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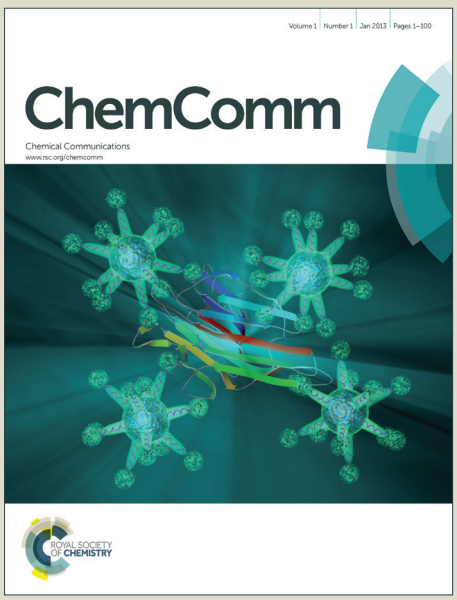

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A simple and efficient approach to realize difunctionalization of arylketones with malonate esters via an electrochemical oxidation

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Huihui Gao,[a] Zhenggen Zha,[a]* Zhenlei Zhang,[a] Huanyue Ma,[a] and Zhiyong Wang[a]*

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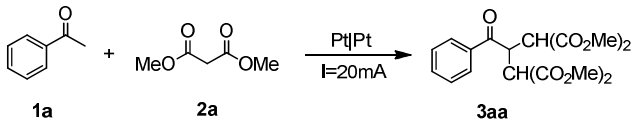
A facile difunctionalization of arylketones with malonate esters via an electrochemical oxidation was achieved under mild condition. A variety of difunctionalized products were obtained with good to excellent yields.

Sp^3 C-H functionalization of arylketones have attracted considerable attention because of their wide applications, especially in organic synthesis.[1] Consequently, considerable efforts have been devoted to develop this kind of reaction under mild reaction conditions, including α-oximation of arylketones,[2] synthesis of α-diazo ketones,[3] α-azido ketones,[4] aryl α-keto esters,[5] α-ketoamides[6] and α,β-unsaturated carbonyl compounds,[7] direct α-hydroxylation,[8] α-acidification[9] and α-halogenation[10] of aryl ketones. Compared with these direct functionalized reactions, arylketone difunctiolization reactions are less developed, which can provide an efficient method to access multisubstituted arylketones. Bis(β-dimethoxycarbonyl) derivatives have the potential to serve as bone affinity agents in the treatment of bone disease.[11] More importantly, these derivatives are usually employed as the precursor for the synthesis of glutaric acid,[12] which is very useful in industrial chemistry.

Electrochemical synthesis makes use of electron directly without the assistance of transition-metal-catalyst or toxic oxidant, therefore it is much more environmentally friendly and sustainable in comparison with the conventional redox process.[13] Our group has recently developed a series of useful electrochemical reactions for different transformation.[14-19] Encouraged by these successful transformations, we developed an arylketone difunctionalization reaction via an electrochemical oxidation. This strategy provides a facile access to the preparation of multisubstituted arylketones.

Initial optimization was performed with a model reaction of acetophenone **1a** with dimethyl malonate **2a**. The reaction was conducted in an undivided cell when KI was employed as the electrolyte and MeOH as the solvent with a constant current of 20 mA. To our delight, the difunctionalized product **3aa** was obtained in 40% yield (Table 1, entry 1). However, the electrolyzed process was too slow and it took more than 7 hours to get this poor yield. To promote the reaction, base was added to the reaction. When Na_2CO_3 was chosen as a base, the yield of **3aa** increased to 75% (Table 1, entry 2) and the reaction time was shortened to 3 h. Then other kinds of bases were examined. The result showed that KOH was the best choice for the electrochemical reaction (Table 1, entries 2-8). Afterwards, different kinds of electrolytes were examined. It was found iodide ion was necessary to this transformation. In the absence of iodide ion, the reaction didn't occur (Table 1, entries 8-12). After

Table 1 Optimization of the reaction conditions[a]



