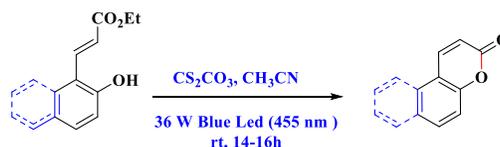


# Photosensitizer Free visible Light Synthesis of multifunctional Coumarins from Trans-hydroxy acrylates

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A photosensitive and transition metal-free technique without inert gas shielding is reported for the facile synthesis of multifunctional coumarins. The current procedure avoids the inherent drawbacks of the previous coumarin production protocol in the presence of transition metal. The prominent aspects of the methodology also include the absence of photocatalyst, the absence of external additives including transition metals, and the employment of a straightforward precursor. Additionally, we went into great detail on the mechanistic investigation and utilization of multifunctional coumarins.



**Photosensitizer free**  
**Does not require any transition metal**  
**without any inert atmosphere protection**  
**Room Temperature**  
**14 examples up to 94 % yield**

## INTRODUCTION:

Numerous natural compounds and biologically active intermediates contain coumarin motifs, which serve as one of the most significant structural scaffolds for the numerous pharmaceutical medication molecules available on the market (Figure 1)<sup>8</sup>. Considering that coumarins and their derivatives have anti-HIV, antioxidant, anti-fungal, anti-helminthic, and anti-bacterial activities, there is an increasing interest in them<sup>10</sup>. They are commonly used as an additive in the food and cosmetics sectors and are also used as pesticides, optical brighteners, fluorescent, and laser dyes<sup>11</sup>. Notably, various photophysical properties have been explored by the alkenyl<sup>6</sup> and alkenyl<sup>7</sup> substituted coumarin systems. Unsaturated lactone skeletons, present in coumarins are traditionally synthesized by aldol or Knoevenagel,<sup>15-16</sup> Pechmann,<sup>17</sup> Reformatsky,<sup>19</sup> and Wittig<sup>20</sup> condensations. Recently, a convergent synthetic tool, *i.e.*, cross-coupling technology,<sup>21</sup> has emerged to allow rapid assembly of diversified coumarin structures. All of these methods provide elegantly substituted multifunctional coumarins, but they require the use of metal catalysts and/or external oxidants, which make dangerous byproducts and limit the compatibility of the functional groups. So, it would be great to come up with a new, sustainable way to make multifunctional coumarins.

In the recent years, visible light driven photoredox catalysis has gained colossal interest in the exploration of novel transformations employing photocatalyst to promote the reactions under external oxidant-free or reductant-free conditions. Visible light driven synthesis of coumarins were reported such as synthesis of 3-acyl coumarins framework was reported with the help AQN as a photocatalyst<sup>7</sup>, radical aryl difluoroacetylation of alkynes with ethyl bromodifluoroacetate for the synthesis of 3-difluoroacetylated coumarins<sup>1</sup>, coumarin biosynthesis with (-)-riboflavin<sup>4</sup>. To be the best of

our knowledge, herein we describe the first example of Photosensitizer Free Approach for Synthesizing Multifunctional Coumarins With visible light.

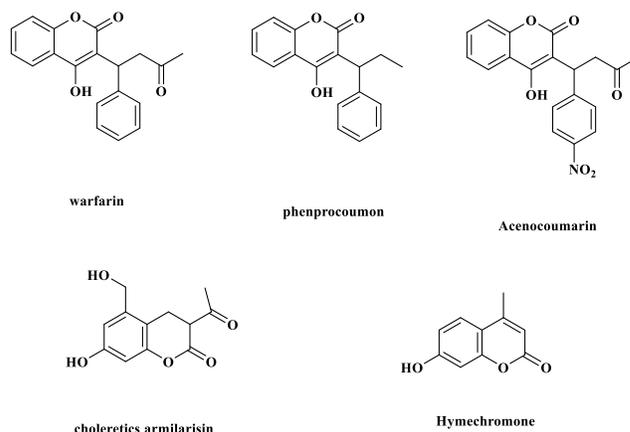


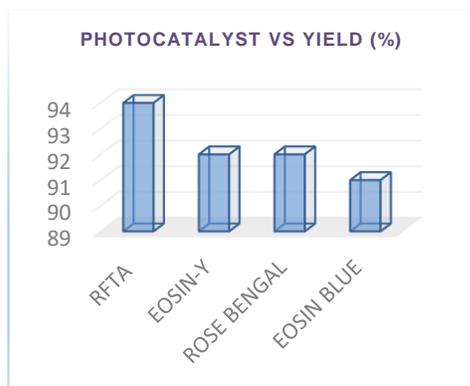
Figure 1: Structure of some coumarin drug

## RESULTS AND DISCUSSION:

Herein, we describe the first example of Photosensitizer Free Cascade Approach for Synthesizing Multifunctional Coumarins with visible light. Accordingly, our investigation initiated with a model substrate **1a** to test our hypothesis multifunctional coumarin frameworks (Table 1).

