



*n*Bu₄NI-catalyzed C—C bond formation to construct 2-carbonyl-1,4-diketones under mild conditions

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ARTICLE INFO

Article history:

Received 13 December 2017

Revised 3 March 2018

Accepted 5 March 2018

Available online 6 March 2018

Keywords:

C—C bond formation

C—H functionalization

Cross-dehydrogenative-coupling

Environmental friendliness

Metal-free

ABSTRACT

An *n*Bu₄NI-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.

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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 approaches⁸ (Scheme 1). For the synthesis of 1,4-dicarbonyl compounds via a nucleophilic substitution reaction, prefunctionalization of the α -position of ketones

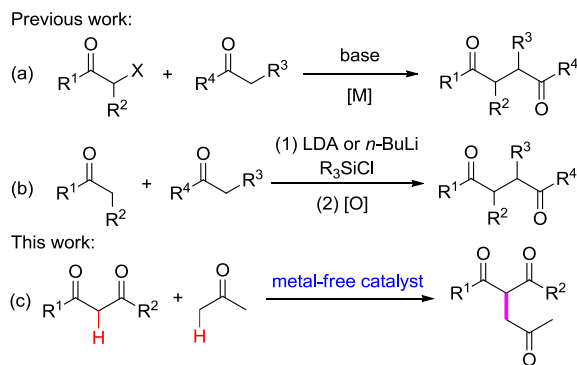
is needed (for example, Scheme 1, Eq. (a)). For an oxidative coupling reaction, pre-preparation of enolates or silyl enol ethers is required (for example, Scheme 1, Eq. (b)). Obviously, the most simple and efficient route for the synthesis of 1,4-dicarbonyl compounds might be the oxidative C—C bond coupling reaction of C(sp³)—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 *n*Bu₄NI-catalyzed oxidative CDC of 1,3-diketones and β -keto esters with acetone under mild reaction conditions (Scheme 1, Eq. (c)). To the best of our knowledge, this is the first report on C—C cross coupling reaction of C(sp³)—H bonds of two different ketones to generate a C—C bond with high selectivity under metal-free conditions.

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*Bu₄NI, 0.2 equiv.) and *tert*-butylhydroperoxide (TBHP, 2.0

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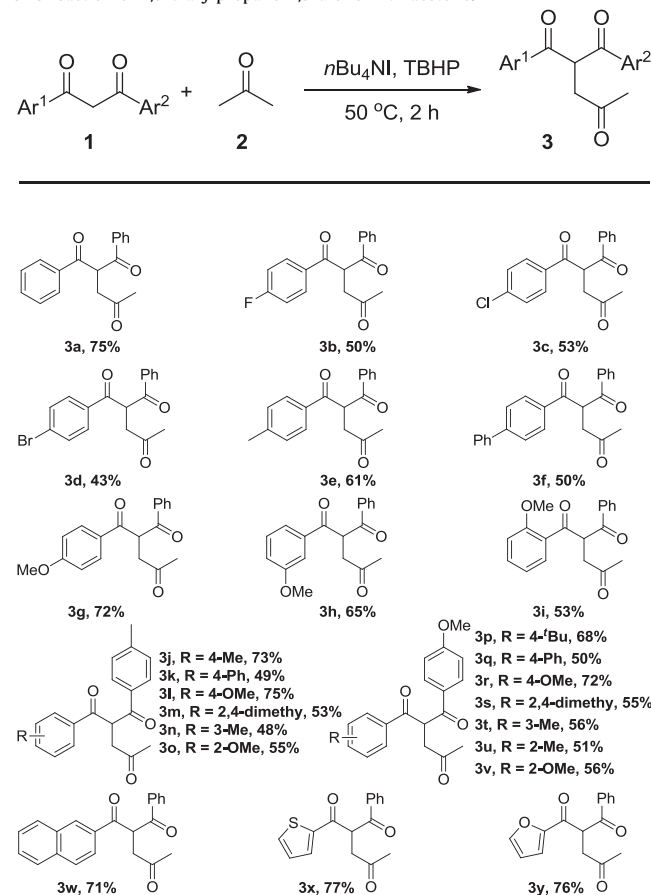
Scheme 1. Different pathways for the synthesis of 1,4-dicarbonyl compounds.

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, NH₄I, NIS, and *n*Bu₄NBr 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 K₂S₂O₈, *di*-*tert*-butylperoxide (TBP), 30% H₂O₂, 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*Bu₄NI 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.

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-

Table 2

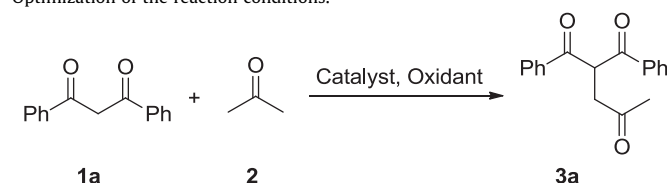
CDC reaction of 1,3-diarylpropane-1,3-dione with acetone.^{a,b}



^a Standard reaction conditions: **1** (0.3 mmol), **2** (3.0 mL), TBHP (0.6 mmol, 70% in water), *n*Bu₄NI (0.06 mmol), 50 °C, 2 h.

^b Yield of the isolated products.

Table 1
Optimization of the reaction conditions.^a



Entry	Oxidant ^b	Catalyst	T (°C)	Yield (%) ^c
1	TBHP	<i>n</i> Bu ₄ NI	100	45
2	TBHP	<i>n</i> Bu ₄ NI	80	61
3	TBHP	<i>n</i> Bu ₄ NI	60	73
4	TBHP	<i>n</i>Bu₄NI	50	75
5	TBHP	<i>n</i> Bu ₄ NI	40	62
6	TBHP	<i>n</i> Bu ₄ NI	30	5
7	TBHP	KI	50	Trace
8	TBHP	NH ₄ I	50	Trace
9	TBHP	NIS	50	0
10	TBHP	<i>n</i> Bu ₄ NBr	50	0
11	K ₂ S ₂ O ₈	<i>n</i> Bu ₄ NI	50	Trace
12	TBP	<i>n</i> Bu ₄ NI	50	Trace
13	H ₂ O ₂ ^d	<i>n</i> Bu ₄ NI	50	Trace
14	<i>m</i> -CPBA	<i>n</i> Bu ₄ NI	50	Trace
15	–	<i>n</i> Bu ₄ NI	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 H₂O₂ 30% in water.

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).

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