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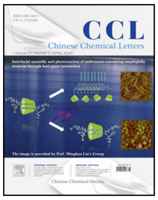

Original article

Visible-light photoredox-mediated oxidation of *N*-methyl tertiaryamines under catalyst free conditions: Direct synthesis of methylene-bridged bis-1,3-dicarbonyl compounds

Xiao-Jun Dai[a], Xiao-Liang Xu[a,*], Dong-Ping Cheng[b], Xiao-Nian Li[a,*]

[a] *Institute of Industrial Catalysis, College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, China*
[b] *College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, China*

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ABSTRACT

Mediated by visible light-induced photoredox catalysis and free of other catalysts, a new and efficient synthesis of methylene-bridged bis-1,3-dicarbonyl derivatives has been developed. A variety of *N*-methyl tertiaryamines and 1,3-dicarbonyl compounds were investigated in this reaction.

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1. Introduction

The catalytic oxidation of sp^3 C–H bond adjacent to a nitrogen atom to form a new carbon–carbon or carbon–hetero bond has been widely applied in organic synthesis [1]. Using the iminium ions generated from the direct oxidation of tertiaryamines *in situ*, Strecter reaction, Mannich reaction, aza-Henry reactions and so on have been successfully realized [2]. Recently, visible light photoredox catalysis aroused great interest due to its green chemistry characteristics [3]. Many metal complexes and organic dyes were frequently used as photocatalysts in photoredox chemistry [4,5]. In particular, several highly efficient chemical transformations were established using Ir or Ru photocatalysts [5]. The photocatalytic oxidation of tertiaryamines is a very important research topic.

Kobayashi reported that a Ru complex, in the presence of visible light, catalyzed the cross oxidative coupling of 1,3-diphenylpropane-1,3-dione and tertiary aliphatic amines to form methylene-bridged bis-1,3-dicarbonyl compounds [6,7]. However, in the course of our study, it was found that without metal photocatalyst, 1,3-diphenylpropane-1,3-dione and *N*,*N*-dimethylcyclohexylamine reacted smoothly to give the methylene-bridged bis-1,3-dicarbonyl compounds even using only visible light, albeit in very low yield. Although the exact mechanism was unclear, the observation may be ascribed to the differences in reaction conditions between Kobayashi's and ours.

2. Experimental

All reactions were carried out without the exclusion of air or moisture. Toluene, cyclohexane, DCE, DCM, DMSO, DMF, EtOAc, 1,4-dioxane and MeCN were analytical reagents and used directly as received. *N*,*N*-dimethylcyclohexylamine, *N*,*N*-dimethylbutylamine, *N*,*N*-dimethylbenzylamine, *N*,*N*-dimethylaniline, *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine, *N*-methyldiisopropylamine, *N*-methyldicyclohexylamine were purchased from the Sigma–Aldrich company and used directly as received. 1,3-Dicarbonyl compounds were prepared according to literature procedures [8]. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ on a Bruker AMX-500 MHz instrument with TMS as an internal standard. Low-resolution MS was obtained using EI or ESI ionization. HRMS was obtained using ESI ionization.

General procedure for the preparation of compounds **2**: to a mixture of 1,3-diphenylpropane-1,3-dione **1a** (0.5 mmol) and 9/1 (v/v) DMSO/H_2O (2 mL) in a 10 mL two-necked round-bottom flask was added *N*-methyl-dicyclohexanamine (0.25 mmol). The resulting mixture was stirred under 1 atm of O_2 (balloon) for 24 h at ambient temperature under the irradiation by three 45 W white fluorescent bulbs (Arrow BHSL 45) at a distance of 5 cm. Then the reaction mixture was washed three times with dilute hydrochloric

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* Corresponding authors.
E-mail addresses: xuxiaoliang@zjut.edu.cn (X.-L. Xu), xnli@zjut.edu.cn (X.-N. Li).

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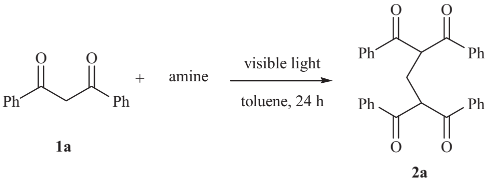
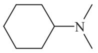
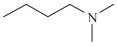
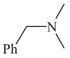
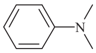
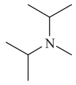
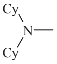
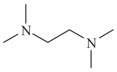
Table 1
Evaluation of tertiaryamines as methylene donors.[a]

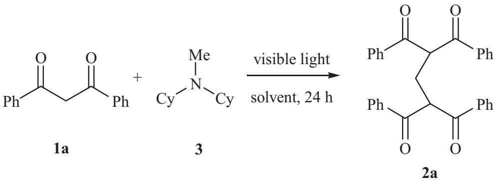


Entry	Amine	Yield (%)[b]
1		10
2		9
3		4
4		<5
5		5
6		15
7		7

[a] Reaction conditions: 1,3-diketone **1a** (0.5 mmol), amine (0.6 mmol), in toluene (2 mL) at r.t. for 24 h under irradiation by a 45 W fluorescent lamp at a distance of 5 cm.

