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

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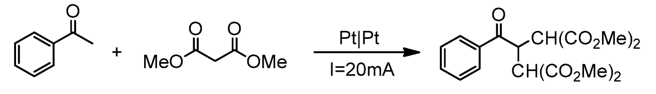
A facile difunctionalization of arylketones with malonate esters *via* electrochemical oxidation was achieved under mild conditions. A variety of difunctionalized products were obtained in good to excellent yields.

sp^3 C–H functionalization of arylketones has 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 arylketones. Compared with these direct functionalization reactions, arylketone difunctionalization 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 precursors for the synthesis of glutaric acid,[12] which is very useful in industrial chemistry.

Electrochemical synthesis makes use of electrons directly without assistance from transition-metal-catalysts or toxic oxidants; 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 transformations.[14–19] Encouraged by these successful transformations, we developed an arylketone difunctionalization reaction *via* electrochemical oxidation. This strategy provides a facile access to the preparation of multisubstituted arylketones.

The initial optimization was performed using 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.

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.

To our delight, the difunctionalized product **3aa** was obtained in 40% yield (Table 1, entry 1). However, the electrolytic 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 the 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 results 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 that the iodide ion was necessary for this transformation. In the absence of iodide ions, the reaction did not occur (Table 1, entries 8–12). After optimization of various iodide salts, KI proved to be the most efficient for this reaction (Table 1, entries 8 and 9 *vs.* 12). Finally, different solvents were also optimized (Table 1, entries 12–15). It was found

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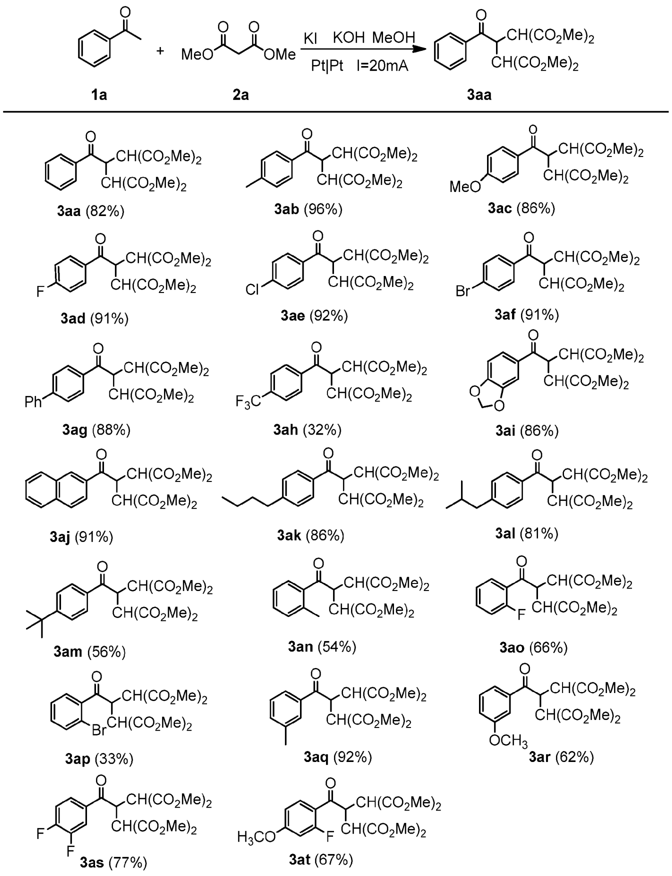
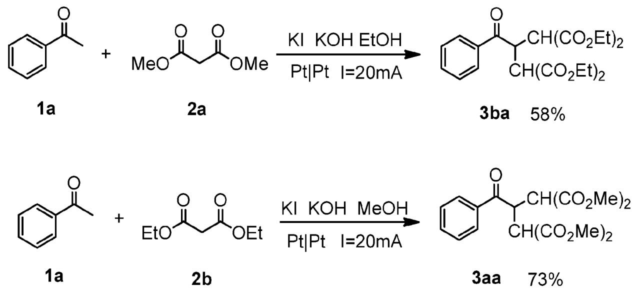
that MeOH was the best choice, while other solvents could not promote the reaction at all. Therefore, the optimal conditions were described as follows: KOH as the base, KI as the electrolyte, MeOH as the solvent and the reaction being electrolyzed at a constant current of 20 mA for 3 h with two platinum electrodes in an undivided cell at room temperature.

With the optimal conditions 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 the arylketone 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 could still 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 (Scheme 1).

