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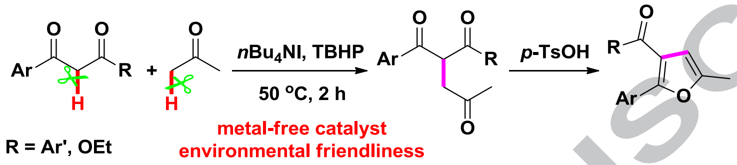

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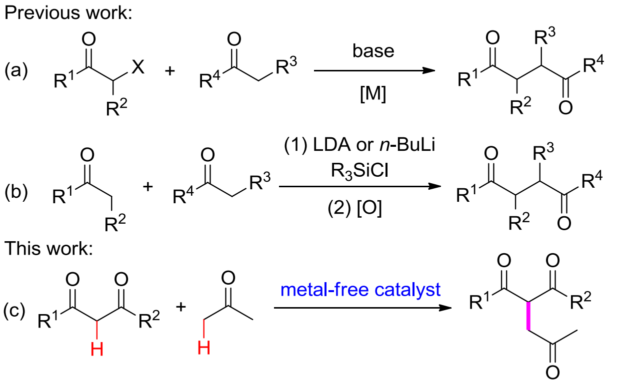
ABSTRACT

An nBu$_4$NI-catalyzed oxidative cross-dehydrogenative-coupling of β-dicarbonyl compounds with acetone under mild reaction conditions is described. This methodology provides a straightforward pathway to synthesize 2-carbonyl-1,4-diketones and features a simple system, low reaction temperature, and environmental friendliness.

Introduction

C–C bond formation is one of the most important reactions in organic synthesis because they provide key steps in building more complex molecules from simple substrates.[1] In this context, cross-dehydrogenative-coupling (CDC) reaction directly from two simple C–H bonds represents the most efficient and straightforward route for the synthesis of the target molecules due to their operational simplicity and atom economy.[2] Although great progress has been made in this area, CDC reaction is dominated by transition-metal catalysis and the application of organocatalysis is largely lagging behind.[3] Therefore, new synthetic methods for the construction of C–C bonds starting from C–H bonds under metal-free conditions are still required.

1,4-Dicarbonyl compounds are often used as the common substructures of natural products. Additionally, these compounds are useful precursors for the synthesis of cyclopentenone and heterocyclic compounds.[4] 1,4-Dicarbonyl compounds are traditionally prepared by the substitution reaction of α-halo ketones with nucleophilic enolates,[5] Stetter reaction,[6] oxidative coupling of enolates or silyl enol ethers,[7] and other approaches[8] (Scheme 1). For the synthesis of 1,4-dicarbonyl compounds via a nucleophilic substitution reaction, prefunctionalization of the α-position of ketones is needed (for example, Scheme 1, eqn a). For an oxidative coupling reaction, pre-preparation of enolates or silyl enol ethers is required (for example, Scheme 1, eqn b). Obviously, the most simple and efficient route for the synthesis of 1,4-dicarbonyl compounds might be the oxidative C–C bond coupling reaction of C(sp^3)–H bonds of two different ketones. Baran and co-workers reported intermolecular oxidative enolate heterocoupling using stoichiometric amounts of iron(III)-acetylacetonate (2.0 equiv) or copper(II)-2-ethylhexanoate (2.75 equiv) as the oxidant in the presence of LDA at -78 °C.[9] As part of our continuing interest in metal-free catalyzed oxidative C–N, C–O cross-coupling reaction directly from a C–H bond,[10] we present herein a simple and straightforward method to obtain 2-carbonyl-1,4-diketones by nBu$_4$NI-catalyzed oxidative CDC of 1,3-diketones and β-keto esters with acetone under mild reaction conditions (Scheme 1, eqn c). To the best of our knowledge, this is the first report on C–C cross coupling reaction of C(sp^3)–H bonds of two different ketones to generate a C–C bond with high selectivity under metal-free conditions.



Scheme 1. Different pathways for the synthesis of 1,4-dicarbonyl compounds.