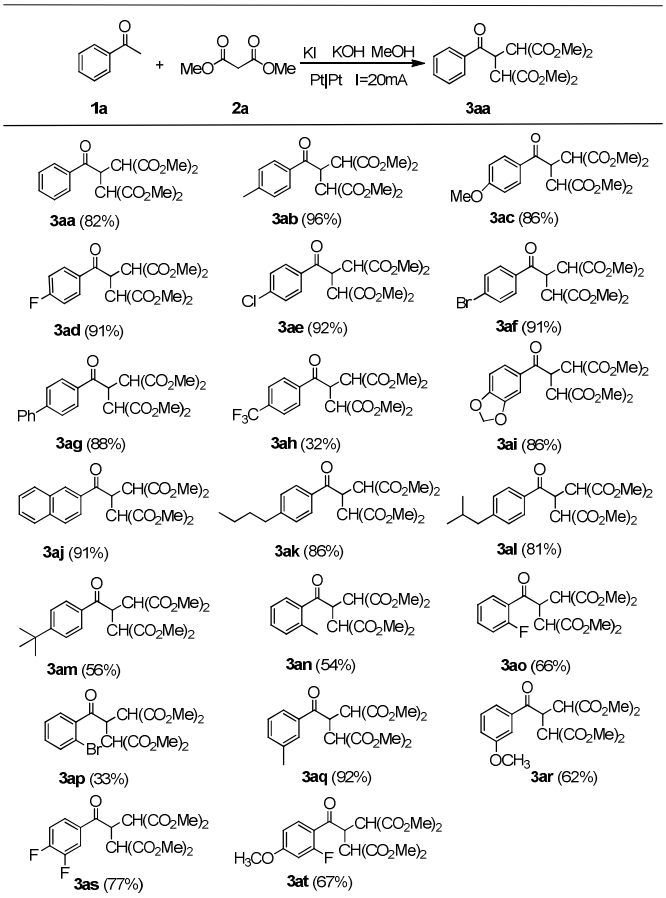
1a 2a 3aa

Entry	Base	Electrolyte	Solvent	Yield(%)[b]
1[c]	–	KI	MeOH	40
2	Na_2CO_3	KI	MeOH	75
3	K_2CO_3	KI	MeOH	42
4	$Ca(OH)_2$	KI	MeOH	57
5	$LiOH\cdot H_2O$	KI	MeOH	76
6	$K_3PO_4\cdot 3H_2O$	KI	MeOH	51
7	Et_3N	KI	MeOH	7
8	KOH	KI	MeOH	82
9	KOH	NaI	MeOH	63
10	KOH	$LiClO_4$	MeOH	0
11	KOH	Bu_4NBr	MeOH	0
12	KOH	Bu_4NI	MeOH	72
13	KOH	Bu_4NI	DMSO	0
14	KOH	Bu_4NI	CH_2Cl_2	0
15	KOH	Bu_4NI	CH_3CN	0

[a] Reaction conditions: acetophenone (0.5 mmol), dimethyl malonate (2 mmol), base (1 mmol), electrolyte (1 mmol), solvent (8 mL), two platinum electrodes, was electrolyzed at a constant current of 20 mA for 3 h in an undivided cell. [b] Isolated yields. [c] The reaction was electrolyzed for 7 h.

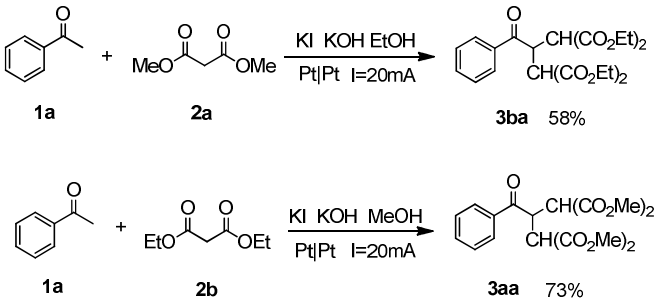
optimization of various iodide salts, KI proved to be the most efficient for this reaction (Table 1, entries 8-9 *vs* 12). Finally, different solvents were also optimized (Table 1, entries 12-15). It was found that MeOH was the best choice while other solvents couldn't promote the reaction at all. Therefore, the optimal condition was described as below: KOH as the base, KI as the electrolyte, MeOH as the solvent and the reaction being electrolyzed at a constant current of 20mA for 3 h with two platinum electrodes in an undivided cell under room temperature.

