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Chlorophyll-catalyzed tandem oxidation /[3+2] cycloaddition reactions toward the construction of pyrrolo[2,1-a]isoquinolines under visible light

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ABSTRACT

Chlorophyll as a green, cheap, and affordable natural pigment was used in the one-pot synthesis of pyrrolo[2,1-a] isoquinoline scaffold under visible light. This photocatalytic approach has handled oxidation/[3 + 2] cycloaddition/aromatization cascade reaction using air as the final oxidant. Under this condition, a vast variety of *N*-substituted tetrahydroisoquinolines were treated with dipolarophiles in good to excellent yields.

1. Introduction

After a great milestone in 2008 [1,2], the photoinduced electron transfer (PET) process was extensively followed as an efficient, environmentally benign, and versatile strategy to construct the complex scaffolds under visible light [3,4]. Thus, in recent years tremendous advances in the field of visible-light-driven photoredox catalysis have been achieved. In this context, photocatalytic reaction based on inorganic complexes, e.g., Ru(II) and Ir (III) polypyridine turned out to be robust alternative tools in current synthetic chemistry [5–7].

Chlorophyll has known as the most abundant natural photocatalyst in our world which triggers the PET process toward the synthesis of carbohydrates in photosynthesis. Hence, green leave is an efficient factory for solar energy conversion by using this natural inorganic complex [8,9]. Up to now, six types of chlorophylls (a-f) have been known which chlorophyll-a is the most abundant type of chlorophyll in nature [10]. Inspired by photosynthesis in green plants, vast efforts on artificial photosynthesis and solar fuels are going on [11]. Moreover, chlorophyll as a safe, cheap, and natural pigment has been applied in modern luminescence materials, cosmetic, food, and textile industry [9]. However, there are just two reports to survey the potential of this natural photosensitizer in the organic transformations. First, Boyer et al. reported the PET process for polymerization *via* chlorophyll, in 2015 [11]. Then, He et al. developed the chlorophyll-catalyzed synthesis of tetrahydroquinolines through triplet energy transfer under visible light, in 2017 [12]. Hence, it is highly demanded to explore the potential of this green and efficient photosensitizer in the more organic transformations.

Although Ru (II) and Ir (III) polypyridine are versatile effective photocatalysts, some drawbacks such as toxicity, high price ([Ru(bpy)$_3$]Cl$_2$; 1 kg ~ 122000 USD, from Sigmaaldrich website) and difficult separation are associated with Ru(II), Ir (III) polypyridine photocatalysis. In comparison with these inorganic complexes, chlorophyll is cheap (1 kg ~ 45-60 USD; chlorophyll extracted powder, the price is from commercial website), safe, biodegradable, and abundant natural inorganic complex. Considering some environmental problems associated with using organic dyes [13] (e.g. eosin Y: 25 g = 168.0 USD and methylene blue: 25 g = 78.0 USD, www.sigmaaldrich.com), chlorophyll as natural pigment might also be a low-price alternative. Redox potentials and selected photophysical properties of these photocatalysts have been summarized in Fig. 1.

Compounds containing pyrrolo[2,1-a]isoquinoline have been found to be very prominent building blocks in synthetic chemistry and natural compounds due to several biological activities like anti-depressant [17] and cardiotonics [18–20]. Other alkaloids containing this scaffold, marine lamellarin alkaloids, shows prominent pharmacological properties. For example, lamellarin I and lamellarin K exhibit the competency of antitumor activities [21,22] and lamellarin α-20-sulfate inhibits HIV integrase selectively [23,24]. In this regard, some preparation methods of pyrrolo[2,1-a]isoquinoline scaffolds have been established so far [25,26]. Early methods went through Diels-Alder cycloaddition, oxidative dimerization, and double-barreled Heck cyclization [27]. Later, due to facility and atom economy, a tandem reaction based on dipolar [3 + 2] cycloadditions between azomethines and active alkenes was established as an effective straightforward strategy for the rapid synthesis of pyrrolo

