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A metal-free visible light promoted three-component facile synthesis of 4-oxo-tetrahydroindoles in ethanol-water

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Abstract

A mild and efficient visible light mediated one-pot multicomponent tandem approach to construct 4-oxo-tetrahydroindoles in ethanol-water medium at room temperature has been described. The characteristics of reported methodology are the utilization of visible light, an ideal source of energy to generate C—C and C—N bonds from commercially available substrates namely dimedone, phenacyl bromides and amines. The presented protocol is highly compatible for developing 4-oxo-tetrahydroindole derivatives with improved selectivity and high yields. Moreover, metal-free synthesis, environmental friendly solvent, easy workup process, high atom economy, cost effectiveness, short reaction time and broad substrate scope are the major advantages of reported protocol.

Keywords

Green chemistry, mild reaction conditions, visible-light, ethanol-water, 4-oxo-tetrahydroindoles

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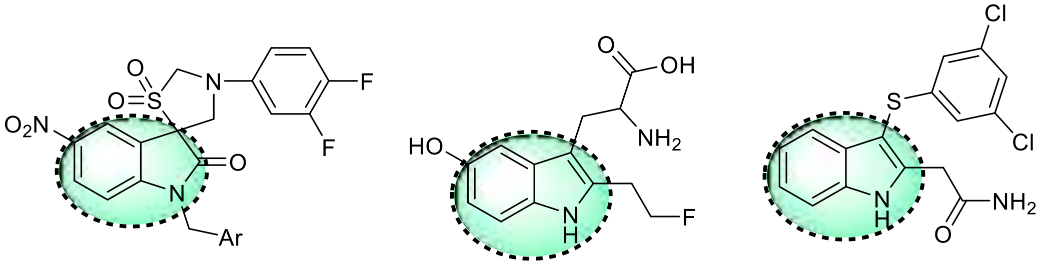
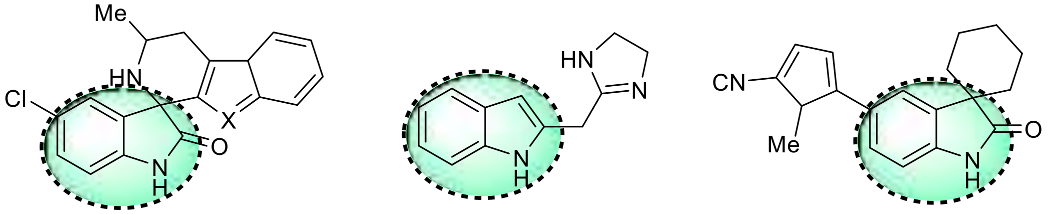
Introduction

Heterocycles are vital parts of organic compounds with potential applications in medicinal chemistry and agrochemistry.[1,2] Among them, indoles are privileged scaffold usually found in various pharmacological drugs and natural products which exhibited numerous biological potency such as anti-tuberculosis activity, antitumor activity, antiviral agent, antimalarial agent, anti-depressant agent and progesterone receptor agonist (Figure 1).[3,4] 4-oxo-tetrahydroindoles, a subclass of indoles, having enormous significances in pharmaceutical industry and organic synthesis. These molecules also displayed therapeutic potential in treatment of several diseases including cancer, tuberculosis, malaria and tumor.[5,6]



Anti-tuberculosis activity **Anti-tumor imaging agent** **Antiviral agent**



Antimalarial activity **Antidepressant agent** **Progesterone receptor agonist**

Figure 1. Some biologically active compounds containing indole core

Over the past years, development of synthetic transformations in the presence of visible light have been largely exploited from various research groups in the area of synthetic green chemistry.[7,8] The noticeable features of visible light are nontoxicity, easy handling, as an infinite source of energy, eco-compatibility and inexpensive nature showing its increasing demand towards environmentally benign synthesis.[9,10] Moreover visible light is a clean, non-hazardous and most importantly selective as no side reactions are associated with it. The use of visible light has in fact solved biggest problem of current energy demand.[11-12] Hence,

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employing visible light to carry out required photochemical organic transformation would serve as a valuable "green tool" for organic synthesis. Designing attractive framework of potential drugs using visible light as a main energy source will induce useful and safer tool in organic synthesis and in drug design. However several organic molecules are inactive towards visible light and generally do not absorb visible light radiation and hamper to achieve the target, in order to achieve the required synthesis various photocatalysts and photosensitizers have been used.[13-14] In spite of great efficiency of these photocatalysts, they too possess many problems such as high toxicity, catalyst recyclability, utilization of imperishable catalysts, typical reaction workup and high cost.[15,16] Thus achieving organic transformations by the application of visible light in absence of photocatalysts was more challenging that we have successfully achieved (Scheme 1).