Table 2 Substrate scope of acetophenones[a]

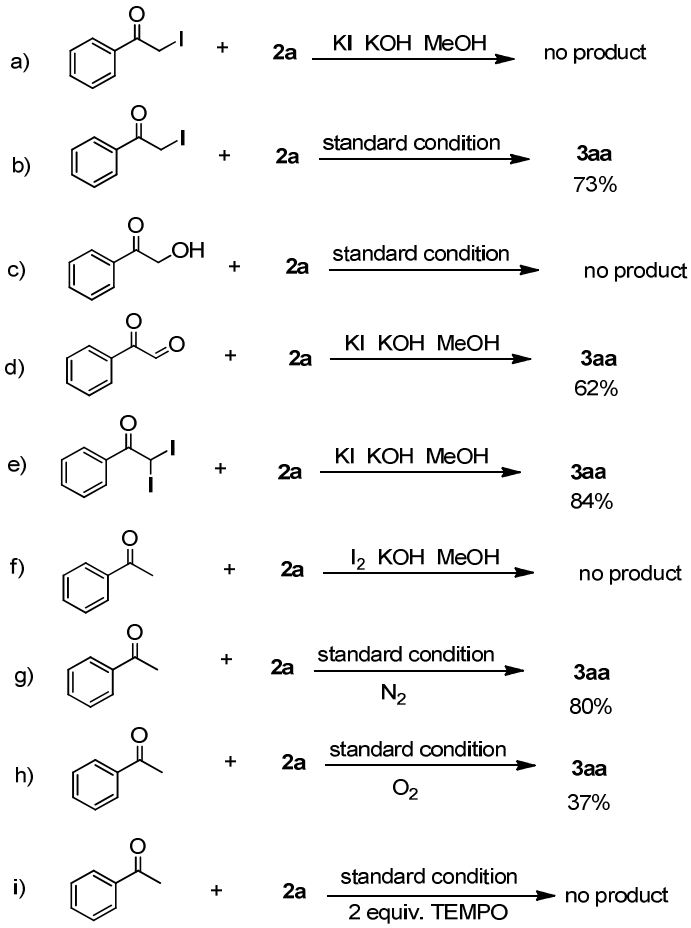


[a] Reaction conditions:1a (0.5mmol), 2a (2mmol), KI (1mmol), KOH (1mmol), MeOH (8mL), two platinum electrolytes, at a constant current of 20mA for 3 h in an undivided cell. [b] Isolated yields.

With the optimal condition in hand, the scope of arylketone was investigated first. The results were summarized in Table 2. Both electron-rich and electron-deficient aryl methyl ketones could be smoothly transformed into the desired products with high yields (Table 2, **3aa**-**3am**). In general, the electron-rich methyl ketones were more reactive than electron-deficient ones. It was found that *p*-CF_3 substitution on the aromatic ring of aryl ketone led to a poor yield (Table 2, **3ah**). Besides, a notable steric effect was observed: *ortho* substitution resulted in a lower yield compared with *para* and *meta* substitutions (Table 2, **3ab**, **3an** and **3aq**; **3ad** and **3ao**; **3af** and **3ap**). Furthermore, when multisubstituted ketones were employed as the substrates, the corresponding products still could be obtained with good yields (Table 2, **3as-3at**). Interestingly, when the reaction substrate was dimethyl malonate (**2a**) with the solvent EtOH, the product **3ba** was obtained with the yield of 58%. In contrast, when the substrate was switched to diethyl malonate (**2b**) with the solvent MeOH , **3aa** was generated in 73% yield. These experiment results clearly revealed that transesterification occurred easily in the reaction (Scheme1).



Scheme 1 The process of transesterification.



