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# Electrochemical Synthesis of the Aryl α-Ketoesters from Acetophenones Mediated by KI

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α-Ketoesters play an essential role in biological processes. They serve as the backbones in some natural products,[1] such as the 3-deoxy-2-ulosonic acids and their derivatives.[2] In addition, α-ketoesters are also used as key intermediates for the synthesis of highly valued substrates.[3]

Over the past several decades, chemists have paid great attention to the synthesis of α-ketoesters. Classical methods include oxidation of α-hydroxy esters with various kinds of oxidant,[4] oxidation of methyl 2-phenylacetate,[5] Friedel–Crafts acylation,[6] hydrolysis and esterification of acyl cyanides,[7] hydrolysis of 2-aryl-2-nitroacetates,[8] and other methods.[9] However, these protocols usually require stoichiometric amounts of metal oxidants, and thus a large amount of waste is formed in the reaction. It has been known that electrochemistry is a green method for fine chemical synthesis.[10] Recently the synthesis of esters from aldehydes and the corresponding alcohols was realized by virtue of an anode oxidation in the presence of N-heterocyclic carbine (NHC)/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[11] In our laboratory, we have been attempting to prepare α-ketoesters from aryl ketones and the corresponding alcohols by an anode oxidation. We conceive that this oxidation of methyl ketones in the presence of potassium iodide could avoid the waste pollution under electrochemical conditions.

Previously, the reaction of methyl ketones with iodine was a typical haloform reaction, affording carboxylic acids or esters with a loss of one carbon atom.[12] It is a challenge to functionalize the methelene of methyl ketones without losing the methyl carbon atom. Herein, we describe a novel method to synthesize α-ketoesters via an anode oxidation from acetophenones under mild conditions inhibiting the occurrence of the haloform reaction without any chemical waste.

Initially the reaction was carried out in an undivided cell, while MeOH was employed as the solvent, acetophenone as the model substrate, and amine as the additive under an oxygen atmosphere. It was found that the acetophenone can be oxidized into 2-oxo-2-phenylacetaldehyde (see Table S1 in the Supporting Information). Then we screened various amines and *tert*-butylamine was found to be the most effective additive to afford the desired product with a yield of 64% (see Table S1 in the Supporting Information). To our knowledge, the 2-oxo-2-phenylacetaldehyde could be an intermediate and further transformed into a hemiacetal in the presence of alcohol. Then this hemiacetal can be converted into the α-ketoester under electrochemical oxidation. To enhance the anode oxidation, we increased the electric current from 20 to 40 mA. As expected, the α-ketoester was obtained in 30% yield (Table 1, entry 1), which encouraged us to further optimize the reaction conditions.

Under the electric current of 40 mA, the reaction base amine was examined again. After examination of various amines, 2,2,6,6-tetramethylpiperidine (TMP) was the best choice for this reaction (see Table S2 in the Supporting Information). From the result of Table S2, it was found that only the amines with a large steric hindrance could catalyze the reaction well. Perhaps the amines without steric hindrance could be converted into α-ketoamides.[13] Subsequently, we attempted to improve the hemiacetal yield by the addition of some additive. At first, we assumed that this additive could catalyze the formation of hemiacetal. This meant that the additive should be an acidic compound. At the same time, this additive could not protonize the amine in the reaction mixture. Therefore ammonium acetate, nitroalkanes, and phenols were examined in the reaction. To our delight, when two equivalents of nitromethane were added to the reaction, a significant increase in yield was observed (Table 1, entry 3). When more than two equivalents of nitromethane was added, the yield decreased a little. Inspired by this result, other nitro compounds were examined and it was found that the *p*-nitrophenol was the best additive for this transformation, giving the α-ketoester with a high yield of 81% (entry 10). The dosage of *p*-nitrophenol in this reaction was also very important. When the amount of *p*-nitrophenol was increased from 0.5 to 1.0 equivalents, the reaction yield was decreased to 78% although the reaction time was prolonged to 3 h (entry 11). When the *p*-nitrophenol was de-

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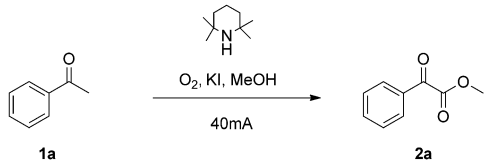
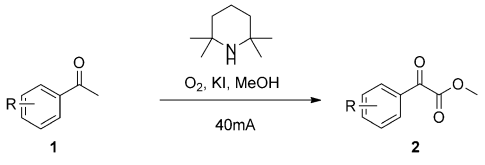
Table 1. Optimization of the reaction conditions.[a]