Multicomponent reactions (MCRs) are extremely exploited for diversity oriented synthesis of complex organic molecules in one-pot and single step.[17,18] Multicomponent reactions usually require less amount of solvent and catalyst for isolation and purification of products.[19] Moreover, multicomponent reactions gain over many traditional methods because of high efficiency, short reaction durability, easy reaction workup procedure, waste reduction and highly atom economic nature.[20,21]

As a consequence, number of synthetic protocols for construction of 4-oxo-tetrahydroindole derivatives have been reported.[3a,22,23] Very recently, Pal and co-workers reported β-cyclodextrin mediated synthesis of 4-oxo-4,5,6,7-tetrahydroindoles under neutral conditions.[24] Also, Lambat and collaborators described a microwave assisted one-pot process for the synthesis of 4-oxo-tetrahydroindoles using ZnO-β zeolite nanoparticle.[25] Although some of the reported methods are significant but poor yield, high cost, typical reaction workup procedure, harsh reaction conditions and prolonged reaction time limit and remained the challenge for their future development. Therefore, a clean and eco-sustainable method for the synthesis of 4-oxo-tetrahydroindole derivatives are extremely desirable. A comparative study of proposed protocol with the previously reported methods is depicted below (Scheme 1). Thus in continuation of our research program for the synthesis of biologically relevant heterocyclic compounds via green methods,[26] we herein reported an efficient and eco-compatible one-pot synthetic strategy for the synthesis of 4-oxo-tetrahydroindole derivatives in the presence of visible light under aqueous

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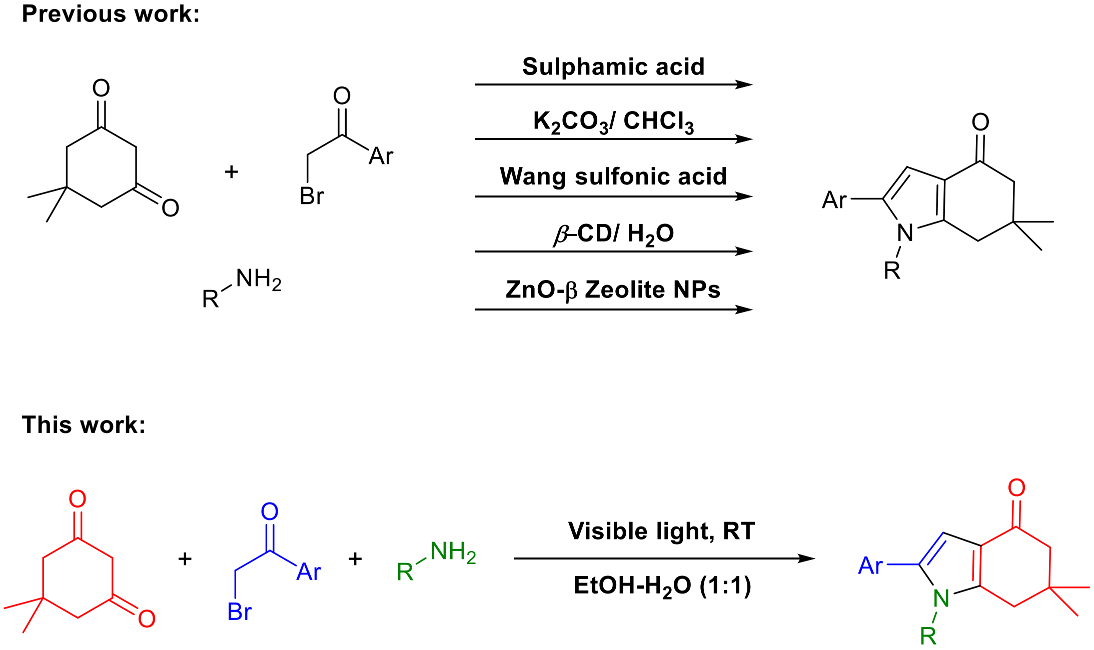
ethanol at room temperature. Binary solution of ethanol-water (1:1) was found more suitable solvent system owing to its green credential.[27]