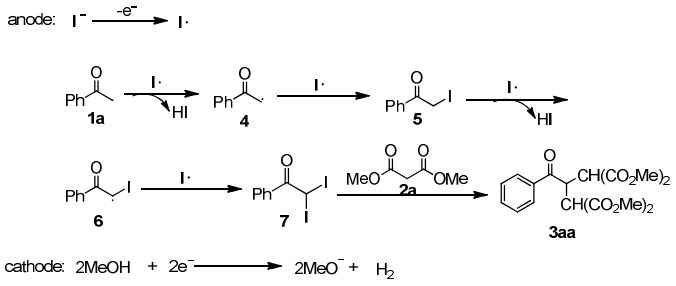
Scheme 2 Control experiments for the reaction.

In order to gain the insight of the mechanism, several control experiments were carried out (Scheme 2). First, the reaction of 2-iodo-1-phenylethanone with **2a** under standard condition without electrolysis did not produce the desired product (Scheme 2a) and the

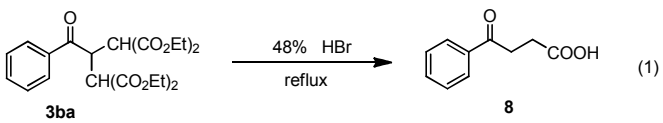
reactants were completely recovered. However, when the reaction mixture was electrolyzed, the desired product was obtained in 73% yield (Scheme 2b). This indicated that the electrolysis is necessary for this reaction. When 2-hydroxy-1-phenylethanone reacted with **2a** under standard condition, on the other hand, we could not get the desired product (Scheme 2c). Subsequently, 2-oxo-2-phenylacetaldehyde was mixed with **2a** under standard condition without electrolysis, the desired product was generated in 62% yield (Scheme 2d). Moreover, the desired product can be obtained in 80% under nitrogen atmosphere (Scheme 2g) while in 37% under oxygen atmosphere (Scheme 2h). This implied that 2-oxo-2-phenyl-acetaldehyde was not the intermediate. Furthermore, 2,2-diiodo-1-phenylethanone was also employed as the reaction substrate to replace 2-oxo-2-phenylacetaldehyde under the same condition, the desired product was formed in 84% yield (Scheme 2e). These results revealed that 2,2-diiodo-1-phenylethanone should be a key intermediate of the reaction. In addition, acetophenone with **2a** was carried out in the presence of iodine, we failed to get the desired product (Scheme 2f). Finally, the reaction was completely suppressed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2 equiv.) (Scheme 2i), which suggested that the reaction probably involved a radical process.

According to the experiment results mentioned above, we proposed a plausible mechanism (Scheme 3). First, iodine ion is oxidized into iodine radical on the surface of the anode, and then catches a hydrogen atom from acetophenone (**1a**) to give the radical **4**. Then the radical **4** combines with iodine radical to form 2-iodo-1-phenylethanone (**5**), which obtains an electron to give the radical **6**. The radiacl **6** is unstable and can easily integrate with iodine radical to generate 2,2-diiodo-1-phenylethanone (**7**), which is then attacked by dimethyl malonate (**2a**) to produce the desired product **3aa** under alkaline condition. Simultaneously, MeOH is reduced to methoxide anion with the release of hydrogen gas in the cathode.

Scheme 3 Proposed mechanism for the reaction.



Decarboxylation of the bis(β-dimethoxycarbonyl) derivative **3ba** was promoted by heating in the presence hydrobromic acid, affording 3-Benzoylpropanoic acid **8** in 71% yield (eq 1).



(1)

In summary, we have developed a new method to realize sp^3 C-H difunctionalization of arylketones under mild conditions. A series of multisubstituted arylketones were synthesized efficiently by virtue of environmentally friendly electrochemistry. Further studies on C-H functionalization via electrochemical method are underway in our lab.

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Notes and references

[a] *H. H. Gao, Z. G. Zha, Z. L. Zhang, H. Y. Ma, Prof. Dr. Z. Y. Wang*
Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Soft Matter Chemistry & Collaborative Innovation Center of Suzhou Nano Science and Technology, University of Science and Technology of China, Hefei, 230026, P. R. China
Fax: (+) 86-551-3603185
E-mail: zwang3@ustc.edu.cn

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