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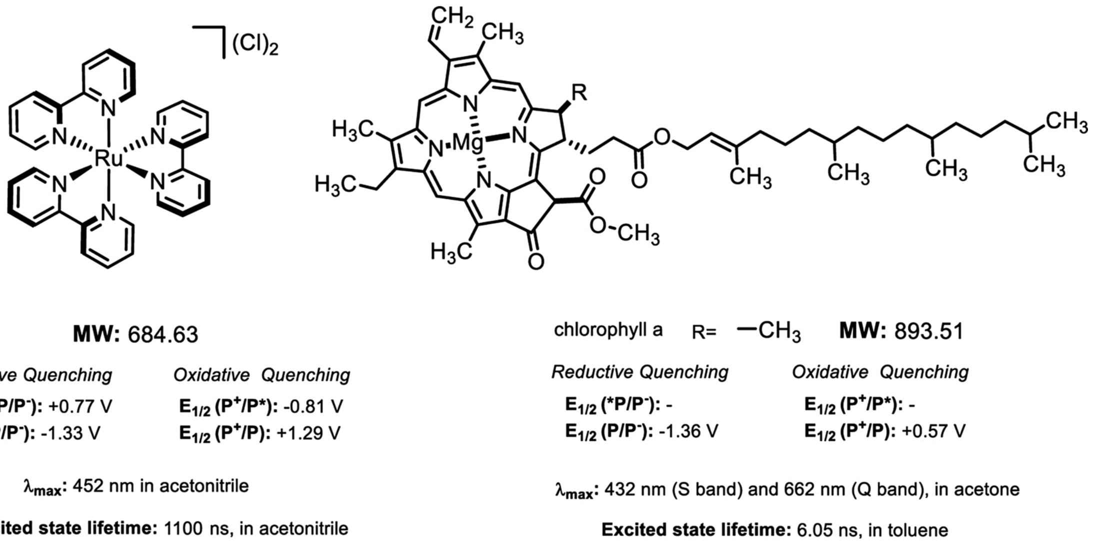


Fig. 1. Redox potentials (vs the saturated calomel electrode in acetonitrile) and selected photophysical properties of $[Ru(bpy)_3](Cl)_2$ [3] and chlorophyll-a [14–16].

[2,1-a]isoquinoline scaffolds [28–30]. Xiao's group developed the first visible-light-driven dipolar [3 + 2] cycloadditions report for the synthesis of pyrrolo[2,1-a]isoquinoline *via* $[Ru(bpy)_3]Cl_2$ as photosensitizer [31]. Then, some more photosensitizers namely C60-Bodipyhybrids [32], iodo-Bodipy immobilized on the support [33] and two organic dyes [27,34] were investigated in this methodology. These protocols proceeded through single electron transfer (SET) between photoredox catalyst and *N*-substituted tetrahydroisoquinoline followed by the stoichiometric addition of extra oxidants such as *N*-bromosuccinimide (NBS) which they were usually required to aromatize the pyrrolidines to the pyrroles.