Previous work:

This work:

Scheme 1. Comparison of present work with previously reported methods

Results and Discussion

We initially chose dimedone (**1**, 1 mmol), phenacyl bromide (**2a,** 1 mmol) and aniline (**3a,** 1 mmol) as model substrates to synthesize the product. The reaction mixture was placed in a simple round bottom flask and exposed under the illumination of 22W compact florescent lamp (CFL) on a magnetic stirrer at room temperature (RT) to optimize reaction conditions (Table 1). In the initial experiment, we tested the role of solvent for the synthesis of product. The reaction was investigated in presence of various polar and nonpolar solvents. A poor yield of reaction clearly revealed that polar solvents facilitated the reaction much faster than nonpolar solvents (Table 1, entries 1–4). However low yield of reaction was observed in case of THF which revealed that non-consumption of reactive substances occurred (Table 1, entry 5). In order to find more suitable reaction medium for present synthesis, we further examined our reaction in presence of polar solvents such as acetonitrile, DMSO and DCM but there was no improvement in the product yield. (Table 1, entries 6–7). However good results were obtained with ethanol or

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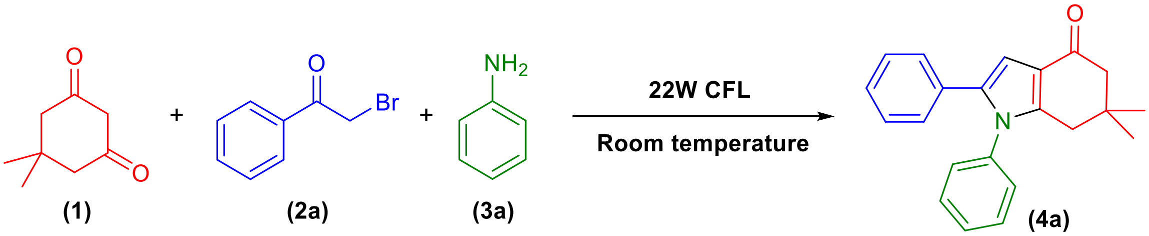
water and reaction time was also reduced. (Table 1, entries 8-9). Further improvement in the yield of reaction was observed when binary solution of ethanol/water was introduced. Keeping the idea of utilization of environmentally benign solvent, we further prepared the mixture of ethanol/water in different ratio (Table 1, entries 10–12). The result of this study showed that 1:1 ratio of ethanol-water was more favorable reaction medium for the present synthesis (Table 1, entry 12).

Table 1. Optimization of solvent for the synthesis of compound (**4a**)[a]



Entry	**Solvent**	**Time[b] (h)**	**Yield[c] (%)**
1	Benzene	12	Trace[d]
2	Hexane	10	Trace
3	Diethyl ether	9	Trace
4	1,4-dioxane	10	Trace
4	THF	11	27
5	Acetonitrile	8	35
6	DMSO	8	28
7	DCM	7.5	30
8	EtOH	5	55
9	H_2O	5	51
10	EtOH-H_2O (4:1)	3.5	92
11	EtOH-H_2O (2:1)	3.5	91
12	EtOH-H_2O (1:1)	3.5	92

[a] Reaction conditions: dimedone, **1** (1 mmol), phenacyl bromide, **2a** (1 mmol) and aniline, **3a** (1 mmol) were stirred in a round bottom flask in the presence of 22W CFL under different solvents at room temperature (25 °C). [b] Reaction time. [c] Isolated yield product. [d] Observed on TLC