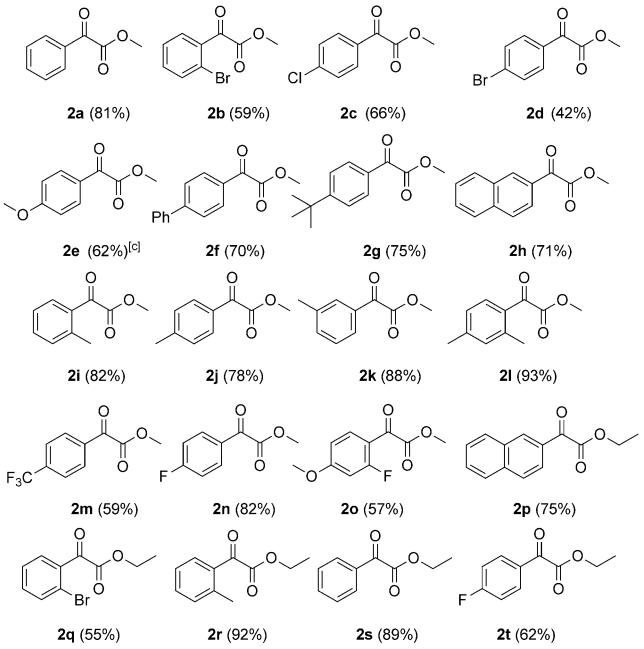



| Entry | Additive | Equiv | Yield [%][b] |
|---|---|---|---|
| 1 | none | | 30 |
| 2 | $NH_4OAc$ | | 35 |
| 3 | $CH_3NO_2$ | | 50 |
| 4 | $CH_3CH_2NO_2$ | | 55 |
| 5 | $CH_3CH_2CH_2NO_2$ | | 58 |
| 6 | $CH_3CH(NO_2)CH_3$ | | 61 |
| 7 | $PhNO_2$ | 1 | 57 |
| 8 | 4-Me-$PhNO_2$ | 1 | 62 |
| 9 | 3,5-dinitrophenol | 1 | trace |
| 10 | 4-nitrophenol | 0.5 | 81 |
| 11[c] | 4-nitrophenol | 1 | 78 |
| 12 | 4-nitrophenol | 0.25 | 42 |
| 13 | 4-*tert*-butylphenol | 1 | 45 |
| 14[d] | 4-nitrophenol | 0.5 | 76 |
| 15[e] | 4-nitrophenol | | 80 |

[a] Reaction conditions: **1a** (0.5 mmol), TMP (1 mmol), KI (1 mmol), additive (1 mmol), MeOH (10 mL), $O_2$ (balloon), platinum sheet as the anode and cathode, at a constant of 40 mA for 1.5 h. [b] Isolated yield. [c] The reaction time prolonged to 3 h. [d] Electrolyte was KI (0.1 mmol), $LiClO_4$ (1 mmol). [e] **1a** (3 mmol), 4-nitrophenol (0.25 mmol), **1a** was added in 0.5 mmol per 1.5 h, the reaction was completed in 10 h.

Table 2. Synthesis of α-ketoesters.[a,b]



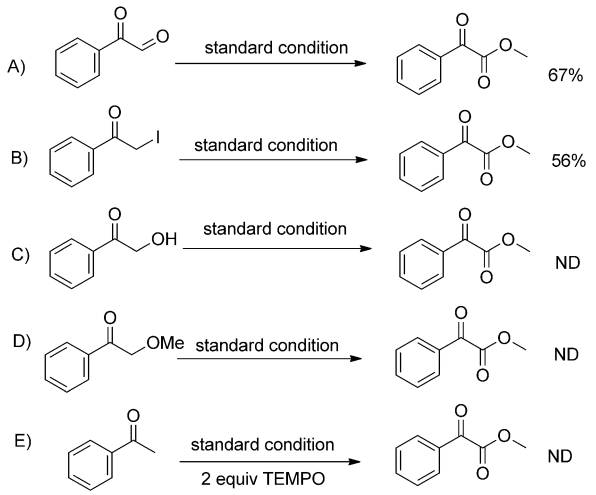

[a] Reaction conditions: **1** (0.5 mmol), TMP (1 mmol), KI (1 mmol), 4-nitrophenol (0.25 mmol), MeOH (10 mL), $O_2$ (balloon), platinum sheet as the anode and cathode, at a constant of 40 mA for 1.5 h. [b] Isolated yield. [c] Reaction time: 3 h.

creased to 0.25 equivalents, on the other hand, the yield of α-ketoester was dropped remarkably (entry 12). The oxygen was also very important to the reaction, only a trace of the product was obtained when the reaction was carried out under air or $N_2$ atmosphere. When KI was decreased to 0.2 equivalents, the product was obtained in 76% yield (entry 14). Upon increasing the amount of acetophenone to 3 mmol, the product was obtained with an enhanced yield of 80% (entry 15). After the optimization, the reaction conditions were established, as shown in entry 10.