[b] Isolated yield based on **1a**.

Table 2
Solvent screening.[a]

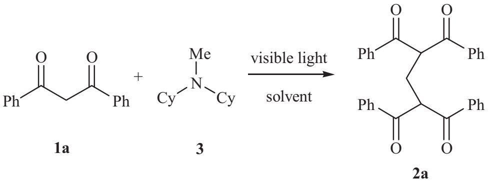


Entry	Solvent	Yield (%)[b]
1	Toluene	12
2	Cyclohexane	26
3	DCM	17
4	DCE	18
5	DMSO	70
6	DMF	20
7	EtOAc	22
8	1,4-Dioxane	30
9	MeCN	32

[a] Reaction conditions: 1,3-diketone **1a** (0.5 mmol), amine **3** (0.6 mmol), in solvent (2 mL) at r.t. for 24 h under irradiation by a 45 W fluorescent lamp at a distance of 5 cm.

[b] Isolated yield based on **1a**.

Table 3
Solvent and light source screening.[a]



Entry	Solvent	Light source	Time (h)	Yield (%)[b]
1	DMSO	Three 45 W fluorescent lights	12	74
2	H_2O/DMSO (1:1)	Three 45 W fluorescent lights	20	86
3	H_2O	Three 45 W fluorescent lights	23	89
4	DMSO	Two 45 W fluorescent lights	24	78
5	DMSO/H_2O (9/1)	Two 45 W fluorescent lights	35	90
6[c]	DMSO	Two 45 W fluorescent lights	20	82
7[d]	DMSO	Two 45 W fluorescent lights	30	80
8	DMSO	Dark	24	n.r.
9	H_2O	Dark	24	n.r.

[a] Reaction conditions: 1,3-diketone **1a** (0.5 mmol), amine **3** (0.6 mmol), in solvent (2 mL) at r.t. for 24 h under irradiation by visible light at a distance of 5 cm under air until otherwise noted.

[b] Isolated yield based on **1a**.

[c] Under O_2.

[d] Solvent was dried, under N_2.

acid. Purification was done by column chromatography on silica gel (200–300 mesh) using petroleum ether and ethyl acetate (5:1–10:1) as the eluent to give the pure product **2a**.

Synthesis and characterization of all products are described in Supporting information.

3. Results and discussion

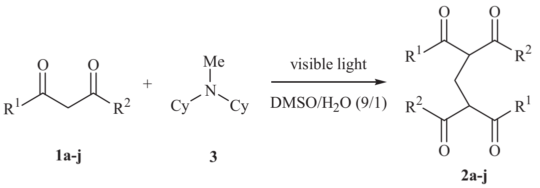
Our initial studies focused on the visible light-mediated reaction of 1,3-diphenylpropane-1,3-dione **1a** and *N*,*N*-dimethylcyclohexylamine. Unfortunately, the reaction proved to be very sluggish and the starting material could not be fully consumed within 30 h (Table 1, entry 1). Various *N*-methyl tertiaryamines as potential methylene donors were examined. To our disappointment, all aliphatic *N*-methyl tertiaryamines tried led to the desired product with very low yields. When *N*,*N*-dimethylaniline was introduced, the reaction resulted in a complex mixture (Table 1, entry 4).

However, it was interesting to find that the photocatalytic reaction of *N*-methyldicyclohexylamine was significantly faster, compared with other *N*-methyl tertiaryamines. This reaction could occur in all solvents tried. It was gratifying that, in contrast to other solvents (Table 2), the desired product was obtained in 70% isolated yield after 24 h using DMSO as a solvent (Table 2, entry 5).

Based on these results, various conditions were evaluated. It was found that strong light emission could accelerate the reaction. Interestingly, use of H_2O as a solvent also resulted in high yields (Table 3, entry 3). The mixed solvent of DMSO and H_2O gave reasonable result as well. Importantly, no conversion was observed when the reaction was conducted in the dark (Table 3, entries 8 and 9). Under O_2, the reaction was more rapid than under air, while a very slow background reaction was observed under N_2. These observations indicated that oxygen was essential in this reaction.