Initially, we utilized **1a** as the model substrate to optimize the reaction conditions and in presence of various type of photocatalyst in the visible-light driven approach of multifunctional coumarins and thereby, a model reaction condition was established as follows: **1a** (0.02 mmol), CS<sub>2</sub>CO<sub>3</sub> (3equiv) and (10 mol%) of photocatalyst such as Eosin-Y, RFTA, Rose bengal, Eosin Blue (Table 1, entry 1-4) were mixed in 3 mL of solvent under irradiation of single 36 W blue LED (455 nm) without inert gas protection at room

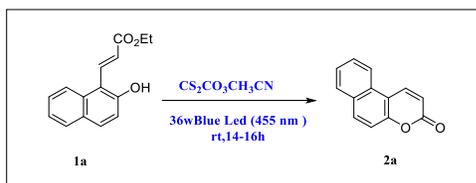
temperature for 14-16h. we showed the variation of yield in presence of different type of photocatalyst (**Figure 2**).



**Figure 2:** Yield variation in presence of different types of photocatalyst

As the reaction conditions were optimized, the following became the model reaction conditions: **1a** (0.02 mmol) and  $\text{Cs}_2\text{CO}_3$  (1-3equiv) were mixed in 3 mL of solvent and exposed to a single 36 W blue LED (455 nm) without protection from an inert gas at room temperature (rt) for 14–16 hours. A significant yield was found in the absence of a photocatalyst (**Table 1**, entry 5,14,15).

**Table 1.** Reaction Condition Optimization



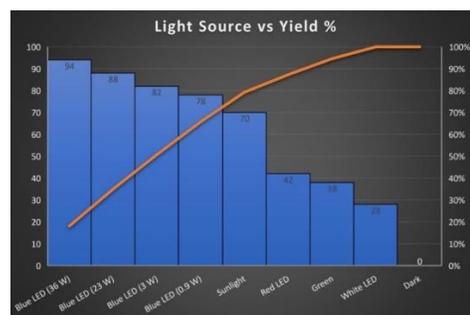
entry	Solvent/Di-electric constant ( $\kappa$ )	Base/eq	Catalyst	(T°C)/(h)	isolated yield (%)	Light
1	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	RFTA	25/16	94	Yes
2	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	Eosin-y	25/16	92	Yes
3	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	Rose Bengal	25/16	92	Yes
4	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	Eosin-blue	25/16	91	Yes
5	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	-	25/14	94	Yes
6	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	-	25/15	traces	-
7	MeCN/(37.5)	-	-	25/15	0	-
8 <sup>a</sup>	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/3$	-	90/15	0	-
9 <sup>b</sup>	MeCN/(37.5)	$\text{K}_2\text{CO}_3/3$	-	25/16	72	Yes
10	MeCN/(37.5)	$\text{Li}_2\text{CO}_3/3$	-	25/16	73	Yes
11	MeCN/(37.5)	$\text{Na}_2\text{CO}_3/3$	-	25/16	76	Yes
12	MeCN/(37.5)	NaOH/3	-	25/16	82	Yes
13	MeCN/(37.5)	Pyridine/3	-	25/16	28	Yes
14	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/2$	-	25/16	79	Yes
15	MeCN/(37.5)	$\text{Cs}_2\text{CO}_3/1$	-	25/16	64	Yes
16	MeCN/(37.5)	KOH/3	-	25/16	76	Yes
17	DCM/(8.9)	$\text{Cs}_2\text{CO}_3/3$	-	25/16	56	Yes

18	Methanol/33	$\text{Cs}_2\text{CO}_3/3$	-	25/15	79	Yes
19	DMSO/(46.6)	$\text{Cs}_2\text{CO}_3/3$	-	25/19	79	Yes
20	Acetone/(20.7)	$\text{Cs}_2\text{CO}_3/3$	-	25/16	63	Yes
21	1-4 Dioxane	$\text{Cs}_2\text{CO}_3/3$	-	25/16	56	Yes
22	Toluene/(2.4)	$\text{Cs}_2\text{CO}_3/3$	-	25/16	43	Yes
23	Water	$\text{Cs}_2\text{CO}_3/3$	-	25/16	-	Yes
24	DMF/(37.7)	$\text{Cs}_2\text{CO}_3/3$	-	25/16	76	Yes
26	THF/(7.6)	$\text{Cs}_2\text{CO}_3/3$	-	25/16	46	Yes