With the optimal conditions in hand, we applied this electrochemical oxidation to construct the C–O bond between acetophenones and alcohols, affording the desired α-ketoesters. When methanol was employed as the solvent, the desired products were obtained with moderate to high yields (Table 2, **2a–o**). As for the reaction substrates, a range of substituents on the aryl ring of acetophenones were compatible under the reaction conditions regardless of the variation of electronic and steric effects. For instance, methyl, isobutyl, methoxyl, and phenyl acetophenone could be employed as the reaction substrates to afford the α-ketoesters with comparable yields (**2e–l**). As for the electron-withdrawing groups, the reactions could be also carried out smoothly to give the products with moderate to high yields (**2m–n**). The position of the substituent on the acetophenone had little influence on the reaction, as illustrated by the three isomers of methyl-substituted acetophenone (**2i–k**). It was noted that C–Cl, C–Br, and C–F bonds could survive the reaction (**2b–d**, **2n**), providing a versatile means for further elaboration of the products. When the reaction solvent was switched to ethanol, the corresponding products were also obtained with good yields (**2q–t**). Other alcohols, such as propyl alcohol or butanol, could not be used in this reaction to give the desired α-ketoesters, perhaps due to the low conductivity and poor nucleophilicity of these alcohols.

To probe the mechanism of the reaction, a series of control experiments were performed. When 2-oxo-2-phenylacetaldehyde was used as the substrate, the desired product was obtained in 67% (Scheme 1A). When the reaction substrate acetophenone was replaced with 2-iodo-1-phenylethanone, the desired product α-ketoester could be obtained in 56% yield (Scheme 1B). On the other hand, 2-hydroxy-1-phenylethanone, which was a probable precursor of 2-oxo-2-phenylacetaldehyde, was employed as the reaction substrate but none of the desired product was obtained (Scheme 1C). This implied that 2-oxo-2-phenylacetaldehyde did not come from 2-hydroxy-1-phenylethan-one. 2-Methoxy-1-phenylethanone was also a hypothetical intermediate and we assumed it could be oxidized further to afford α-ketoester. However, the experimental result showed that 2-methoxy-1-phenylethanone could not be oxidized to the product α-ketoester (Scheme 1D). These control experiments suggested




Scheme 1. Control experiments for the reaction. ND = not detected.

that 2-iodo-1-phenylethanone was directly converted into 2-oxo-2-phenylacetaldehyde instead of 2-methoxy-1-phenylethanone under the electrochemical oxidation and then this 2-oxo-2-phenylacetaldehyde was further oxidized to the α-ketoester. When two equivalents of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) were added to the reaction (Scheme 1E), it was completely suppressed. This implied that the reaction involved a radical process. To verify this radical mechanism, electron paramagnetic resonance (EPR) spins trapping was applied to detect the possible radical intermediate. As shown in Figure 1, EPR spectra were monitored by the addition of the radical trap 5,5-dimethyl-1-proline-*N*-oxide (DMPO) and a complicated signal was acquired. In the EPR spectra, a signal **a** corresponding to DMPO-OH was identified, as shown in Figure 1. The hyperfine constants for the nitrogen and proton in **a** were $A_{14N}=14.6$ and $A_{1H}=14.6$, respectively. Another signal **b** was assigned to the oxidized DMPO with an $A_{14N}=17.1$ G for the nitrogen.[14] The DMPO was possibly oxidized by iodine radical or superoxide radical although the precise mechanism was not clear. In the absence of acetophenone, we did not observe the signal **a** (see Figure S1 in the Supporting Information). As a result, the generation of hydroxyl radical should involve the participation of acetophenone.