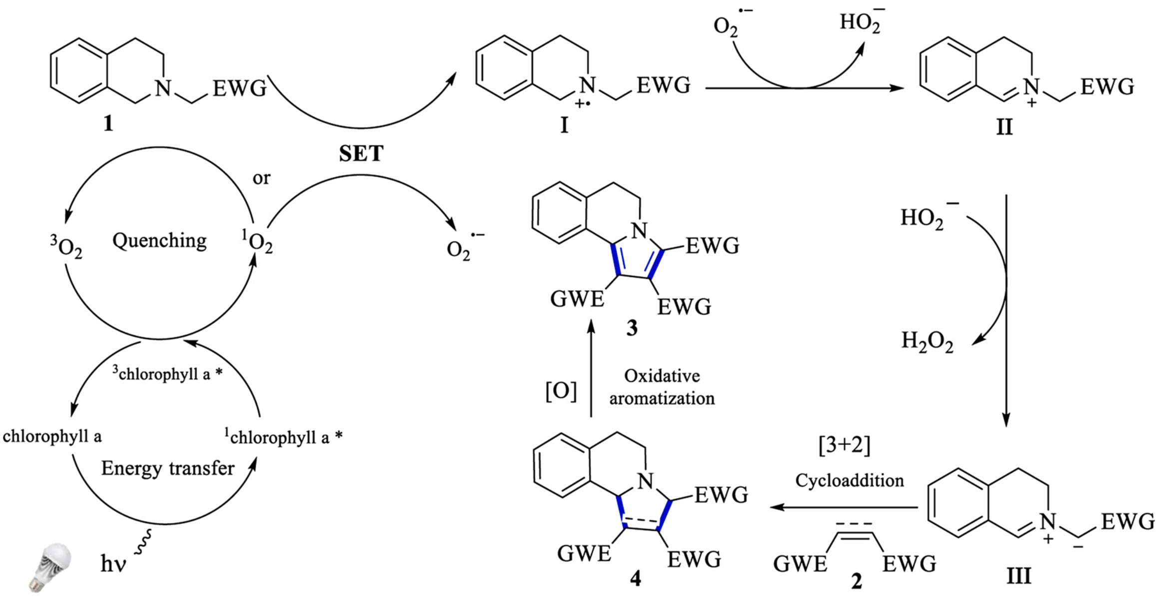
2. Experimental

2.1. Materials and methods

Unless otherwise noted, starting materials were purchased from Acros and Merck chemical companies and used without further purification. UV-Vis absorptions were recorded using a Hewlett-Packard Model 8452A diode-array spectrophotometer. Elemental analysis was performed on a 2400 series PerkinElmer analyzer. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ using Bruker Avance DPX FT 250 MHz and Bruker Ultrashield 400 MHz spectrometry respectively, with TMS as an internal standard (multiplicity: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet), coupling constants: Hz). (FT-IR) spectra were obtained by a Shimadzu FT-IR 8300 spectrophotometer. The products purified by hand-made column chromatography: short columns of SiO_2 60 (230–400 mesh) in glass columns (1.0 –1.5 cm); 10 –20 g of SiO_2 per nearly 0.4-gram crude mixture. The reactions were monitored by thin-layer chromatography (TLC): silica gel PolyGram SIL G/UV 254 plates.

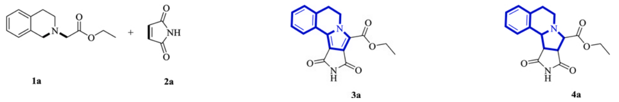
2.2. Extraction of chlorophyll-a

Chlorophyll-a extracted from leaves of spinach according to the reported procedure [35,36]. First, fresh leaves of spinach (50 g) were washed with cold water, cut and crushed. Then, it was extracted with 25 mL of 80 % aqueous acetone (four times). The combined extracts (100



Scheme 1. The proposed reaction mechanism.

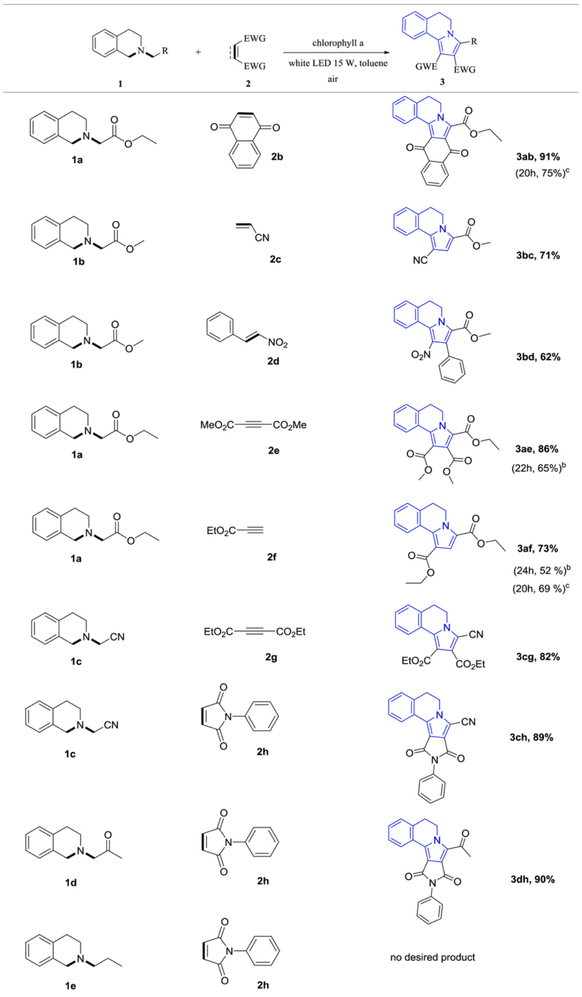
Table 1
Screening optimization condition for the reaction between 1a and 2a^{a}.