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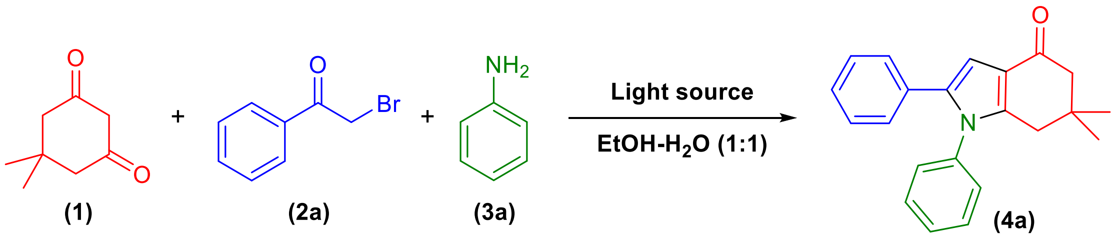
Next, we screened the effect of energy sources for the present reaction. Initially, the reaction was investigated in the presence of various compact fluorescence lamps (CFLs) by varying their intensities and the results showed that CFLs below 22W reduced reaction yield however CFLs above 22W did not affect reaction yield (Table 2, entries 1–4). Therefore 22W CFLs considered to be more appropriate light source for the synthesis of 4-oxo-tetrahydroindole. The reaction was also investigated in the presence of light emitting diodes (LEDs) with various intensities but no significant increment in the yield of product was noticed (Table 2, entries 5–8). Furthermore, reaction was carried out in daylight, sunlight and dark but very poor yield of product was observed (Table 2, entries 9–11). We also performed our reaction in dark at 60 ^{o}C and 100 ^{o}C and again only trace amount of product was detected (Table 2, entries 12–13). These observations clearly pointed out that temperature has no role for synthesis of titled compound.

Table 2. Optimization of light source for the synthesis of compound (**4a**)^{a}



Entry	Reaction conditions	Time^{b} (h)	Yield^{c} (%)
1	18W CFL, RT	3.5	90
2	22W CFL, RT	3.5	92
3	24W CFL, RT	3.5	92
4	30W CFL, RT	3.5	92
5	White LED (6W), RT	5	78
6	White LED (8W), RT	5	80
7	Green LED (6W), RT	4.5	82
8	Blue LED (6W), RT	4.5	81
9	Daylight, RT	8	Trace

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10	Sunlight, RT	8	Trace
11	Dark, RT	12	Trace
12	Dark, 60 ^{o}C	10	Trace
13	Dark, 100 ^{o}C	10	Trace

[a]Reaction conditions: 1 mmol of each dimedone (**1**), phenacyl bromide (**2a**) and aniline (**3a**) were stirred in a simple round bottom flask under different reaction conditions. [b]Time required for the completion of reaction. [c]Isolated yield of purified product.

To investigate the probable mechanistic pathway for the present reaction, an on/off visible light photo-irradiation experiments was performed using 1 mmol of each dimedone (**1**), phenacyl bromide (**2a**) and aniline (**3**) in 5 ml aqueous ethanol (1:1) under the illumination of 22W CFL on a magnetic stirrer at room temperature. The observed results lead us to draw most probable mechanism of the synthesized products (Figure 2).[26(a),28]

