediates, and they exist as structural motifs in a variety of natural products.[1] Traditionally α-ketoamides have been synthesized mainly by the following strategies: (1) the amidation of α-ketoacids and α-keto acyl halides;[2] (2) the oxidation of α-hydroxyamides and α-aminoamides;[3] (3) the oxidation of acyl cyanophosphoranes followed by the amidation of the resulting α,β-diketone nitrile;[4] (4) the double carbonylative amidation of aryl halides catalyzed by transition-metal;[5] and (5) the reaction of isocyanides with aromatic acyl chlorides.[3c,6] Recently, a range of new approaches has been developed by using O_2,[7] NIS[8a] or TBHP[8b–d] as an oxidant. In spite of the availability of these synthetic methodologies, a more mild, convenient and efficient synthesis of α-ketoamides is still in high demand.

As far as we know, there has been no report on the synthesis of α-ketoamides *via* electrochemical oxidation yet. The direct formation of α-ketoamides from primary aliphatic amines has been hardly reported either. On the other hand, dioxygen is an ideal oxygen source for synthetic chemistry. However, oxidation involving both oxygen and electrochemistry is rare. Herein we report a new method for the synthesis of α-ketoamides from acetophenones and amines by using dioxygen as a reactant.

Initially, under an oxygen atmosphere, the reaction of acetophenone with *n*-butylamine was performed to examine the different supporting electrolytes, including KI, NaI, *n*-Bu_4NI, *n*-Bu_4NBr and $LiClO_4$. As shown in ESI,† Table S1, among these electrolytes (Table S1, ESI,† entries 1–5), all iodine salts could promote this reaction to give the corresponding products with moderate to high yields while $LiClO_4$ and *n*-Bu_4NBr did not work for the reaction. Among various solvents examined, EtOH turned out to be the best choice, while others such as THF, DMSO, CH_2Cl_2 and CH_3OH were less effective (Table S1, ESI,† entries 7–10). When the reaction was performed under N_2, no desired product was observed (Table S1, ESI,† entry 11). Under the air atmosphere, the product could be obtained with a very low yield (< 5%). On the other hand, water had a significant influence on this reaction (Table S1, ESI,† entry 6). When 2 equivalents of H_2O were added to the reaction mixture, the yield dropped from 80% to minute quantity. After an extensive screening of the reaction parameters (Table 1), the optimal reaction conditions were obtained as follows: acetophenone (0.5 mmol), *n*-butylamine (2 mmol), *n*-Bu_4NI (1 mmol), EtOH (10 ml), and O_2 (balloon) in an undivided cell equipped with a platinum anode and a cathode at ambient temperature under a constant current of 20 mA for 3 hours.

Under the optimized conditions, the scope of the reaction substrates was investigated with various combinations of acetophenones **1** and amines **2** (Table 1). In general, when **1** was employed as the reaction substrate, both primary and secondary amines (including cyclic and acyclic amines) could react with **1** smoothly to afford the corresponding amides **3a–3z** in moderate to high yields. As for the substrate acetophenones, both electron-rich and weak electron-deficient aromatic ketones could be transformed into the desired products with the yields from 56% to 90% (Table 1, entries 1–8). Nevertheless, 4-nitro acetophenone, a strong electron-deficient aromatic ketone, failed to afford the corresponding α-ketoamide (Table 1, entry 9). As for the secondary amines, the reactions could be carried out smoothly to afford the corresponding products with moderate to high yields (Table 1, entries 20–23). As for the primary amines and benzylamines, which were hard to form α-ketoamides by the conventional method,[5e] the amidation reaction could also be carried out smoothly to give the products with good yields (Table 1, entries 1–8, 14–19 and 24–28). It was noted that laurylamine, which was a weak nucleophile, could be converted into the α-ketoamide with a moderate yield (Table 1, entry 25).

When the substrate amine was replaced by ammonium acetate, to our delight, α-oxophenylacetamide derivatives can be obtained with good reaction yields. As far as we know, α-oxophenylacetamide is an important intermediate in organic synthesis with interesting

