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Metal-Free Synthesis of Methylene-Bridged bis-1,3-Dicarbonyl Compounds *via* Oxidative C-C Bond Cleavage of Tertiary Aliphatic Amines

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A metal-free Bu₄NI mediated oxidative reaction utilizing tertiary aliphatic amines and 1,3-dicarbonyl compounds for the synthesis of methylene-bridged bis-1,3-dicarbonyl
10 **compounds has been developed. This reaction involved an unexpected C-C bond cleavage of tertiary aliphatic amines. With this approach, the completely regioselective functionalization of β-carbon on tertiary amines was realized.**

Oxidative functionalization of α-carbon in tertiary amines with
15 subsequent formation of C-C or C-heteroatom bonds is an attractive transformation in organic synthesis.[1] This approach, termed cross-dehydrogenative coupling (CDC) reaction, allows use of less functionalized reagents and often reduces the number of steps to the target molecule.[2] In most cases, N, N-
20 dialkylanilines or tetrahydroisoquinolines are used as coupling partners (Figure 1a), which have proved to be very efficient for the generation of electrophilic iminium ions in the presence of metal catalysts and terminal oxidants.[1,2] These highly reactive iminium ion intermediates can be readily trapped by a variety of
25 nucleophiles (step *a*). In some cases, the coupling product A was subsequently converted to a methylene-bridged compound B through a sequential CDC reaction and C-N bond cleavage (step *b*).[3]
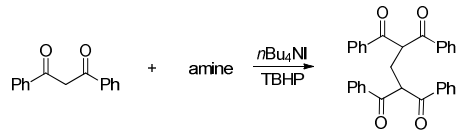
While a variety of synthetic methods are available for
30 oxidative coupling of N-methyl tertiary aromatic amines and the reactions occur regioselectively at α-carbon (Figure 1a), there are relatively few general and practical approaches for the oxidative functionalization of tertiary aliphatic amines, particularly the selective functionalization of β-carbon in non-N-methyl-
35 substituted trialkylamines.[4] Moreover, the current oxidative coupling reactions of tertiary amine require metal catalysts, regardless of whether the reaction occurs at α-carbon or β-carbon. The development of metal-free oxidative coupling reactions with complete regioselectivity and environmental benign oxidants
40 would be highly desirable.

In continuation of our work on the development of green and efficient synthetic methods for the oxidative coupling reactions,[5] we have recently reported quaternary ammonium iodides mediated C3-selective formylation of indoles using N-methyl
45 anilines as the carbonyl source.[5b, 5c] In this study, we demonstrate a Bu₄NI-catalyzed oxidative coupling of tertiary aliphatic amines

with 1, 3-dicarbonyl compounds. This metal-free transformation, involving unprecedented C-C bond cleavage of trialkylamines, provides an efficient access to methylene-bridged bis-1, 3-
50 dicarbonyl compounds, which are valuable precursors for heterocycles and materials synthesis[3c, 6] (Figure 1b).
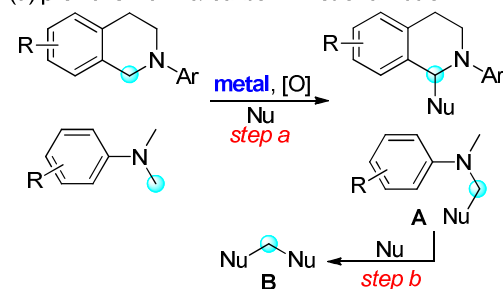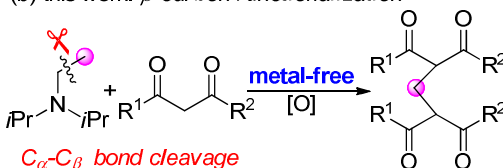
Figure 1. Oxidative functionalization of tertiary amines