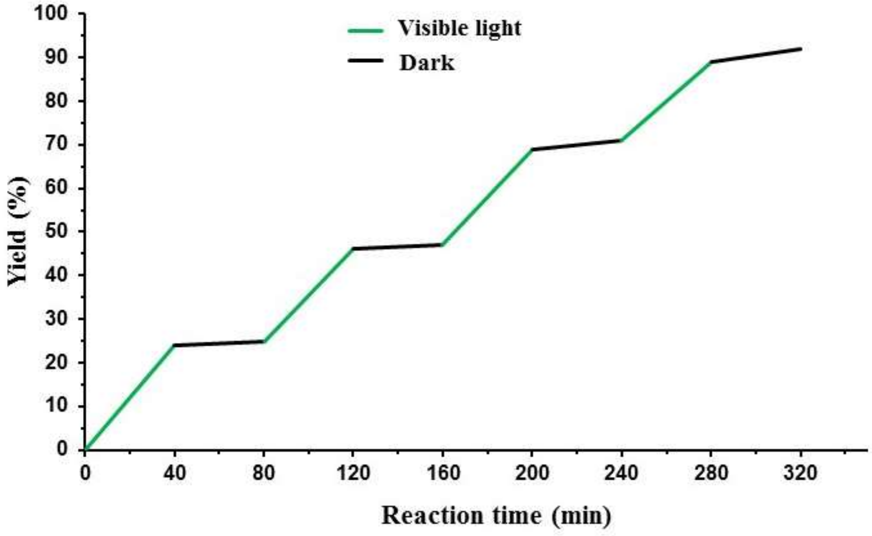

Figure 2. On/off visible light photo-irradiation experiment

To study scope, efficiency and limitation of reported methodology, we explored the synthesis of 4-oxo-tetrahydroindoles by using dimedone (**1**) and derivatives of phenacyl bromides (**2a-d**) and amines (**3a-j**) (Table 3). It was noticed that the reported methodology is highly tolerable with variety of substituents on 4-oxo-tetrahydroindole. The observed products in each results were obtained in high yield and short reaction time (3.5–4 h). It was also observed that electron

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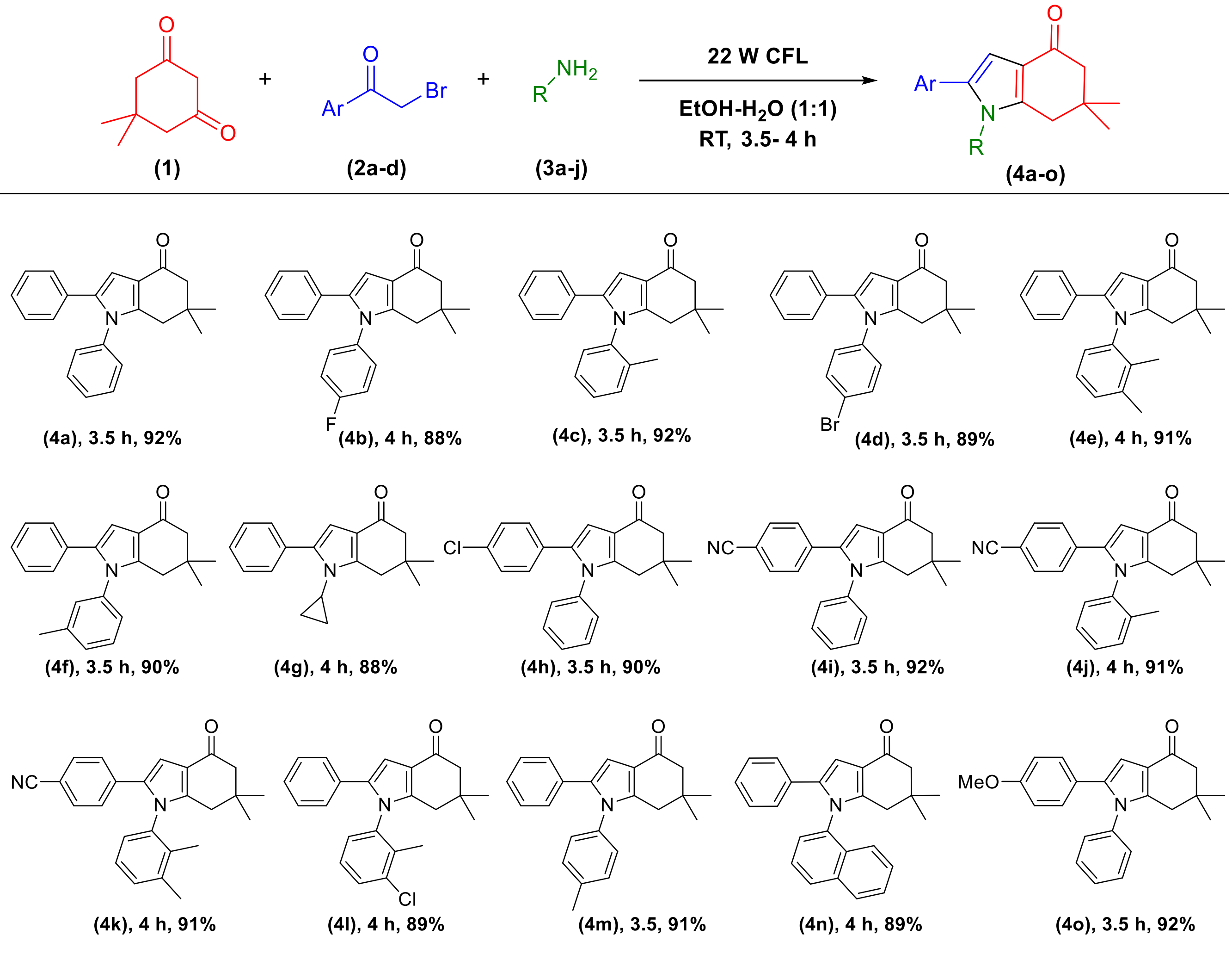
donating substituents on amines proceeded reaction faster while electron withdrawing substituents slowed down the reaction. Also electron withdrawing substituents on phenacyl bromide underwent reaction faster than electron donating substituents (Table 3). It is important to mention that reagents like alkyl / acyl bromides and alkyl amines were not well tolerated with very low product yield, hence were not further investigated. The functionalized 4-oxo-tetrahydroindole scaffolds showed numerous biological significances which might be the subject of future studies. Hence, from these observations it can be concluded that present protocol is highly promising for diversity oriented synthesis (DOS). Further studies on 4-oxo-tetrahydroindoles by investigating molecular complexity are in the process.

