



Metal-free visible light driven synthesis of tetrahydroquinoline derivatives utilizing Rose Bengal



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ABSTRACT

The visible-light driven reaction for the synthesis of tetrahydroquinoline derivatives via tandem radical cyclization of *N,N*-dimethylanilines with 2-benzylidenemalononitriles has been developed. Corresponding products were obtained with yields of up to 74% under mild conditions by using Rose Bengal as a triplet sensitizer, which is inexpensive, environmentally-friendly and easily acquired. This work demonstrates the potential benefits of Rose Bengal for the production of tetrahydroquinoline derivatives.

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1. Introduction

Visible light is an abundant, readily available and renewable clean energy. Its application for organic synthesis has received great attention from the chemical workers.¹ However, since most of organic molecules cannot directly absorb visible light, thereby they require a medium to play this important role in the reaction system.² Recently, MacMillan,³ Yoon,⁴ Stephenson,⁵ et al. have demonstrated that metal complexes, such as ruthenium (II) and iridium (III), have good photocatalytic properties, which make visible light widely used in the organic synthesis. Although numerous photocatalysts based on Ru or Ir have been investigated during the past decades, these complexes are expensive and potentially toxic. Meanwhile, organic dyes possess the distinguishing qualities of high extinction coefficients in the visible-light range, long excited-state lifetimes, and low cost, which make these organic photosensitizers desirable for photoredox transformations. Therefore, more and more organic dyes have been used in photocatalytic reactions.⁶ For example, the economical Rose Bengal has been employed in decarboxylative amination,⁷

alkylation reaction,⁸ cycloaddition reaction,⁹ thiocyanation reaction¹⁰ and formylation reaction.¹¹ Taking into consideration of the advantages of Rose Bengal as the photosensitizer, we decided to further explore the application of Rose Bengal in organic synthesis.

Tetrahydroquinoline derivatives are a class of very important compounds, and the fragments of tetrahydroquinoline moiety are also vital building blocks generally found in many natural products and bioactive molecules.¹² Due to their ubiquitous distribution in natural products and medicinal agents, tetrahydroquinolines have become important synthetic targets for chemists.¹³ The tandem cyclization of free radical and unsaturated olefin is widely used in organic synthesis.¹⁴ The synthesis of tetrahydroquinoline derivatives by cyclization of benzylidenemalononitriles with α -amino radical has been reported. In 2011, Miura¹⁵ et al. used CuCl_2/O_2 at 60 °C to obtain the corresponding tetrahydroquinolines in moderate yields. In 2013, Rueping group¹⁶ reported the photoinitiated cycloaddition reactions of *N*-methylanilines with 2-benzylidenemalononitriles for the synthesis of tetrahydroquinolines using $[\text{Ir}(\text{ppy})_2\text{bpy}]\text{PF}_6$ under blue LED, and yields of up to 71% were obtained. In 2016, Bissember¹⁷ et al. used $[\text{Cu}(\text{dap})_2]\text{Cl}$ as a photosensitizer under green LED to obtain the tetrahydroquinolines in moderate yields. However, the catalysts used in these reports are metals including noble metal and costly ligands, and the photocatalytic methods used high-intensity monochromatic LEDs as light

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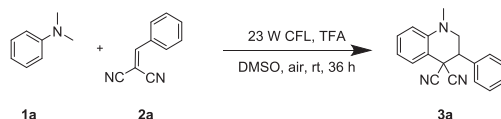
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source. Taking into account the importance of tetrahydroquinolines, the exploration of more economical, environmentally-friendly and easily acquired catalysts for the synthesis of tetrahydroquinolines still has greatly practical value. Herein, we report a metal-free visible light driven synthesis of tetrahydroquinoline derivatives from 2-benzylidenemalononitriles and substituted anilines, in which Rose Bengal was used as a triplet sensitizer and the compact fluorescent lamp (CFL) as light source. This process might provide a promising alternative protocol for the synthesis of tetrahydroquinoline derivatives.