Our initial studies focused on Bu₄NI-catalyzed oxidative-
55 coupling of 1,3-diphenyl-1,3-propanedione **1a** with a variety of different tertiary amines in the presence of aqueous *tert*-butyl hydroperoxide (TBHP).[7] All reactions was carried out in 1, 4-dioxane at 25 °C for 24 h or 60 °C for 5 h, and the results were shown in Table 1. The oxidative coupling reaction of **1a** with N,
60 N-dimethylaniline **2a** as the carbon source afforded methylene-bridged product **3a** in 25% yield at 25 °C, while higher temperature led to complex reaction mixtures and compound **3a** was not detected (Table 1, entry 1). The reaction produced **3a** in a moderate yield (48%) at 25 °C when 4-methyl-N, N-
65 dimethylaniline **2b** was used as the amine component, but it also proved to be unsuccessful at 60 °C (Table 1, entry 2). Both N, N-diethylaniline **2c** and N, N-dimethylbenzylamine **2d** were

Table 1. Reactions of **1a** with different amines

Entry	Amine	Yield[a]	Yield[b]
1	PhNMe$_2$ **2a**	25%	0
2	TolNMe$_2$ **2b**	48%	0
3	PhNEt$_2$ **2c**	0	0
4	BnNMe$_2$ **2d**	0	0
5	Et$_3$N **2e**	38%	16%
6	(*i*-Pr)$_2$NEt **2f**	72%	73%
7	(*i*-Pr)$_2$NMe **2g**	0	0
8	Et$_2$NMe **2h**	0	0
9	(*n*-Pr)$_3$N **2i**	3%	9%
10	(*n*-Bu)$_3$N **2j**	trace	10%
11	Cy$_2$NMe **2k**	26%	0
12	Cy$_2$NEt **2l**	38%	59%

Reaction conditions: 1,3-diketone **1a** (0.5 mmol), amine(1.5 mmol), *tert*-butyl hydrogenperoxide (TBHP, 2.0 mmol, 70% aqueous solution), tetrabutylammonium iodide (Bu$_4$NI, 0.1 mmol, 36.9 mg) in 1, 4-dioxane (1 mL).
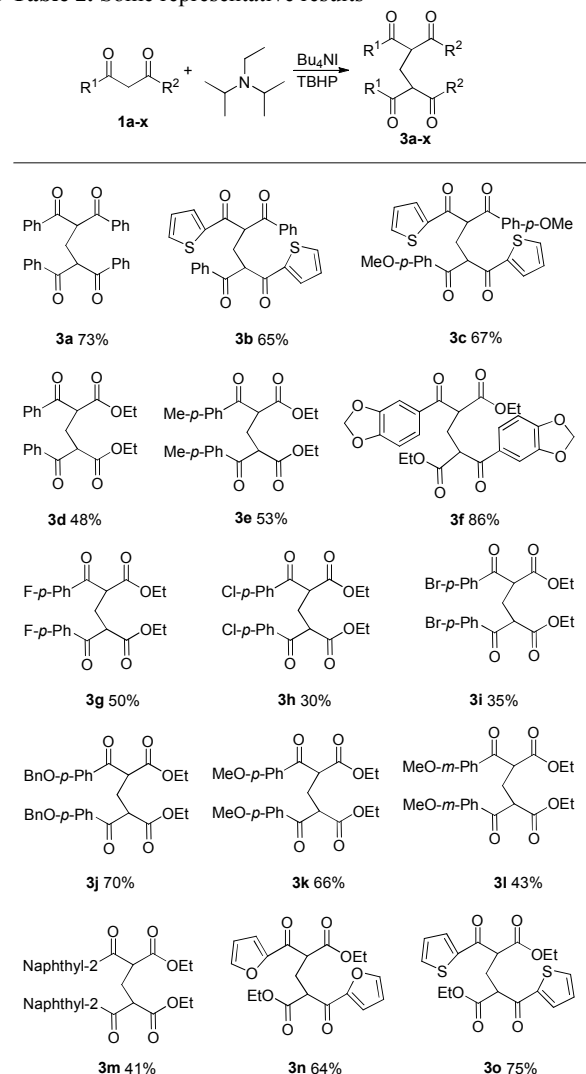[a] Isolated yield based on compound **1a** at 25 °C, 24h.
[b] Isolated yield based on compound **1a** at 60 °C, 5h.
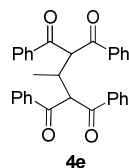
Figure 2. Possible ethyl *bis*-adduct **4e**