Entry	Solvent	Yield 3a/4a (%)[b]
1	CH3CN	trace/0
2	Acetone	12/0
3	THF	14/0
4	EtOAc	9/0
5	CHCl3	0/0
6	EtOH	0/0
7	DMF	26/0
8	toluene	69/0
9[c]	toluene	86/0
10[d]	toluene	87/0
11[e], [c]	toluene	85/0
12[f], [c]	toluene	92/0
13[g], [c]	toluene	0/0
14[h]	toluene	trace/0
15[i], [c]	toluene	0/0
16[j] [f]	toluene	74

[a] Reaction conditions: Dihydroisoquinoline ester 1a (1.0 mmol), maleimide 2a (1.0 mmol) and photocatalyst (2.0 mg) in solvent (4.0 mL) was irradiated by 15 W white LED for 30 h at room temperature. [b] Isolated product. [c] 4.0 mg of photocatalyst [d] 8.0 mg of photocatalyst. [e] 1.0 mmol 1a and 1.2 mmol 2a. [f] 1.2 mmol 1a and 1.0 mmol 2a. [g] In the dark. [h] Without chlorophyll-a. [i] The degassed reaction mixture was carried out under Ar. [j] 8.0 mg of chopped and crushed spinach leaves.

Table 2
The scope of oxidation/[3 + 2] cycloaddition/aromatization cascade reaction^{a}.



[a] *Reaction condition*: Dihydroisoquinoline 1 (1.2 mmol), dipolarophile 2 (1.0 mmol) and chlorophyll-a (4.0 mg) in toluene (4.0 mL) were irradiated by 15 W white LED for 30 h at rt, the yield of the isolated product. [b] The value in the bracket is belonged to $[Ru(bpy)_3]Cl_2$-catalyzed [3 + 2] cycloaddition reaction [31]. [c] The value in the bracket is belonged to methylene blue-catalyzed [3 + 2] cycloaddition reaction [27].

mL) were concentrated under vacuum to about 25 mL and washed with 10 mL of hot petroleum ether (three times). The aqueous acetone phase, containing carotenes and other plant constituents, was removed and thrown away. The petroleum ether phase was washed with H_2O: MeOH (65:35 v/v) and it was loaded on a silica gel column. The column was eluted with petroleum ether and then with petroleum ether: n-propanol (95:5 v/v) to afford chlorophyll-*a.*