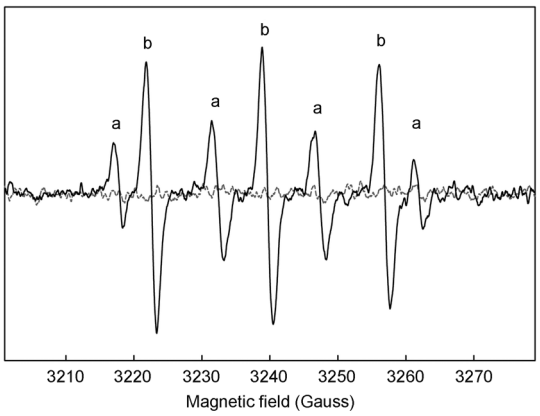
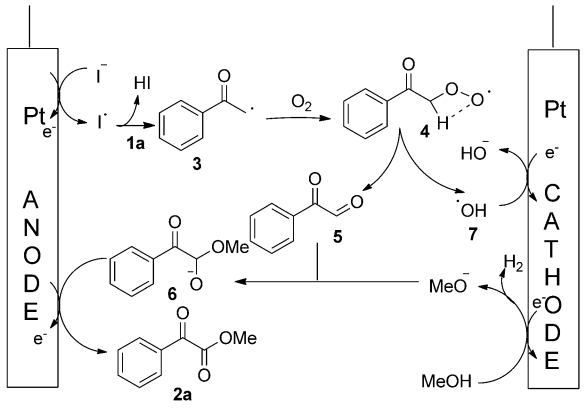



Figure 1. EPR spectra (X band, 9.07 GHz, room temperature) for reaction mixtures in the presence of the radical trap DMPO ($2.5\times10^{-2}$ M) and the pure DMPO. In the spectra, a is assigned to the DMPO-OH radical while b is assigned to oxidized DMPOX ( -----: pure DMPO; ——: experiment).

Based on the experimental results above, we proposed a tentative reaction pathway as shown in Scheme 2. Firstly, iodine anion is oxygenated into iodine free radical in the anode, and then iodine free radical reacts with acetophenone (**1a**) to generate acetophenone radical **3**. Another possible pathway is that the acetophenone is firstly transformed




Scheme 2. Proposed reaction mechanism.

into 2-iodo-1-phenylethanone, which gains one electron and then forms the radical **3**. The radical **3** catches oxygen to form **4**.[15] Compound **4** is unstable and is transferred further into 2-oxo-2-phenylacetaldehyde **5**, accompanying the formation of a hydroxyl radical **7** as a leaving group.[16] Radical **7** can be trapped by DMPO by a known Fenton's reaction. Radical **7** is a very active compound, which can be reduced to a hydroxyl anion in the cathode. At the same time, methanol is reduced in the cathode to give methoxide anion, which attacks **5** to afford **6**. Compound **6** can be oxidized to the desired α-ketoester **2a** in the anode.

In conclusion, we have developed an anode oxidative reaction of acetophenones with alcohol by a dioxygen activation under mild conditions, affording α-ketoesters with good yields. This novel transformation not only provides a simple and efficient approach to synthetize α-ketoester derivatives, but also develops a new method to construct a C–O bond by an anode oxidation. The EPR experiment supports the proposed mechanism strongly. Further investigations toward the applications are ongoing in our laboratory.

## Experimental Section

**Representative procedures for the synthesis of α-ketoesters**: An undivided cell was equipped with a magnet stirrer, platinum electrode as the

working electrode, and counter-electrode. In the electrolytic cell a solution of acetophenone (0.5 mmol), TMP (1 mmol), KI (1 mmol), *p*-nitrophenol (0.25 mmol), $O_2$ (balloon), and MeOH (10 mL) was allowed to stir and electrolyze at a constant current of 40 mA for 1.5 h until the quantity of the electricity 4.5 F/mol was passed at room temperature. Upon completion of the reaction, the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel, and the product was dried under high vacuum for at least 0.5 h before it was weighed and characterized by NMR spectroscopy.

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**Keywords:** bond-forming reactions · electrochemistry oxidation · esterification · iodine radical · oxygen

[1] a) J. T. Moon, J. Y. Jeon, H. A. Park, Y.-S. Noh, K.-T. Lee, J. Kim, D. J. Choo, J. Y. Lee, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 734–737; b) E. J. Iwanowicz, J. Lin, D. G. M. Roberts, I. M. Michel, S. M. Seiler, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607–1612; c) M. R. Angelastro, S. Mehdi, J. P. Burkhart, N. P. Peet, P. Bey, *J. Med. Chem.* **1990**, *33*, 11–13.

[2] L.-S. Li, Y.-L. Wu, *Tetrahedron Lett.* **2002**, *43*, 2427–2430.