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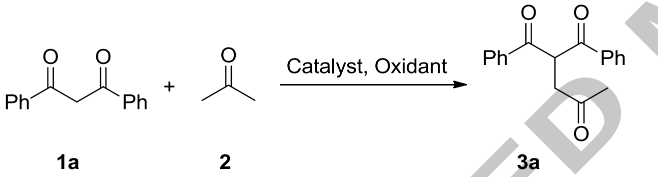
Results and Discussion

We initiated our investigation with 1,3-diphenylpropane-1,3-dione **1a** and acetone **2** as model substrates to identify suitable reaction conditions (Table 1). To our delight, the direct C–C cross coupling reaction took place in the presence of *n*-butylammonium iodide (*n*Bu_4NI, 0.2 equiv.) and *tert*-butylhydroperoxide (TBHP, 2.0 equiv.) at 100 °C under air, affording product **3a** in 45% yield along with some unidentified by-products (Table 1, entry 1). Because the high temperature may lead to decomposition of the product, the reaction temperature was decreased from 100 to 50 °C, and **3a** was isolated in 61-75% yield (Table 1, entries 2–4). However, the use of temperatures below 50 °C reduced the reactivity and conversion (Table 1, entries 5 and 6). Other iodine catalysts such as KI, NH_4I, NIS, and *n*Bu_4NBr were not effective (Table 1, entries 7–10). TBHP played a paramount role in this transformation. As shown in Table 1, TBHP was the most effective peroxide in the process. A trace amount of **3a** was observed when $K_2S_2O_8$, *di-tert*-butylperoxide (TBP), 30% H_2O_2, or *m*-CPBA was used as the oxidant (Table 1, entries 11–14). In addition, no desired coupling product was observed in the absence of *n*Bu_4NI or TBHP (Table 1, entries 15 and 16). Notably, this coupling reaction was performed under environmentally benign condition (with *tert*-butyl alcohol and water as by-products) without utilizing any metal.

Table 1

Optimization of the reaction conditions.[a]



Entry	Oxidant[b]	Catalyst	T (°C)	Yield (%)[c]
1	TBHP	*n*Bu_4NI	100	45
2	TBHP	*n*Bu_4NI	80	61
3	TBHP	*n*Bu_4NI	60	73
4	**TBHP**	**nBu_4NI**	**50**	**75**
5	TBHP	*n*Bu_4NI	40	62
6	TBHP	*n*Bu_4NI	30	5
7	TBHP	KI	50	trace
8	TBHP	NH_4I	50	trace
9	TBHP	NIS	50	0
10	TBHP	*n*Bu_4NBr	50	0
11	$K_2S_2O_8$	*n*Bu_4NI	50	trace
12	TBP	*n*Bu_4NI	50	trace
13	H_2O_2[d]	*n*Bu_4NI	50	trace
14	*m*-CPBA	*n*Bu_4NI	50	trace
15	-	*n*Bu_4NI	50	0
16	TBHP	-	50	0

[a] Reaction conditions: **1a** (0.3 mmol), **2** (3.0 mL), oxidant (0.6 mmol), catalysts (0.06 mmol), 2 h.

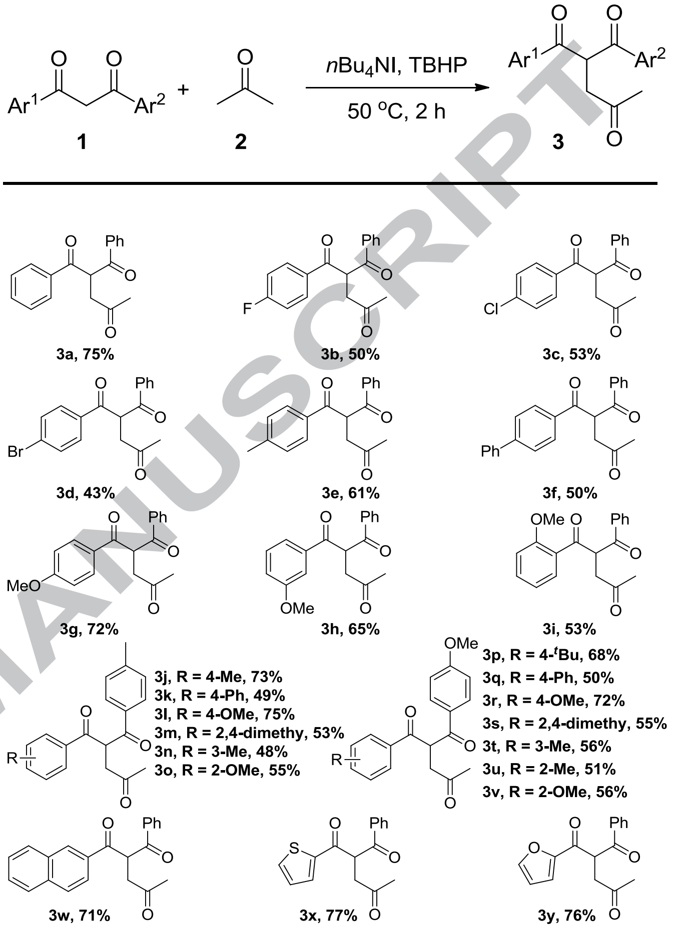
[b] TBHP 70% in water.