2.3. Typical Procedure for synthesis of Pyrrolo[2,1-a]isoquinoline derivatives

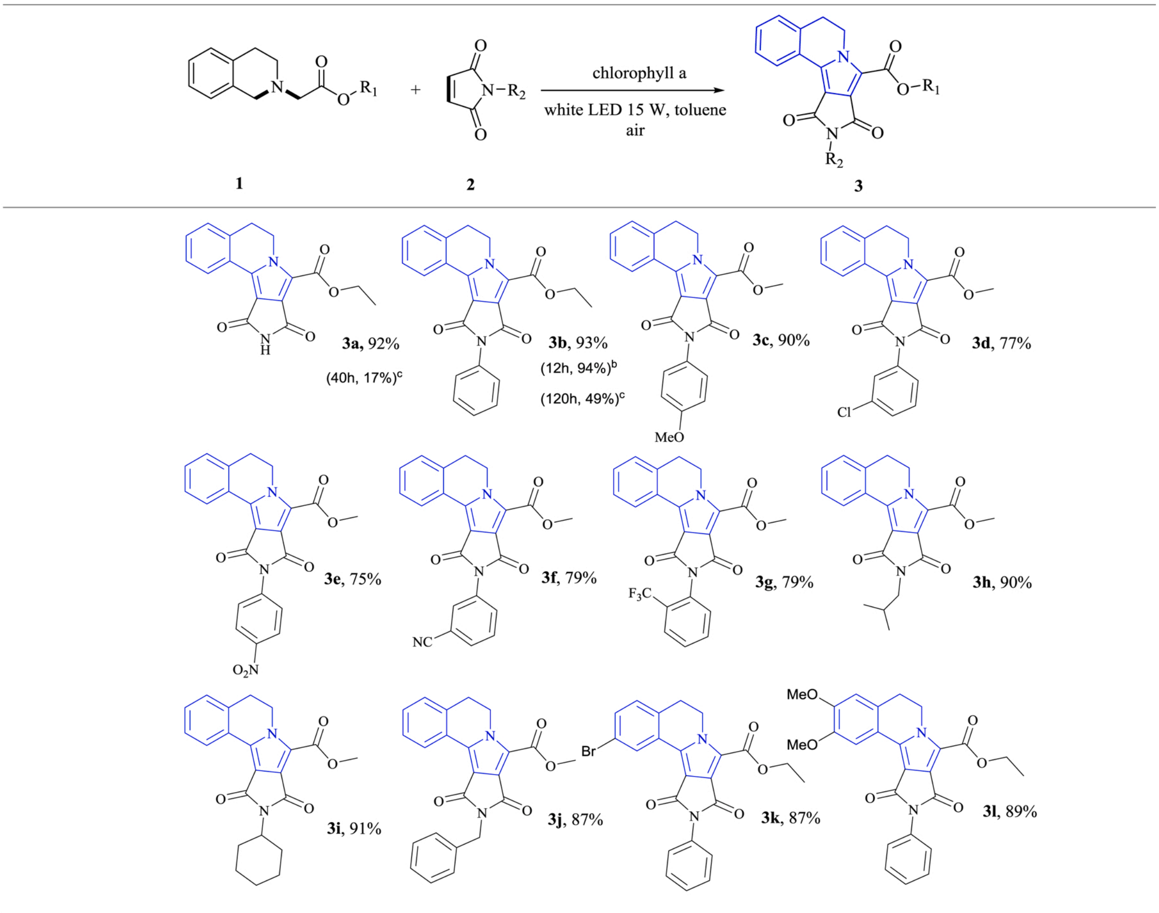
In a test tube, a mixture of dihydro isoquinoline ester 1a (0.263 g, 1.2 mmol), maleimide 2a (0.097 g, 1 mmol), and chlorophyll-a (4.0 mg) in toluene (4.0 mL) was irradiated under air atmosphere by 15 W white LED ($\lambda > 410$ nm, distance app. 9.0 cm) at rt. The reaction was monitored by TLC and after completion (30 h), the reaction mixture concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as eluent (9:1).

3. Results and discussion

We envisioned to survey the merit of chlorophyll in this dipolar [3 + 2] cycloadditions and study whether chlorophyll as natural pigment would afford the criteria of green chemistry such as the tolerance of a vast range of functional groups, low waste, the decrease in the reaction time and catalyst amount, and low toxicity. Chlorophyll is known as a good producer of singlet dioxygen through triplet energy transfer (TET) [37,38]. So, based on related works [12,31], we hypothesized a plausible mechanism to handle the reaction as shown in Scheme 1. After light irradiation, chlorophyll-a becomes excited (chlorophyll-a*) and this photosensitizer transfers its energy to the ground state of molecular oxygen, generating the singlet oxygen. Then, the singlet oxygen oxidizes *N*-substituted tetrahydroisoquinoline (1) through the SET process to generate a radical cation (I) followed by two steps affording azomethine ylide (III). Subsequently, azomethine ylide (III) undergoes the [3 + 2] cycloaddition with dipolarophile to afford pyrrolidine cycloadduct (4), followed by oxidation/aromatization, the corresponding pyrrolo[2,1-a] isoquinoline derivative (3) was provided. Not surprisingly, *in situ* generated singlet oxygen or peroxide are highly likely to become involved in the last step of this reaction.

Our study commenced with the extraction of chlorophyll-a from spinach leaves as cheap and renewable feedstock. Chlorophyll-a was extracted and mostly purified by column chromatography according to the previous reports [35] (See SI, UV-Vis spectrum). Next, one-pot synthesis of pyrrolo [2, 1-a] isoquinoline was examined through the treatment between dihydro isoquinoline ester 1a and maleimide 2a under visible light (Table 1). Accordingly, when the reaction was conducted in CH_3CN, EtOH, and $CHCl_3$, no desired products were found after 30 h under visible light (entries 1, 5, and 6). However, the reaction exhibited slight progress in acetone, THF, and EtOAc up to 14 % of dihydropyrrolo[2,1-a]isoquinoline 3a (entries 2, 3, and 4) in the presence of atmospheric dioxygen as the terminal oxidant. Then, the reaction was performed in DMF and delivered 26 % of 3a without any 4a. Delightfully, the reaction in toluene showed significant improvement in the desired product up to 69 % of 3a, upon isolation (entry 8). In comparison with most previous reports, this chlorophyll-a-catalyzed dipolar

Table 3
The scope of oxidation/[3 + 2] cycloaddition/aromatization cascade reaction[a].