[3] a) V. Bette, A. Mortreux, D. Savoia, J.-F. Carpentier, *Adv. Synth. Catal.* **2005**, *347*, 289–302; b) F. Wang, Y. Xiong, X. Liu, X. Feng, *Adv. Synth. Catal.* **2007**, *349*, 2665–2668; c) S. Suzuki, Y. Kitamura, S. Lectard, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 4581–4585; d) X. Zhu, A. Lin, L. Fang, W. Li, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2011**, *17*, 8281–8284; e) J. M. Aizpurua, C. Palomo, R. M. Fratila, P. Ferrón, A. Benito, E. Gómez-Bengoa, J. I. Miranda, J. I. Santos, *J. Org. Chem.* **2009**, *74*, 6691–6702; f) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881; g) A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2012**, *134*, 12912–12915; h) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421; i) X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc.* **2011**, *133*, 12914–12917; j) S. F. Viózquez, A. Banon-Caballero, G. Guillena, C. Najera, E. Gomez-Bengoa, *Org. Biomol. Chem.* **2012**, *10*, 4029–4035.

[4] a) K. Yamada, M. Kato, M. Iyoda, Y. Hirata, *J. Chem. Soc. Chem. Commun.* **1973**, *4*, 499–500; b) J. P. Burkhart, N. P. Peet, P. Bey, *Tetrahedron Lett.* **1988**, *29*, 3433–3436; c) M. Oba, M. Endo, K. Nishiyama, A. Ouchi, W. Ando, *Chem. Commun.* **2004**, *14*, 1672–1673; d) A. Wusiman, X. Tusun, C.-D. Lu, *Eur. J. Org. Chem.* **2012**, *16*, 3088–3092; e) N. E. Leadbeater, K. A. Scott, *J. Org. Chem.* **2000**, *65*, 4770–4772; f) N. Lu, Y.-C. Lin, *Tetrahedron Lett.* **2007**, *48*, 8823–8828.

[5] a) G. Urgoitia, R. SanMartin, M. T. Herrero, E. Dominguez, *Green Chem.* **2011**, *13*, 2161–2166; b) K. Moriyama, M. Takemura, H. Togo, *Org. Lett.* **2012**, *14*, 2414–2417.

[6] A. Ianni, S. R. Waldvogel, *Synthesis* **2006**, *13*, 2103–2112.

[7] J. M. Photis, *Tetrahedron Lett.* **1980**, *21*, 3539–3540.

[8] A. E. Metz, M. C. Kozlowski, *J. Org. Chem.* **2013**, *78*, 717–722.

[9] a) R. Lerebours, C. Wolf, *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053; b) A. Raghunadh, S. B. Meruva, N. A. Kumar, G. S. Kumar, L. V. Rao, U. K. Syam Kumar, *Synthesis* **2012**, *2*, 283–289; c) J. Zhuang, C. Wang, F. Xie, W. Zhang, *Tetrahedron* **2009**, *65*, 9797–9800.

[10] a) J.-i. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265; b) J. B. Sperry, D. L. Wright, *Chem. Soc. Rev.* **2006**, *35*, 605; c) H. Lund, *J. Electrochem. Soc.* **2002**, *149*, S21; d) K. D. Moeller, *Tetrahedron* **2000**, *56*, 9527.

[11] E. E. Finney, K. A. Ogawa, A. J. Boydston, *J. Am. Chem. Soc.* **2012**, *134*, 12374–12377.

[12] a) R. C. Fuson, B. A. Bull, *Chem. Rev.* **1934**, *15*, 275–309; b) R. T. Arnold, R. Buckles, J. Stoltenberg, *J. Am. Chem. Soc.* **1944**, *66*, 208–210; c) G. I. Nikishin, M. N. Elinson, I. V. Makhova, *Angew. Chem.* **1988**, *100*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1716–1717.

[13] a) X. Zhang, L. Wang, *Green Chem.* **2012**, *14*, 2141–2145; b) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu, X. Wan, *J. Org. Chem.* **2012**, *77*, 7157–7165.

[14] C. M. Jones, M. J. Burkitt, *J. Chem. Soc. Perkin Trans. 1* **2002**, *2*, 2044–2051.

[15] a) T. Hara, T. Iwahama, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2001**, *66*, 6425–6431; b) W. Wu, J. Xu, S. Huang, W. Su, *Chem. Commun.* **2011**, *47*, 9660–9662.

[16] C. Zhang, Z. Xu, L. Zhang, N. Jiao, *Tetrahedron* **2012**, *68*, 5258–5262.

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