2. Results and discussion

The tandem radical cyclization of *N,N*-dimethylaniline (**1a**) with 2-benzylidenemalononitrile (**2a**) under air condition was chosen as a model reaction. Firstly, fluorescence experiments with **1a**, **2a** and Rose Bengal were performed. **1a** and **2a** could not absorb light in the visible light region while Rose Bengal exhibited a strong absorption in the visible light region at $\lambda = 563$ nm ($\epsilon = 122633$ L mol⁻¹cm⁻¹) in DMSO (the spectrum shown in the Supporting Information). Then, some control experiments were conducted. As shown in Table 1, in the presence of Rose Bengal (3 mol%) and under irradiation of a 23 W household CFL ($\lambda = 400$ –720 nm) in DMSO for 36 h,¹⁸ the model reaction gave product (**3a**) in 55% yield (Table 1, entry 1). To verify both visible light and Rose Bengal are necessary in this catalytic process, control experiments were conducted. In the absence of both visible light and Rose Bengal, or either one of them, only trace amount of product (**3a**) could be observed (Table 1, entries 2–4). Those results indicated that both Rose Bengal and visible light are indispensable for the model reaction. When the model reaction was conducted under N₂ instead of air, the product was only obtained in 7% yield (Table 1, entry 5), showing that O₂ was involved in the reaction process. To get an insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, was added to the reaction system, which completely inhibited the reaction (Table 1, entry 6). This revealed that the reaction must proceed through a radical process. Taking into consideration of the possibility that Rose Bengal can generate singlet oxygen through energy transfer,^{11,19} 1,4-diazabicyclo[2.2.2]octane (DABCO) as a quencher of ¹O₂ was added to the model reaction. Only trace amount of product was observed in the presence of DABCO (Table 1, entry 7), indicating that singlet oxygen participated in the reaction process.

Table 1
Control experiments.^a



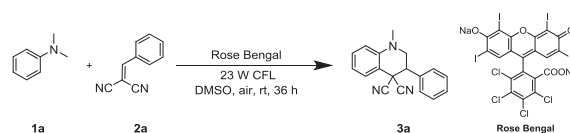
Entry	Visible light	Rose Bengal (3 mol%)	TEMPO (0.6 mmol)	DABCO (0.6 mmol)	Yield (%) ^b
1	+	+	–	–	55
2	–	–	–	–	trace
3	+	–	–	–	trace
4	–	+	–	–	trace
5 ^c	+	+	–	–	7
6	+	+	+	–	trace
7	+	+	–	+	trace

^a Reaction conditions: a mixture of **1a** (0.3 mmol), **2a** (0.2 mmol), Rose Bengal (3 mol%) and TFA (1 eq. relative to **2a**) in DMSO (1.0 mL) was irradiated using a 23 W CFL in air for 36 h.

^b Yield of the isolated product.

^c Under N₂.

Table 2
Influence of acids.^a



Entry	Acid	Acid equivalents (relative to 2a)	Yield (%) ^b
1	None	–	37
2	TFA	2	52
3	HCOOH	2	34
4	TsOH·H ₂ O	2	22
5	TFA	0.5	47
6	TFA	1	55
7	TFA	1.5	53
8	TFA	2.5	50

^a Reaction conditions: a mixture of **1a** (0.3 mmol), **2a** (0.2 mmol), Rose Bengal (3 mol%) and acid in DMSO (1.0 mL) was irradiated using a 23 W CFL in air for 36 h.

^b Yield of the isolated product.

Next, we optimized the reaction conditions in terms of solvent, molar ratio, catalyst dosage, wattage of lamp and solvent volume. Since solvent effect also affects the rate of free radical reaction,²⁰ we firstly screened the solvents. DMSO was found to be the best solvent among DMSO, MeCN, MeOH, THF, toluene, CHCl₃, CH₂Cl₂, 1-methyl-2-pyrrolidinone and cyclohexane (Table S1). Then, we investigated other reaction conditions. To conclude, the optimized reaction conditions for a 0.2 mmol scale reaction were found to consist of the following: 1 mL of DMSO, a molar ratio of **1a/2a** = 3:2, a Rose Bengal dosage of 3 mol%, and a fluorescent lamp wattage of 23 W (For more details, please see the Supporting Information Tables S1–S4).

Some literature revealed that acid additive could control formation rate of α -amino radical through affecting the balance between free amine and its corresponding (unreactive) ammonium salt.^{17,21} Therefore, the species of acid additive were investigated. Among the tested acid additives, TFA could promote the reaction significantly, giving a yield of 52% (Table 2, entry 2). When formic acid and *p*-toluenesulfonic acid were used, very low yields were obtained (Table 2, entries 3 and 4). Moreover, influence of the TFA loading was investigated. When 1 equivalent of TFA relative to **2a** (0.2 mmol) was employed, the best yield of 55% was received (Table 2, entry 6). Therefore, 1 equivalent of TFA relative to **2a**

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