[a]*Reaction condition*: Dihydroisoquinoline 1 (1.2 mmol), dipolarophile 2 (1.0 mmol) and chlorophyll-a (4.0 mg) in toluene (4.0 mL) were irradiated by 15 W white LED for 30 h at rt, the yield of the isolated product. [b]The value in the bracket is belonged to $[Ru(bpy)_3]Cl_2$-catalyzed [3 + 2] cycloaddition reaction [31]. [c] The value in the bracket is belonged to methylene blue-catalyzed [3 + 2] cycloaddition reaction [27].

[3 + 2] cycloadditions did not need to add any extra oxidant to aromatize the pyrrolidine ring (4a). When the photocatalyst amount was enhanced to 4.0 mg and 8.0 mg, the reaction yielded 86 % and 87 % of 3a products, respectively (entries 9 and 10). Besides, when we changed the molar ratio of substrates (1.2 equiv. and 1.0 equiv.) the yield of 3a increased to 92 %, upon isolation (entries 11 and 12). So, 4.0 mg of chlorophyll-a and 1.2 equiv. of 1a substrate were selected as optimum values. Besides, when the reaction was separately carried out in the absence of the visible light, chlorophyll-a, and dioxygen, corresponding products were not observed (entries 13-15). Hence, photocatalyst, light, and molecular oxygen were critical for this process. Interestingly, when the reaction was performed by using chopped and crushed spinach leaves, 74 % of the target product was isolated (entry 16). However, to remove the effect of other plant constituents, the extracted chlorophyll was used in the next reactions as photocatalyst.

To survey the synthetic potential of this procedure, we then embarked upon the investigation of the generality and scope under our optimized reaction condition (Table 2). First, we examined other dipolarophiles in this oxidation/[3 + 2] cycloaddition/aromatization cascade reaction employing 1,4-anthraquinone, acrylonitrile, nitroolefin, activated alkynes, and maleimides. This procedure appeared completely general concerning various dipolarophiles and 62 % to 91% of corresponding products were obtained, upon isolation (3ab-3af). Then, other *N*-substituted tetrahydroisoquinolines incorporating nitrile, ester, ketone, and alkyl were tested in the reaction. The results revealed that while the reaction for *N*-substituted tetrahydroisoquinolines bearing electron-withdrawing groups proceeded with good to excellent yields (3 cg, 3 ch, and 3 dh), the reaction was shut down by tetrahydroisoquinolines bearing propyl (1e). Hence, the presence of an electron-withdrawing group on *N*-substituted tetrahydroisoquinolines is essential for the progress of the reaction. Notably, in the case of unsymmetrical dipolarphiles (2c, 2d, and 2f) the reaction displayed regioselectivity in products that are in line with the previous reaction catalyzed by $[Ru(bpy)_3]Cl_2$ [31]. Also, for both symmetrical and unsymmetrical alkynes, chlorophyll-a- catalyzed reaction revealed better efficiency than $[Ru(bpy)_3]Cl_2$-catalyzed [3 + 2] reaction (3ae and 3af).