Table 2 Substrate scope of acetophenones[a,b]

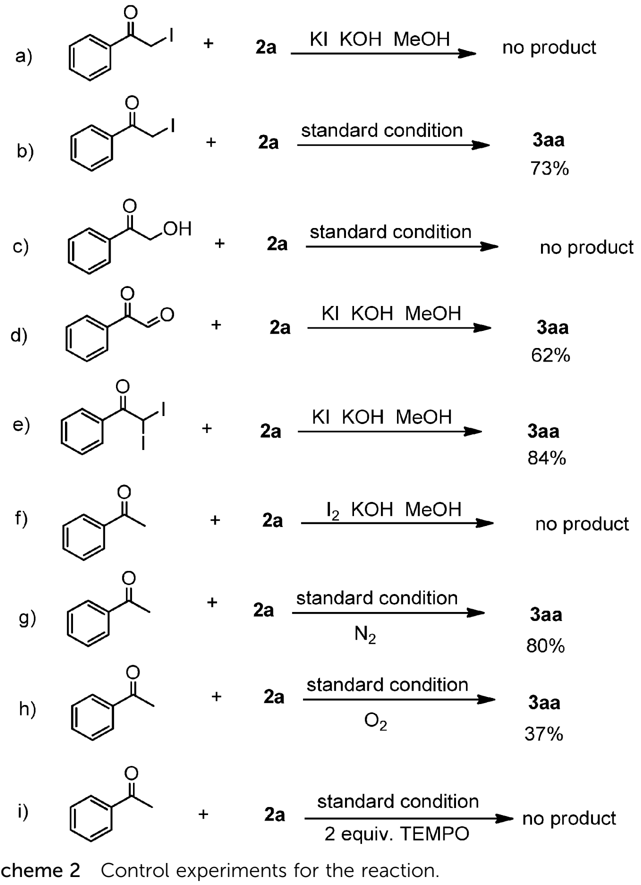


[a] Reaction conditions: **1a** (0.5 mmol). **2a** (2 mmol). KI (1 mmol). KOH (1 mmol). MeOH (8 mL). two platinum electrolytes, at a constant current of 20 mA for 3 h in an undivided cell. [b] Isolated yields.

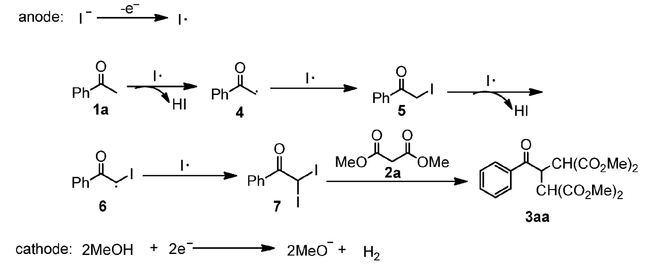


Scheme 1 The process of transesterification.

In order to gain insight into the mechanism, several control experiments were carried out (Scheme 2). First, the reaction of 2-iodo-1-phenylethanone with **2a** under standard conditions 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 conditions, on the other hand, we could not get the desired product (Scheme 2c). Subsequently, 2-oxo-2-phenylacetaldehyde was mixed with **2a**



Scheme 2 Control experiments for the reaction.

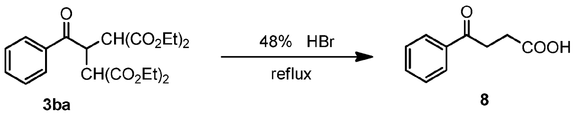


Scheme 3 Proposed mechanism for the reaction.

under standard conditions without electrolysis, and the desired product was generated in 62% yield (Scheme 2d). Moreover, the desired product could be obtained in 80% under a nitrogen atmosphere (Scheme 2g) and in 37% under an 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 conditions, 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, when reaction of 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 experimental results mentioned above, we proposed a plausible mechanism (Scheme 3). First, the iodine ion is oxidized into the 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 the iodine radical to form 2-iodo-1-phenylethanone (**5**), which obtains an electron to give the radical **6**. The radical **6** is unstable and can easily integrate with the 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 conditions. Simultaneously, MeOH is reduced to methoxide anion with the release of hydrogen gas in the cathode.

Decarboxylation of the bis(β-dimethoxycarbonyl) derivative **3ba** was promoted by heating in the presence of hydrobromic acid, affording 3-benzoylpropanoic acid **8** in 71% yield (eqn (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* the electrochemical method are underway in our lab.

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