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc43685c

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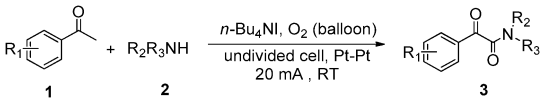
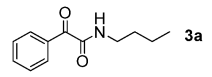
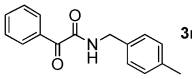
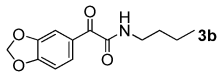
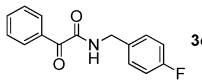
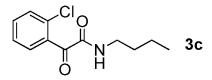
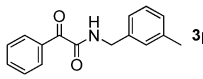
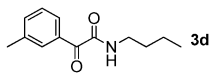
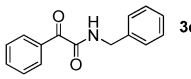
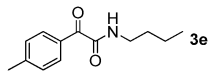
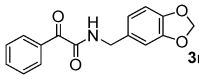
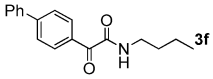
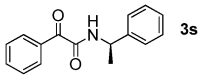
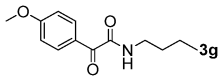
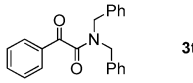
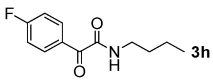
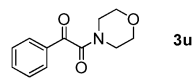
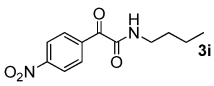
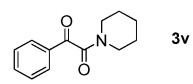
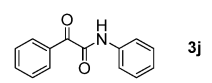
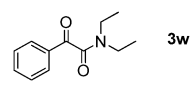
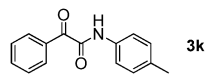
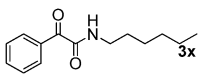
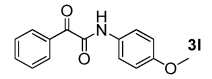
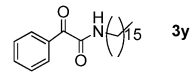
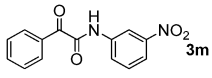
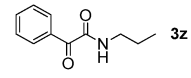
Table 1 Synthesis of α-ketoamides[a]

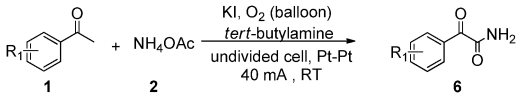


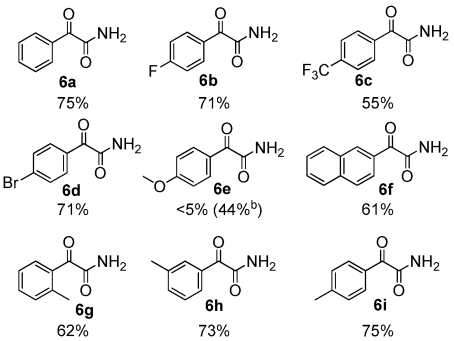
Entry	α-Ketoamide	Yield[b] [%]	Entry	α-Ketoamide	Yield[b] [%]
1	 3a	81	14[c]	 3n	65
2	 3b	77	15[c]	 3o	53
3	 3c	77	16[c]	 3p	76
4	 3d	52	17[c]	 3q	65
5	 3e	90	18[c]	 3r	56
6	 3f	56	19[c]	 3s	85
7	 3g	61	20[c]	 3t	52
8	 3h	78	21	 3u	52
9	 3i	Trace	22	 3v	70
10[c]	 3j	80	23	 3w	73
11[c]	 3k	65	24	 3x	62
12[c]	 3l	65	25	 3y	54
13[c]	 3m	50	26	 3z	64

[a] Reaction conditions: **1** (0.5 mmol), **2** (2 mmol), *n*-Bu_4NI (1 mmol), EtOH (10 ml), O_2 (balloon), platinum sheet as an anode and a cathode, at a constant current of 20 mA for 3 hours. [b] Isolated yield. [c] 1 mmol of aniline and benzylamine were added.

biological properties.[9] However the synthesis of the α-oxobenzeneacetamide is rarely reported.[10] Therefore this method is a useful alternative method to synthesize α-oxophenylacetamide derivatives. In order to increase the solubility of ammonium acetate, the solvent ethanol was replaced with methanol. Among the various electrolytes examined, potassium iodide was found to be the best choice in methanol, as shown in Table S2 of ESI.† Besides, the basic environment of the reaction also played a crucial role in the reaction and the amines were chosen as the additives to modulate the basic environment of the reaction. After optimizing the amines, it was found that *tert*-butylamine was the best choice (see Table S2 of the ESI†). Also, the scope of acetophenones was examined in this reaction. From

Table 2 Synthesis of α-oxobenzeneacetamide[a]

