

Visible-Light-Induced Radical Condensation Cyclization to Synthesize 3,4-Dihydropyrimidin-2-(1*H*)-ones/thiones Using Photoexcited Na₂ Eosin Y as a Direct Hydrogen Atom Transfer (HAT) Catalyst

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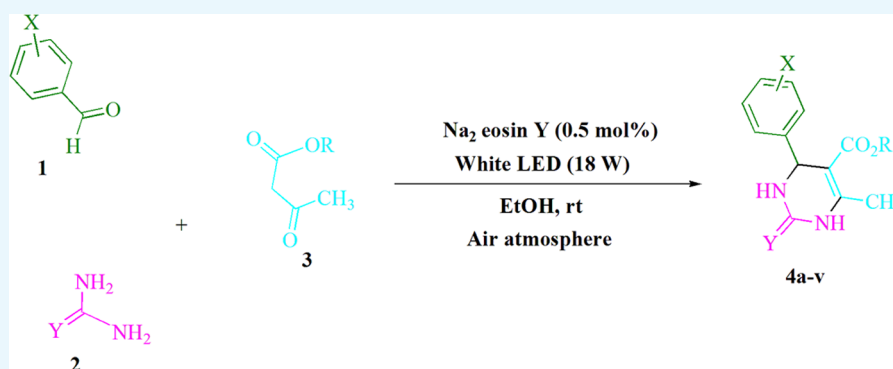
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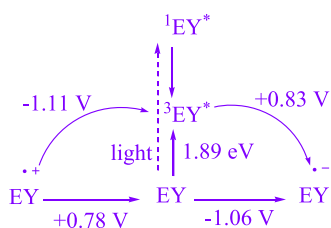


ABSTRACT: The data suggests that Na₂ eosin Y-derived photoinduced states act as a HAT catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones in ethanol at room temperature. This research establishes a novel function for using a nonmetallic natural dye, Na₂ eosin Y, available commercially and at a cheap cost in the photochemical synthesis using the least amount of catalyst, obtaining good results, speeding up the process, and achieving a high atom economy. The TON and TOF of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones are computed. Furthermore, this cycle runs on the gram scale as well, indicating the possibility of industrial purposes.

INTRODUCTION

EY is a readily available nonmetallic natural dye that has recently found widespread use due to its economic and ecological advantages over transition photocatalysts based on metals.¹

Scheme 1. Eosin Y's Oxidative and Reductive Quenching Cycles and Their Associated Potentials^{1a}



In photoredox reactions catalyzed by eosin Y, target substrates reduced or oxidized successfully by their driven manner are based on typically the reducibility or potential oxidability of the substrates within the eosin Y scope (Scheme 1).^{1a}

The spectrum of photochemical processes induced by eosin Y has been constrained by the aforementioned electrochemical requirements. Unlike other organic dyes, eosin Y possesses unique phenol and xanthene moieties and is quite different from other organic dyes. It also has prominent features with an acid basis leading to four different constructs. Ample documentation exists from former reports on photoreactions indicating the photocatalytic property of anionic eosin Y. However, neutral eosin Y has characteristic inactivity, which can be ignored in synthesis processes applied potentially.² Recently, Wang³ and Wu⁴ were motivated by the properties of eosin Y to pioneer the identification of new activation states for photoinduced eosin Y. They revealed that eosin Y-derived driven modes could act as