We also surveyed the scope of *N*-substituted maleimides treated with dihydro isoquinoline ester and the results were demonstrated in Table 3. Accordingly, *N*-aryl maleimide bearing either electron-withdrawing or electron-donating groups were manipulated with good to excellent product yields (3b-3 g). Varied functional groups such as $-CF_3$, $-NO_2$, -CN, $-OCH_3$, and halogen could be well tolerated under the optimized condition (3c-3 g). Moreover, *N*-alkyl maleimide containing isobutyl, cyclohexyl, and benzyl resulted in excellent yields in this condition (3h-3 j). Moreover, to investigate the electronic impact of substitutions on 1, two dihydro isoquinoline core incorporating MeO and Br were examined under optimized condition. The reaction condition well tolerated these substrates and provided 87 % and 89 % of corresponding products, respectively (3k and 3 l). So, the electronic modification of dihydro isoquinoline can be accomplished. Noteworthy, a comparison between

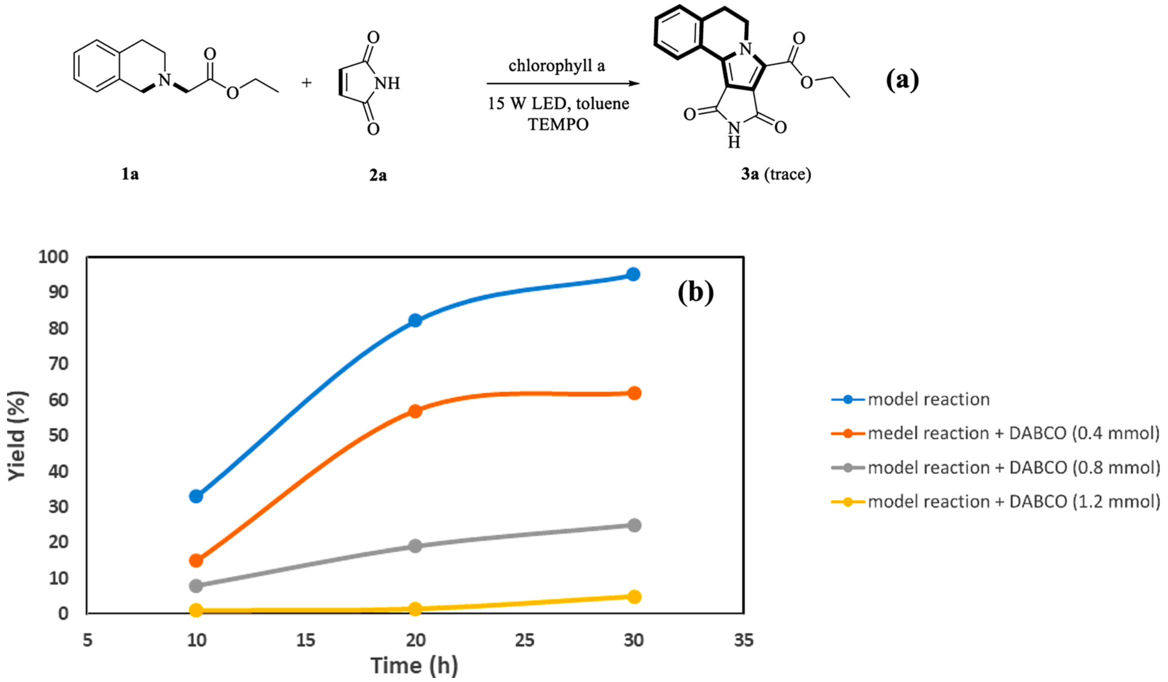


Fig. 2. Control experiments in the presence of TEMPO (a) and DABCO (b).

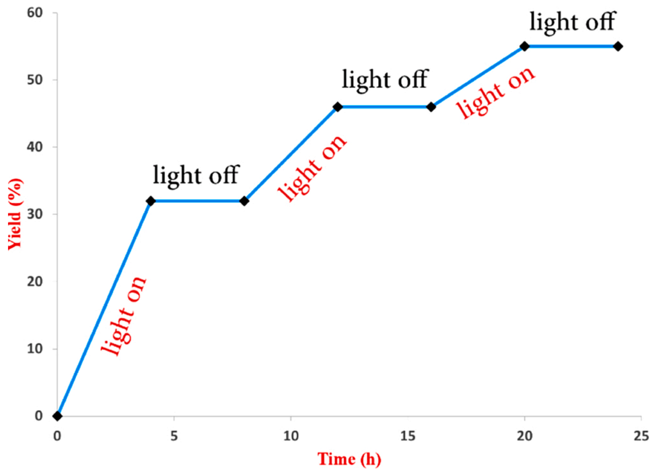
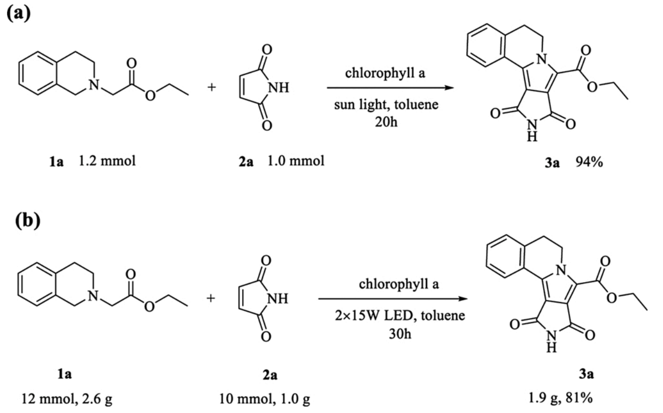