Table 3. Substrates scope for the synthesis of 4-oxo-tetrahydroindole derivatives (**4a-o**)[*a, b,* ***c***]



[a]Reaction conditions: 1 mmol of each dimedone (**1**), phenacyl bromides (**2a-d**) and amines (**3a-j**) were irradiated using 22W CFL in 5 ml aqueous ethanol (1:1) at room temperature. [b]Time required for the

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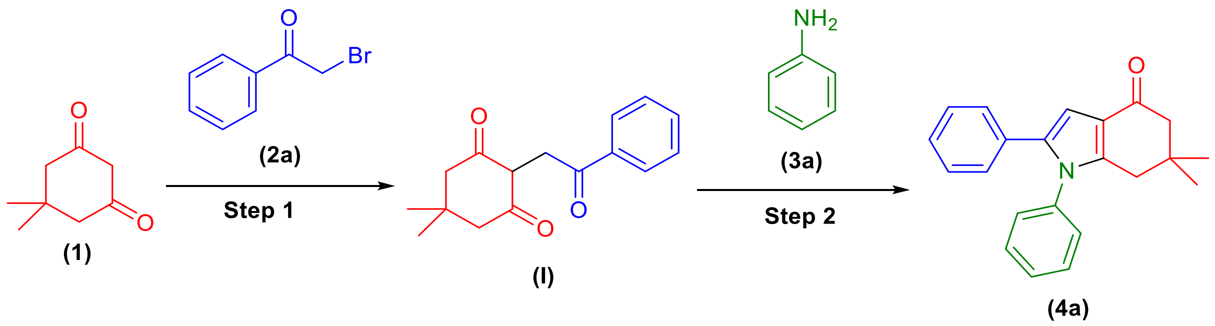
completion of reaction. [c]Isolated yield of purified product.

Additionally, we performed an experiment for deciphering the reaction mechanism (Table 4). We started our reaction in dark by taking dimedone **1**, (1 mmol) and phenacyl bromide, **2a** (1 mmol) during step 1 and observed that reaction was not progressed even after 5 h of stirring. Thus, further addition of aniline, **3a** (1 mmol) in step 2 produced only trace amount of product. We tried the same experiment at 70 ^{o}C but there was no progress in the reaction yield. When the reaction was carried out under visible light (22W CFL) irradiation in N_2 atmosphere, pleasingly it was found that the reaction progressed smoothly in both step 1 & 2 and 92% yield was obtained. Also in our next repeated experiment we performed step 2 in absence of visible light and found that the reaction proceeded smoothly and generated good amount product. However, only trace amount of intermediate (**I**) was detected when 1 eq. of (2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl; TEMPO was added in step 1 and therefore negligible amount of product was formed. Whereas, addition of TEMPO (1 eq.) in step 2 did not affect the reaction yield. These results concluded that utilization of visible light was necessary to achieve present transformation.