[c] Yield of the isolated product.

[d] H_2O_2 30% in water.

Table 2

CDC reaction of 1,3-diarylpropane-1,3-dione with acetone.[a,b]



[a] Standard reaction conditions: **1** (0.3 mmol), **2** (3.0 mL), TBHP (0.6 mmol, 70% in water), *n*Bu_4NI (0.06 mmol), 50 °C, 2 h.

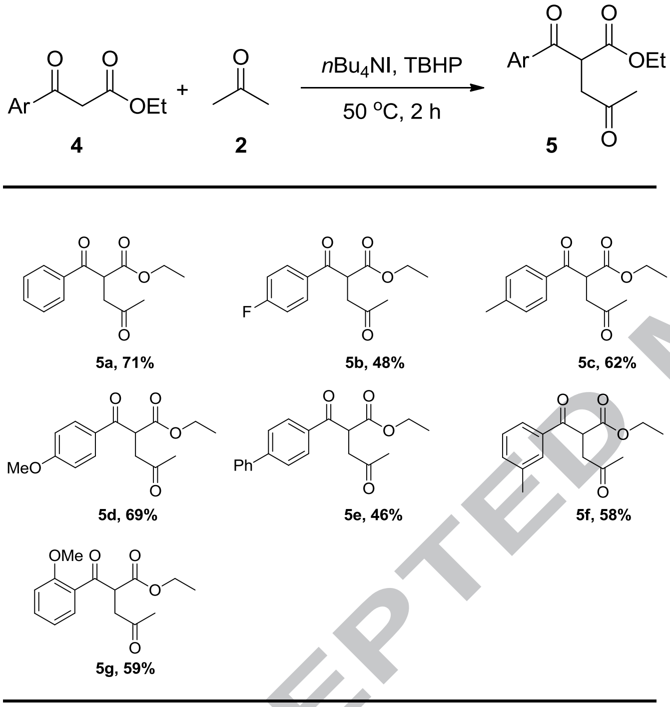
[b] Yield of the isolated products.

The generality of the C–C cross coupling reaction was next examined. As described in Table 2, a broad range of 1,3-diarylpropane-1,3-dione derivatives were investigated. All tested 1,3-diarylpropane-1,3-dione derivatives could be successfully converted to the desired products in moderate to good yields (**3a-y**). Generally, 1,3-diarylpropane-1,3-dione substrates bearing electron-donating substituents provided higher yields than those containing electron-withdrawing substituents on the aromatic ring (**3b-g**). Halo-substituted 1,3-diarylpropane-1,3-dione substrates (**1c**, **1d**) were tolerated in the coupling reaction, allowing for further functionalization through a cross-coupling manifold. In these reactions, the *para*-, *meta*-, and *ortho*-methoxy 1,3-diarylpropane-1,3-dione afforded the corresponding **3g** (72%), **3h** (65%), and **3i** (53%), respectively. The steric hindrance on the aryl ring played little role in the reaction. For further investigation, other unsymmetrical 1,3-diketones such as 1-aryl-3-(p-tolyl)propane-1,3-diones (**3j-o**) and 1-aryl-3-(4-methoxyphenyl)propane-1,3-diones (**3p-v**) were also employed to explore the scope of this transformation, and the corresponding products were obtained in moderate to good yields. In addition, 1-(naphthalen-2-yl)-3-phenylpropane-1,3-dione **1w** was also effective to provide **3w** in 71% yield. Heterocycle 1,3-diarylpropane-1,3-dione were subsequently examined. Starting from 1-phenyl-3-(thiophen-2-yl)propane-1,3-dione **1x** and 1-(furan-2-yl)-3-phenylpropane-1,3-dione **1y**, **3x** and **3y** were obtained in 77 and 76% yields, respectively. Remarkably, the reaction was also highly selective, affording only mono-α-substituted products **3**, and no disubstituted products were detected.