Fig. 3. “On/off” LED irradiation experiment, ^{1}H NMR yields of 3a using 1,3,5-trimethoxybenzene as an internal standard.

some obtained results with [Ru(bpy)$_3$]Cl$_2$-catalyzed (3ae, 3af, and 3b) and methylene blue-catalyzed (3ab, 3af, 3a, and 3b) [3 + 2] cycloaddition reaction [27,31] revealed that chlorophyll as a green, affordable and natural inorganic complex provides high efficiency in this reaction.

Next, two control experiments were performed to verify the radical mechanism, and the singlet oxygen is involved in the reaction. First, the model reaction was carried out in the presence of 1.2 mmol of a radical scavenger, (2,2,6,6-tetramethyl piperidine-1-yl)oxyl, known as TEMPO, and this addition almost completely suppressed the generation of the corresponding product (Fig. 2a). Furthermore, the various amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a quencher of singlet oxygen were added to the reaction vessel, followed by measuring the product yields using ^{1}HNMR at three given times. As depicted in Fig. 2b, by increasing the amount of singlet oxygen quencher, the path of the target product was gradually suppressed. Finally, the reaction was shut down after the addition of 1.2 mmol DABCO. According to these results, a radical pathway and singlet oxygen are highly likely to associate with the reaction.



Scheme 2. Oxidation/[3 + 2] cycloaddition/aromatization cascade reaction under sun light (a), gram-scale reaction (b).

Then, by using typical condition, a “light/dark” experiment was performed and the product yield was monitored during the interval on/off light irritation after every 4 h (Fig. 3). Accordingly, the product formation proceeded through the periods of light irradiation which these results might support the mechanism pictured in Scheme 2.

Finally, to validate the synthetic utility of this method, we experimented with sunlight as well as a gram-scale reaction, and the results were summarized in Scheme 2. A typical reaction was carried out under sunlight irradiation (two consecutive sunny days at Shiraz University, May. 27,28 2019, 29°59′ north latitude and 52°58′ east longitude, 1500 m above the sea level); the reaction proceeded in a shorter time (20 h) and slightly higher yield (Scheme 2a). Also, the gram-scale reaction demonstrated this chlorophyll-based photocatalysis kept high efficiency even for a large-scale experiment (Scheme 2b).

4. Conclusions

In conclusion, a sustainable, effective, and affordable procedure to synthesize pyrrolo[2,1-a]isoquinoline scaffold has been established under visible light. Chlorophyll as a natural inorganic complex turned out to provide a concise and effective method toward oxidation/[3 + 2] cycloaddition/aromatization cascade reaction of biologically active pyrrolo[2,1-a]isoquinolines scaffold.

Authorship statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the Journal of Photochemistry and Photobiology A: Chemistry

Authorship contributions

Please indicate the specific contributions made by each author (list the authors' initials followed by their surnames, e.g., Y.L. Cheung). The name of each author must appear at least once in each of the three categories below.

Conception and design of study: M. Hosseini-Sarvari, M. Koohgard; acquisition of data: M. Hosseini-Sarvari, M. Koohgard; analysis and/or interpretation of data: M. Koohgard.

Drafting the manuscript: M. Hosseini-Sarvari, M. Koohgard; revising the manuscript critically for important intellectual content: M. Hosseini-Sarvari, M. Koohgard.

Approval of the version of the manuscript to be published (the names of all authors must be listed): M. Hosseini-Sarvari, M. Koohgard.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jphotochem.2020.112877.

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