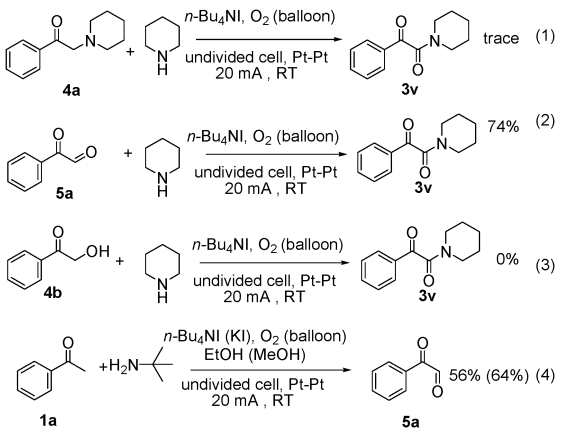




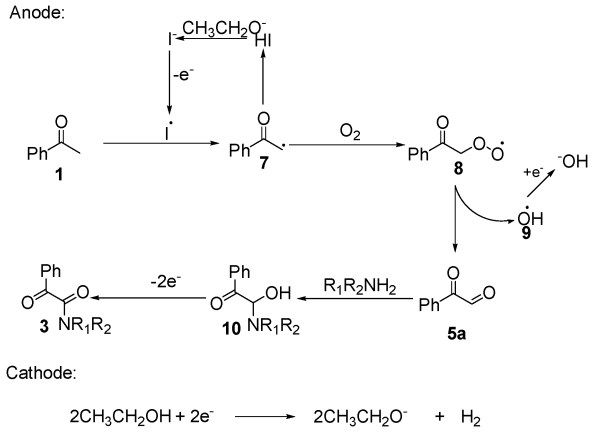
[a] Reaction conditions: **1** (0.5 mmol), **2** (2 mmol), KI (1 mmol), *tert*-butylamine (2 mmol), MeOH (10 ml), O_2 (balloon), platinum sheets as an anode and a cathode, at a constant current of 40 mA for 5 hours. [b] NH_4OAc was added in batches, reaction time was prolonged to 10 hours.

Table 2, it was found that a variety of substituents on the phenyl ring of acetophenone had little influence on the reaction, affording the corresponding α-oxophenylacetamides with moderate to high yields (Table 2). However, the strong electron-donating group, the methoxy group, had a serious negative influence on this reaction. Only 5% yield of the α-oxophenylacetamide can be obtained (Table 2, **6e**). When ammonium acetate was added in batches and the reaction time was prolonged to 10 hours, the desired product could also be obtained in 44% yield (Table 2, **6e**).

To probe the mechanism of the reaction, a series of control experiments were performed under electrochemical conditions. At first, we thought that 1-phenyl-2-(piperidin-1-yl)ethanone (**4a**) was the key intermediate, which was further oxidized to product **3v**. When **4a** was employed as the reaction substrate, only a trace amount of the product was observed, as shown in Scheme 1 [eqn (1)]. This showed that **4a** was not the reaction intermediate. 2-Oxo-2-phenylacetaldehyde (**5a**) could be detected by GC-MS. This implied that **5a** could be the reaction intermediate. Furthermore, treatment of the isolated **5a** with piperidine led to the desired product **3v** in 74% yield, as shown in Scheme 1 [eqn (2)]. Next, we investigated the precursor **4b**. Initially we assumed that



Scheme 1 Control experiments for the reaction.



Scheme 2 The proposed reaction mechanism.

2-hydroxy-1-phenylethanone **4b** could be the precursor of **5a**. However, the experimental results indicated that **4b** could not be converted to **5a**, as shown in Scheme 1 [eqn (3)]. When the amine with a strong steric hindrance was employed as the reaction substrate, **5a** could be obtained with high yield, as shown in Scheme 1 [eqn (4)]. This implied that **5a** could come from **1a** directly. All these experimental results indicated that **5a** should be the key intermediate in the reaction.

In terms of the literature, the participation of iodine in the electrochemical reaction usually involved radical initiation during the reaction since the iodine free radical could be easily generated *via* the anodic oxidation.[11] On the other hand, when 2 equivalents of TEMPO were added to the reaction mixture, the reaction was completely suppressed (Table S1, ESI,† entry 12). This indicated that the reaction should involve a radical process.

To investigate the reaction mechanism, the powerful electron paramagnetic resonance (EPR) spin trapping was applied to detect the intermediate radicals (see Fig. S1 of the ESI†). As shown in Fig. S1 (ESI†), EPR spectra were monitored with the addition of the radical trap 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) and a complicated signal was acquired (spectrum a, Fig. S1, ESI†). After simulation and careful analysis, the complicated spectrum could be ascribed to three different active intermediate radicals trapped by DMPO, DMPO–CH_2COPh (**7′**), DMPO–$OOCH_2COPh$ (**8′**), and DMPO–OH (**9′**) complexes respectively.

Based on the experimental results above, we propose a tentative reaction pathway shown in Scheme 2. Firstly, the iodine anion is oxygenated to the iodine free radical, and then the iodine free radical reacts with acetophenone to generate acetophenone radical **7**, which easily accepts oxygen to form **8**.[12] The formed **8** is unstable and is further transformed into 2-oxo-2-phenylacetaldehyde (**5a**). Then the nucleophilic attack of amine on **5a** affords **10**. **10** can be oxidized to the desired product **3** in the anode. In the cathode, ethanol is reduced to the ethoxide anion and hydrogen. Then the reaction of the ethoxide anion with hydrogen iodide regenerates the iodine anion.

In conclusion, we developed an efficient synthetic method to construct the C–N bond *via* electrochemical oxidation. This anodic oxidation was initiated by the iodine radical and was carried out using dioxygen under mild conditions. By virtue of this method, a new type of coupling of acetophenones with amines was realized, affording α-ketoamides with good yields. This coupling features high atom economy, easily available starting materials, a transition-metal free process, and a wide scope of amines. Further investigations into the scope of the reaction and the synthetic applications are ongoing in our laboratory.

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