Under the optimized conditions, the scope of this photon-mediated coupling reaction was investigated. In general a variety of different dicarbonyl nucleophiles (Table 4), including aryl and alkyl 1,3-diketones, *β*-ketoesters and 1,3-diester, could react with *N*-methyl-dicyclohexylamine. Substrates containing substituents like Me and OMe on the aryl rings underwent the reaction smoothly (Table 4, entries 2 and 3). For substrates with halogenated phenyl rings, a fluoro appeared to be more favorable than a bromo and some unidentified compounds formed in certain

Table 4
Substrate scope.[a]



Entry	Substrate	R^1	R^2	Product	Time (h)	Yield (%)[b]
1[a]	**1a**	Ph	Ph	**2a**	24	91
2	**1b**	Ph	4-MeO-C_6H_4	**2b**	24	80
3	**1c**	Ph	4-Me-C_6H_4	**2c**	24	75
4	**1d**	Ph	4-F-C_6H_4	**2d**	17	66
5	**1e**	Ph	4-Br-C_6H_4	**2e**	24	26
6	**1f**	Ph	3-thienyl	**2f**	24	67
7	**1g**	Ph	Me	**2g**	38	48
8	**1h**	Ph	OEt	**2h**, **2h′**[c]	40	78
9	**1i**	OEt	OEt	**2i**	48	54
10	**1j**	Me	OEt	**2j**	39	15

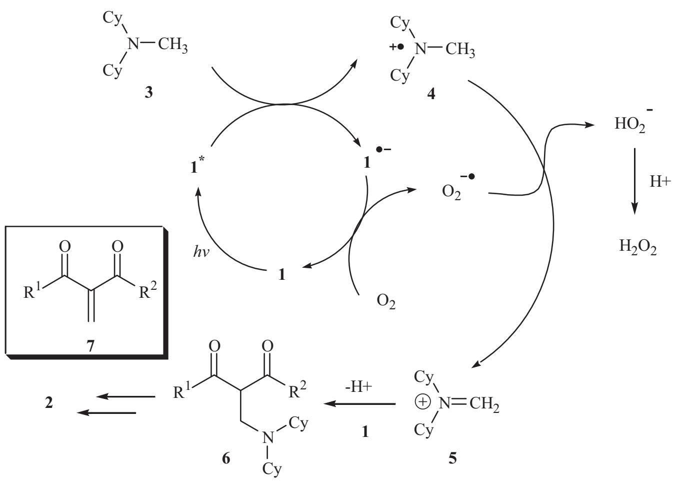
[a] Reaction conditions: 1,3-diketone **1a** (0.5 mmol), amine **3** (0.3 mmol), in DMSO/H_2O (9/1, 2 mL) at r.t. under irradiation by two 45 W white fluorescent lamps under 1 atm of O_2 or air balloon; please see ESI for details.

[b] Isolated yield based on **1**.

[c] de-ethoxycarboxylation product.

reactions (Table 4, entries 4 and 5). Substrates with alkyl ketone moieties gave lower yields of the product (Table 4, entry 7). When β-ketoesters were utilized as substrates, the reactions resulted in modest yields (Table 4, entries 8–10). In the case of ethyl 3-oxo-3-phenylpropanoate **1h**, the desired product **2h** was obtained in 39% yield, accompanied by 39% of a de-ethoxycarboxylated product **2h′**.

A plausible mechanism for the reaction is proposed in Scheme 1. We reasoned that the 1,3-dicarbonyl compounds are effective photo mediators. Upon irradiation, **1** is excited providing **1***, which is then reductively quenched by **3** to produce a radical anion of **1** and amine radical cation **4** *via* a single electron transfer process. **1** is regenerated with the assistance of dioxygen, and the resulting oxygen radical anion abstracts a proton in the methyl group in radical cation **4** to generate the iminium intermediate **5**. Subsequently, nucleophilic trapping of **5** with **1** results in the oxidative coupling product **5**. The desired product **2** is formed by either a direct nucleophilic substitution reaction or a tandem Cope elimination and Michael addition *via* intermediate **7**.



Scheme 1. Proposed reaction mechanism.

4. Conclusion

In summary, without any other photocatalyst, we have developed a useful protocol for the synthesis of methylene-bridged bis-1,3-dicarbonyl compounds in aqueous media using visible light photoredox catalysis. In contrast to the similar reactions reported in recent literature, the mechanism of this reaction needs more experimental studies. Further investigations into the mechanism of this reaction under visible light are currently underway.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.01.021.

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