Encouraged by the abovementioned results, a variety of ethyl 3-oxo-3-arylpropanoates **4** were examined as substrates to react with acetone under the optimized reaction conditions (Table 3). This reaction of acetone with various ethyl 3-oxo-3-arylpropanoates afforded the desired coupling products **5a-g** in yields within the range of 46-71%. In addition, this reaction trend is also consistent with the steric and electronic effect of 1,3-diarylpropane-1,3-diones.

Table 3

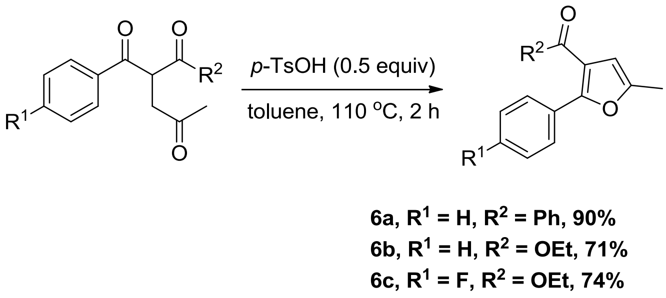
CDC reaction of ethyl 3-oxo-3-arylpropanoates with acetone.[a,b]



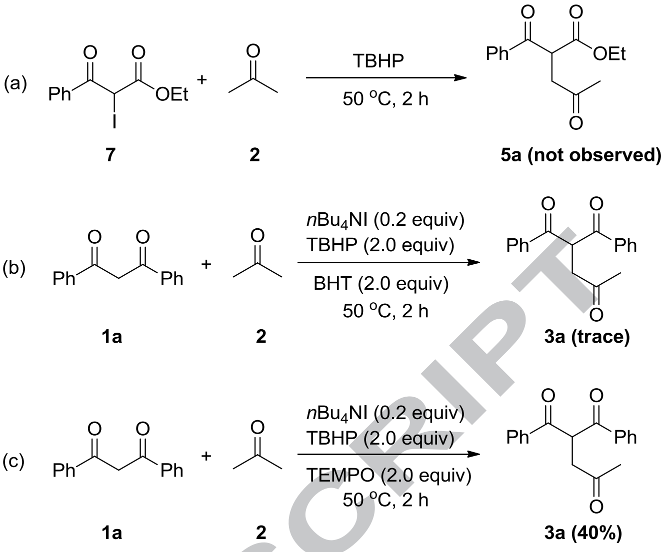
[a] Standard reaction conditions: **4** (0.3 mmol), **2** (3.0 mL), TBHP (0.6 mmol, 70% in water), *n*Bu$_4$NI (0.06 mmol), 50 °C, 2 h.

[b] Yield of the isolated products.

The utility of 1,4-dicarbonyl compounds as synthons in organic chemistry has expanded significantly in recent years.[4,11] For example, **3a** can be readily transformed into the trisubstituted furan **6a** in the presence of TsOH (Scheme 2). In addition, starting from **4a** and **4b**, the corresponding compounds could be obtained in 71% and 74% yields, respectively.