ineffective for this transformation at 25 °C and 60 °C (Table 1, entries 3 and 4). We then investigated tertiary aliphatic amines in this oxidative system. To our delight, the reaction of **1a** with triethylamine **2e** generated the product **3a** in 38% and 16% yields, respectively (Table 1, entry 5). It is noted that ethyl *bis*-adduct **4e**, described by Li and coworkers in their iron-catalyzed oxidative reactions (Figure 2),[8] was not detected in the reaction mixture. Further investigation revealed that N, N-diisopropylethylamine **2f** (DIPEA) reacted smoothly with substrate **1a** to give the product **3a** in good yields under different conditions (Table 1, entry 6). In sharp contrast, when N, N-diethylmethylamine **2g** or N, N-diisopropylmethylamine **2h** was subjected to the present oxidative conditions, the corresponding product **3a** was not detected at all, regardless of changes in the reaction temperature or time (Table 1, entries 7 and 8). Very interestingly, tertiary amines with long alkyl chain such as tripropylamine **2i** and tributylamine **2j** could also afford the methylene-bridged product **3a**, albeit in very low yields (Table 1, entries 9 and 10). In light of the success with DIPEA, we envisioned that bulky amines could be beneficial to the reaction. Two sterically hindered tertiary amines **2k** and **2l** were then investigated respectively. In the case of N-cyclohexyl-N-

methylcyclohexanamine **2k**, the desirable product **3a** was formed only when the reaction was

Table 2. Some representative results

Reaction conditions: 1,3-dicarbonyl compound **1** (0.5 mmol), amine (1.5 mmol), TBHP (2.0 mmol, 70% aqueous solution), Bu$_4$NI (0.1 mmol, 36.9 mg) in 1, 4-dioxane (1 mL), 60 °C, 5h, isolated yield based on compound **1**

performed at 25 °C (Table 1, entry 11). In contrast, another N-ethyl substituted amine **2l** afforded **3a** in moderated yields under different conditions (Table 1, entry 12). It is noted that secondary amines are ineffective for the formation of **3a**.[9]

On the basis of the results achieved with DIPEA, a range of 1,3-dicarbonyl compounds **1** was next examined under optimal conditions. In addition to 1,3-diphenyl-1,3-propanedione **1a**, dissymmetrical 1,3-diketones such as **1b** and **1c** were also successfully applied in this transformation (Table 2, **3b** and **3c**). The present oxidative reaction catalyzed by Bu$_4$NI was easily extended to *β*-ketoesters substrates (Table 2, **3d-o**). Aromatic *β*-ketoesters bearing electron-donating (**3e-f**, **3j-l**) or electron-withdrawing groups (**3g-i**) reacted with DIPEA smoothly,

affording the corresponding products in 30-86% yields. However, substrates bearing electron-withdrawing groups gave lower yields.
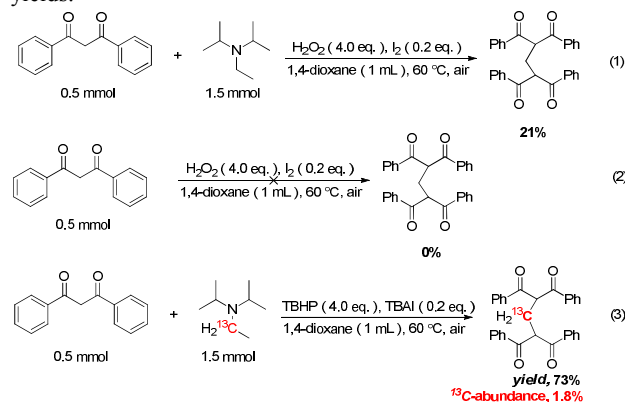
It is noteworthy that heterocyclic 1,3-dicarbonyl compounds, such as thiophene and furan, can be transformed into their corresponding methylene-bridged products in good yields (Table 2, **3b-c** and **3n-o**).