Reactions were performed with **1a** (0.2 mmol) and solvent (3 ml) in Presence of single 36 W Blue Led (455 nm)

We also carried out the model reaction in the absence of light and photocatalyst, but only very little amounts were recovered, and no conversion occurred in the absence of light, base, and photocatalyst (**Table 1**, entry 6,7). We looked into a number of solvents for this change in the interim. In general, we saw higher yields when the process was carried out with solvents particularly with higher dielectric constant values (**Table 1**, entry 5,18,19,24). Lower yields of **2a** were obtained when  $\text{CH}_3\text{CN}$  was substituted with other solvents like DCM, Acetone, 1-4 Dioxane, THF, or Toluene. The reaction took almost longer to complete in the presence of DMSO, and particularly with  $\text{H}_2\text{O}$ , we observed signs of product production while a significant proportion of the starting material was recovered.

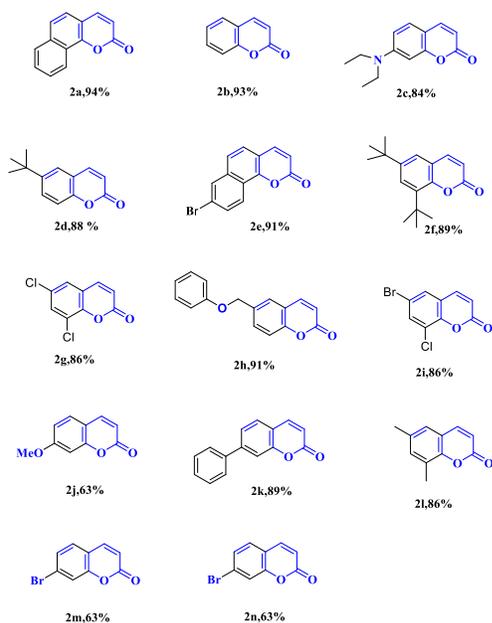
On the other hand, comparatively Lower yields of **2a** were obtained when  $\text{CS}_2\text{CO}_3$  was substituted with other bases like  $\text{K}_2\text{CO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{Li}_2\text{CO}_3$  but showed higher yield in presence of NaOH, or KOH (**Table 1**, entry 9,10,11,12,16) but the reaction showed almost less yield in presence of organic bases like pyridine (**Table 1**, entry 13). While doing this, we optimized different kinds of light sources and compared their yields while deviating from the requirements of the 36 W Blue led (455 nm) standard. We used 23 W, 3 W, and 0.9 W Blue LEDs to optimize the reaction conditions, and we obtained the best yield of 94% while utilizing 36 W Blue LEDs (**Figure 3**).



**Figure 3.** Deviation from the standard condition. illustration of light dependence. Reaction conditions: **1a** (0.02 mmol),  $\text{CS}_2\text{CO}_3$ (3equiv), in 3 mL of Acetonitrile under variable light irradiation without inert gas protection at rt for 16h. Isolated yields were given on the basis of Product **2a** of **Table**

We also used Sunlight, Red Led light, Green light with other light sources and in presence of dark condition for optimization purpose from deviating from the standard reaction conditions: **1a** (0.02 mmol),  $\text{CS}_2\text{CO}_3$ (3equiv), in 3 mL of Acetonitrile under variable light irradiation without inert gas protection at rt for 16h. Isolated yields were given on the basis of Product **2a** of **Table 1**. Our next target was to expand the synthetic utility of our methodology for the formation of multifunctional coumarins with the optimized reaction conditions (**Table 1**). Likewise, 3*H*-benzo[*f*]chromen-3-one coumarins synthesis, a broad range of phenol, naphthol molecules were converted to ethyl (*E*)-3-(2-hydroxynaphthalen-1-yl) acrylate or (*E*)-3-(2-hydroxyphenyl) acrylate types of esters which eventually converted to electronically diverse substituents were tested using the optimized reaction conditions to examine the generalizability of the reaction to furnish the multifunctional coumarin products (**Table 2**) in moderate to excellent yield (**Table 2, 2a-2n**). Electron donating as well as withdrawing groups on ester worked smoothly to provide multifunctional coumarin products in good yields but in case of electron donating group like -OMe, deliver the product with less yield and also compounds containing Halogen groups were also well tolerated by our synthetic methodology.