Table 4. Deciphering the reaction mechanism[a]



Entry	Step 1		Step 2		Overall yield[c] (%)
	Reaction conditions	Reaction progress	Reaction conditions	Reaction progress	
1	Dark, RT, 5 h	Incomplete	Dark, RT, 8 h	Incomplete	Trace
2	Dark, 70 ^{o}C, 4 h	Incomplete	Dark, 70 ^{o}C, 6 h	Incomplete	Trace
3	22W CFL, RT, N_2 atm., 1.5 h	Complete[b]	22W CFL, RT, N_2 atm., 2 h	Complete	92
4	22W CFL, RT, N_2 atm., 1.5 h	Complete	Dark, RT, 2 h	Complete	91
5	22W CFL, RT, TEMPO (1 eq.),	Incomplete	22W CFL, RT, 2 h	Incomplete	Trace

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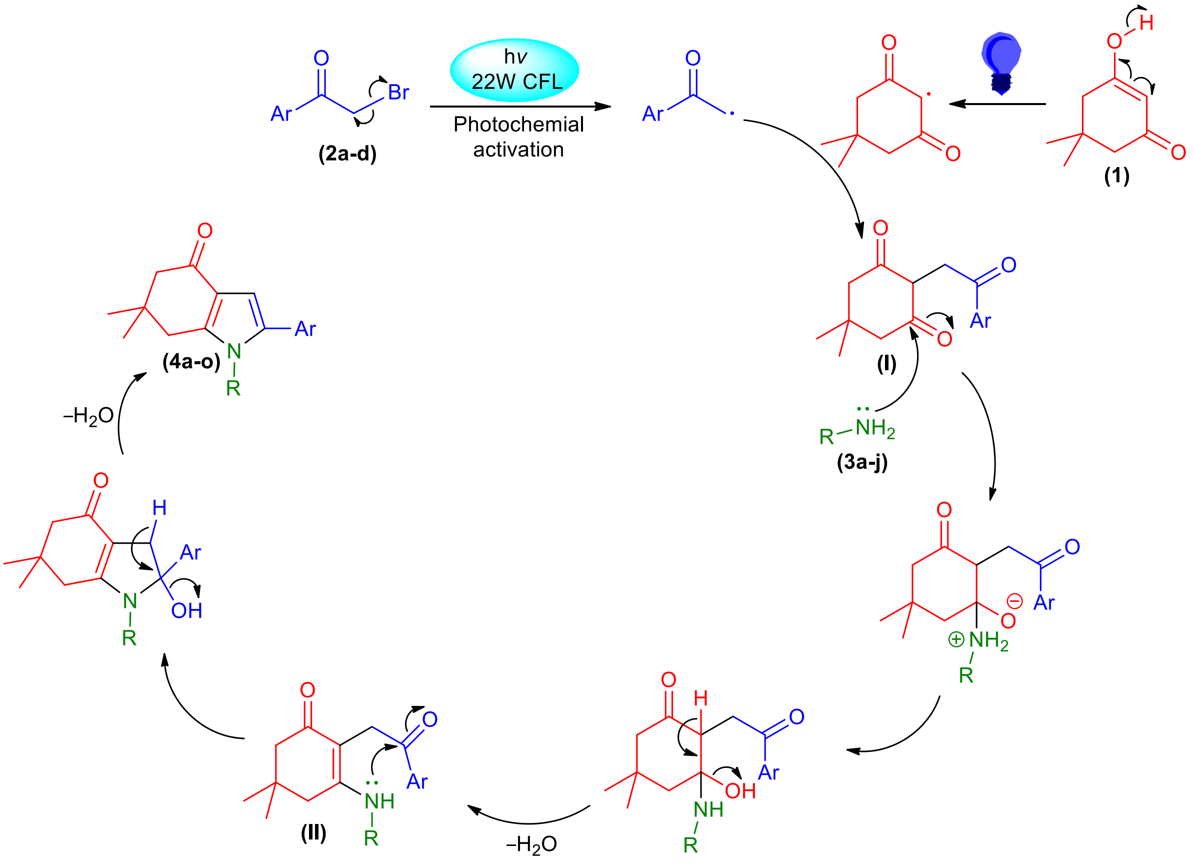
	1.5 h				
6	22W CFL, RT, 1.5 h	Complete	22W CFL, RT, TEMPO (1 eq.), 2 h	Complete	90