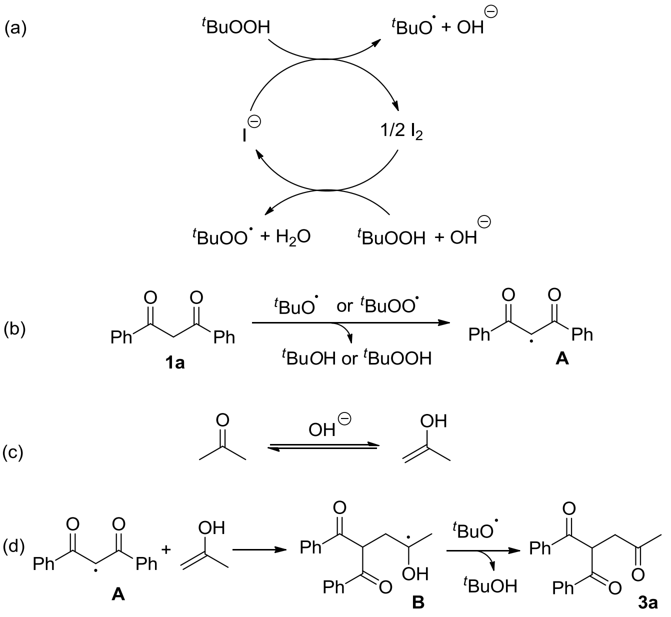


Scheme 2. Synthetic applications of 1,4-dicarbonyl compounds.



Scheme 3. Preliminary mechanism studies.

Some control experiments were performed to gain insight into the reaction. ESI-MS analysis of the reaction system of **1a** (reacted for 30 min) and 50 mL of the mixture was used for the negative ion ESI-MS analysis in CH$_3$CN. The ESI/MS analyses showed the presence of the in situ generated I$_2$ (see ESI). In addition to this, we performed the reactions using α-iodo-*β*-ketoester **7** and acetone as the substrates. No reaction occurred under the same experiment conditions and substrate **7** was recovered in 87% yield (Scheme 3a). When the radical scavenger 2,6-di-tert-butyl-4-methylphenol (BHT, 2.0 equiv.) was added to the reaction of **1a** under the optimal conditions, a trace amount of **3a** was detected after 2 h of reaction (Scheme 3b). In the presence of another radical inhibitor, 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO, 2.0 equiv.), **3a** was isolated in lower yields of 40% (Scheme 3c). These results indicate that a radical mechanism was involved.



Scheme 4. Proposed mechanism.

Although an in-depth discussion should await further investigations, based on the above results and literature precedent, a tentative mechanism was proposed in Scheme 4. Initially, the *tert*-butoxyl, *tert*-butylperoxyl radicals, and hydroxide form catalytically (Scheme 4a).[12] The $^{t}\mathrm{BuO}^{\bullet}$ or $^{t}\mathrm{BuOO}^{\bullet}$ radicals subsequently abstract hydrogen atoms from 1,3-diphenylpropane-1,3-dione **1a** to provide radical **A** (Scheme 4b).[13] Then, in the presence of hydroxide, the enol form of acetone will perform an addition reaction with carbon-centered radical **A** to give a tertiary carbon radical **B**,[14] which was oxidized to product **3a** (Scheme 4c, d).

Conclusions

In conclusion, we have reported a simple and straightforward *n*Bu$_4$NI-catalyzed CDC reaction of β-dicarbonyl compounds with inactivated acetone to construct 2-carbonyl-1,4-diketones under metal-free conditions. Various 1,3-diketones and β-keto esters were well tolerated in this methodology to give the corresponding desired products in moderate to good yields. The mild reaction conditions, inexpensive starting materials, synthetic simplicity, and using TBHP (70% in water) as an environmentally friendly oxidant make this method attractive. Importantly, this strategy can greatly simplify the operation and workup procedures for the efficient and practical synthesizing various 2-carbonyl-1,4-diketones from two different ketones, which may be a good alternative for the established routes. Further studies on the reaction mechanism and its application in other coupling reactions are ongoing in our group.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.xx.xxx.

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Highlights

- The C–C coupling reaction of C(sp^3)–H bonds of two different ketones was achieved.
- The reaction proceeds under metal-free conditions.
- This methodology features mild conditions and environmental friendliness.
- 2-carbonyl-1,4-diketones can be readily transformed into the trisubstituted furan.