The origin of methylene carbon in product **3a** was the major concern in our mechanistic study. Treatment of **1a** with H_2O_2/I_2 gave **3a** in 21% yield in the presence of DIPEA (eq. 1). In contrast, a similar reaction without DIPEA did not take place at all (eq. 2). Obviously, DIPEA was the methylene donor in the reaction, and the possibility of generating methylene carbon from TBHP and Bu_4NI could be excluded. To further investigate the information of methylene group in **3a**, 1-13C-labeled DIPEA was subjected to the reaction conditions. To our surprise, only 1.8% incorporation at methylene carbon was observed (eq. 3). The results unambiguously established that the carbon atom of methylene group was originated from β-carbon of DIPEA, rather than α-carbon. Clearly, the $C\alpha$-$C\beta$ bond of DIPEA was cleaved, resulting in the formation of methylene-bridged bis-1,3-dicarbonyl compound **3**. Further mechanistic investigation indicated that the formation of product **3a** was suppressed in the presence of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). To our knowledge, alkyl hypoiodite can be generated from alkyl iodide by oxidation and rearrangement.[10] The homolytic cleavage of O-I bond can provide an alkoxyl free radical.[11] This radical could undergo β-scission to give a carbonyl compound and another alkyl iodide.[12] In the present reaction, amides were detected through ^{13}C NMR experiments during the course of the reaction (Figure 1S). On the basis of earlier studies and results obtained above, we propose a plausible reaction mechanism (Scheme 1). First, DIPEA reacts with the oxidant via two single electron transfers (SET) to give iminium ion **A**,[7b] which can isomerize to enamine **B**. At the same time, TBHP efficiently oxidizes iodide (I⁻) to hypoiodous acid or molecular iodine.[7b, 13] Then, the reaction of iodine species with enamine **B** yields iodonium ion **C**,[14] which is subsequently opened at the sterically less hindered carbon by compound 1a to give compound **D**. Oxidation of alkyl iodide **D** with TBHP affords iodoso-compound **E**, which readily rearranges to the hypoiodite **F**.[10] The homolytic cleavage of O-I bond takes place to afford the alkoxy radical **G**,[11] followed by rearrangement through C-C bond scission to provide amide **H** and alkyl iodide **I**.[12] Finally, the resulting alkyl iodide **I** reacts with **1a** by either a nucleophilic substitution or a tandem elimination/addition to afford the product **3a**. In addition, it cannot be excluded that the reaction proceeds *via* a 1,2-dioxetane intermediate, which can be
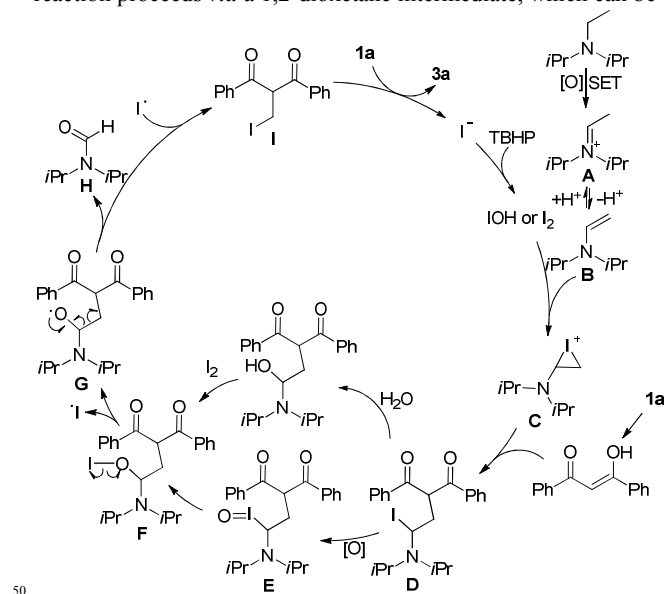
Scheme 1. Proposed reaction mechanism.

generated from enamine and oxidant.[15] The active 1,2-dioxetane then undergoes C-C bond cleavage to produce formaldehyde and amide. The Knoevenagel condensation of formaldehyde with **1a** gives an α, β-unsaturated dicarbonyl compound, which subsequently undergoes Michael addition with remaining excess **1a** to produce the final *bis* adduct **3a**. However, due to the change in color in the reaction, the Nash test[16] is not applicable for detecting formaldehyde.

Conclusions

In conclusion, we have developed a metal-free oxidative coupling reaction mediated by Bu_4NI that allows for the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds from tertiary aliphatic amines and 1,3-dicarbonyl compounds. The β-carbon of DIPEA was converted to the methylene carbon through an oxidative C-C bond cleavage. We believe this C-C bond cleavage of tertiary aliphatic amine holds promise to develop other novel transformations. The methodology is currently under active investigation to explore its detailed mechanism and is also extended to the synthesis of other methylene-bridged *bis* adducts.

Notes and references

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