[a]Reaction conditions: 1 mmol (**1a**), 1 mmol (**2a**) and 1 mmol (**3**) in 5 ml EtOH-H_2O (1/1: v/v); [b]95% utilization; [c]Yield of product.

On the basis of recent literature studies,[28] a probable mechanism for the synthesis of 4-oxo-tetrahydroindoles derivatives has been illustrated (Scheme 2). The reaction seems to be initiated by photo excitation of phenacyl bromides (**2a-d**) to generate radical intermediates via homolytic cleavage of C—Br bond. The radical intermediate further reacted with excited form of dimedone (**1**) and generated stable intermediate (**I**). Hereafter, nucleophilic addition of amines (**3a-j**) on intermediate (**I**) followed by dehydration resulted intermediate (**II**). Finally, intermediate (**II**) immediately proceeded for cyclization along with dehydration yielded corresponding 4-oxo-tetrahydroindoles (**4a-o**).



Scheme 2. Probable mechanism for synthesis of 4-oxo-tetrahydroindoles

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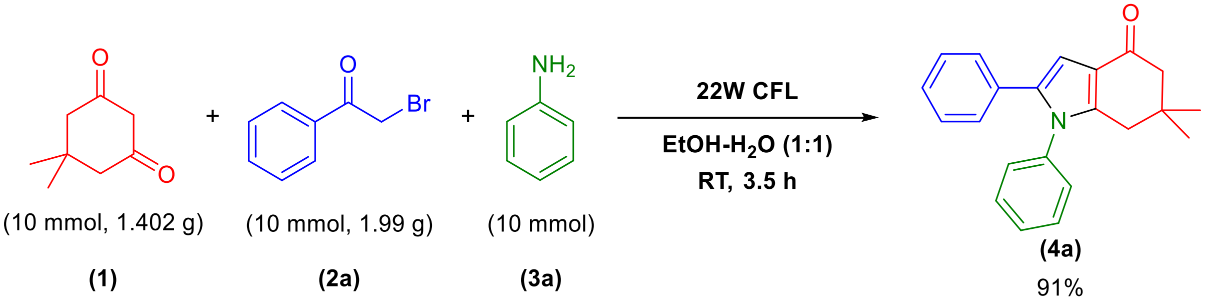
Practicability the above reaction was also tested by conducting an experiment on gram scale by the reaction of dimedone **1,** (10 mmol), phenacyl bromide **2a**, (10 mmol) and aniline **3a**, (10 mmol) to synthesize the compound (**4a**). Common laboratory glassware were used to perform scale-up reaction. The reaction mixture were simply irradiated in the presence of 22W CFL in 50 mL ethanol-water (1:1) solution at room temperature and observed that 91% yield of product was obtained after 3.5 h of stirring. This led to conclude that the present process is highly tolerable over large-scale synthesis (Scheme 3).



Scheme 3. Practicability of present reaction

Conclusion

In summary, we have established a highly efficient and compatible one-pot metal-free strategy for the synthesis of highly functionalized 4-oxo-tetrahydroindoles. The utilization of biodegradable aqueous ethanol solvent and universally available visible light source make the present protocol more efficient and environmentally friendly. The reported methodology shows numerous advantages like highly atom economic nature, functional group tolerating ability, excellent reaction yield, easy reaction workup and short reaction time are some attributes in the context of green chemistry design.

Supporting Information Summary

^{1}H NMR, ^{13}C NMR, HRMS, IR spectral data and other experimental details are available in the supporting information.

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Acknowledgments

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Conflict of interest

The authors declare that they have no conflict of interest.

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