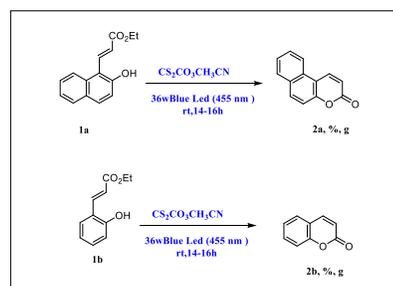
**Table 2:** Scope of substrate Towards multifunctional coumarins scaffolds



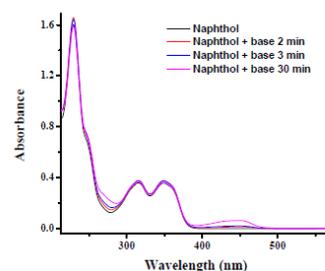
Our next target was to find out the application of our synthetic methodology. we carried out large scale synthesis with our methodology (**Scheme 2**) and successfully synthesized **2a** and **2b** with **72.57%** and **76%** yield respectively. Initially, we started with 1156 mg and got 839 mg and for **2b** we started with 1200 mg and got 912 mg product.

We also successfully synthesized 7-amino coumarin (**Table 2, 2c**) which also have large scope for study of biological molecules due to its strong intermolecular charge transfer marked solvatochromism and high quantum yield<sup>31-32</sup>.

**Scheme 2: Gram Scale Synthesis of 2a,2b**

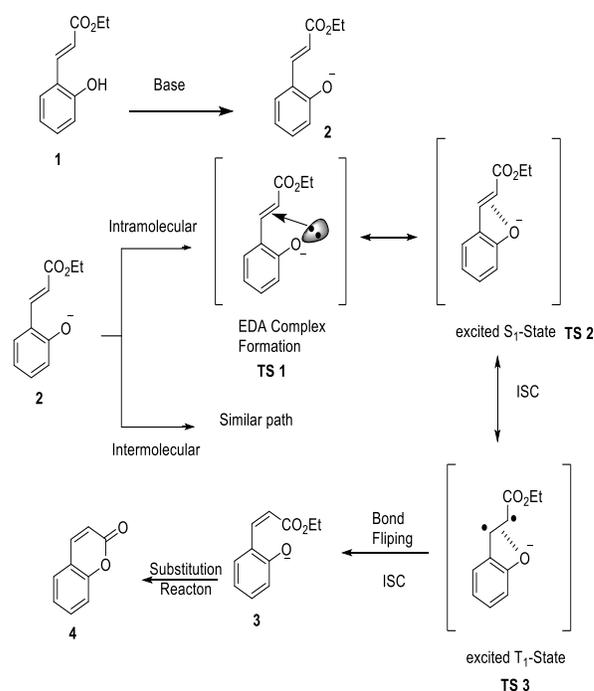


To gain insight into the reaction mechanism, Control experiments was carried out in presence of radical scavengers Further, the reaction hardly exhibited any retarding effect in the presence of radical scavengers such as TEMPO, which abandoned any radical pathways involved in the reaction. The reaction proceeds via the formation of **2** in the presence of base, For the confirmation of electron donor acceptor complex generation **TS1**, we carried out experiment via uv-spectroscopy (**Figure 5**) and got satisfactory result. A peak at 450 nm shows the EDA complex formation which increases with time.



**Figure 4:** UV-spectroscopic experiment

**Scheme 3: Plausible Reaction Pathway**



EDA complex was mainly formed via the intramolecular or intermolecular pathway to form **TS1** and it proceeds via excited single  $S_1$  state **TS2** and Intersystem crossing is happened to form **TS3** then bond flipping is happened to form **E**  $\rightarrow$  **Z** and it was mainly happened due to the stereoselectivity arises from the differing photophysical properties of the reactant and product isomers: the **Z** isomer is not re-excited by energy transfer as a consequence of deconjugation. After that, Substitution reaction in happened to form **4** from **3** (Scheme 3).

## CONCLUSIONS:

In summary, we have achieved the first visible-light-driven, photosensitizer free and transition metal-free technique without inert gas shielding is reported for the facile synthesis of multifunctional coumarins. The method is mild, operationally simple, tolerant of a number of functional groups and exhibit excellent scalability. We believe this methodology provides practitioners with an alternative tool that will permit the scrutiny of unexplored chemical space and find useful applications in organic synthesis.

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## CONFLICTS OF INTEREST

There are no conflicts to declare.

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