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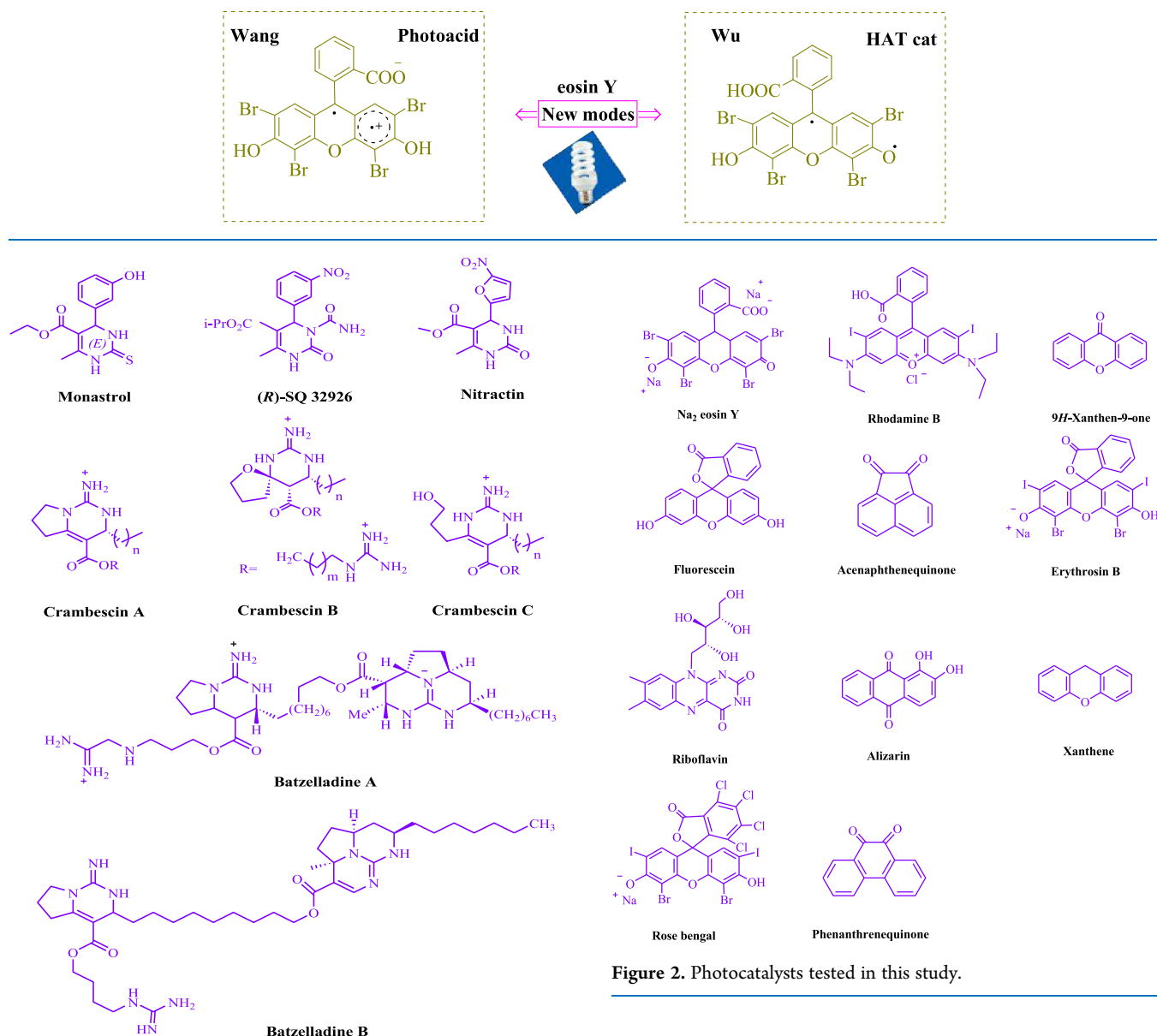
Scheme 2. Exploring EY as a HAT Catalyst/Photoacid^{1a}

Figure 2. Photocatalysts tested in this study.

Figure 1. Structures containing dihydropyrimidines with biological activities.

HAT catalysts or photoacids to activate native C–H bonds and glycals (Scheme 2).^{1a}

HAT is a simple phase probably in charge of multiple chemical, environmental, and biological procedures. Particularly, direct HAT catalysis mediated by quinine and benzophenone has recently been used as a tool for enabling activation of C–H bonds under the radiation of light.^{5,6}

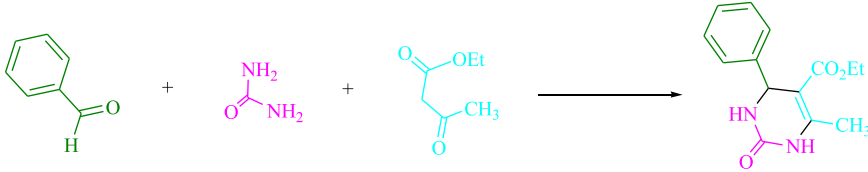
Moreover, green chemists consider visible light irradiation as a reliable method since it has plentiful energy reserves and lower cost and as a renewable energy source in the environment-friendly synthesis of organic compounds.^{7–9} Normally, compact fluorescent lights and diodes emitting light are visible light sources for different transformations.

We describe dihydropyrimidines with a variety of pharmacological properties (Figure 1).^{10–16}

Numerous strategies are available.^{17–36} Numerous instances occurred from these treatments. However, certain synthesis

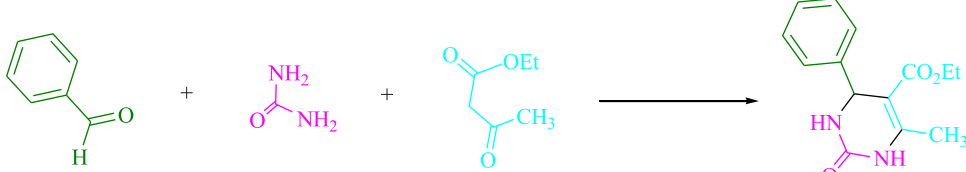
routes have drawbacks, such as limitations on the use of metal catalysts, severe reaction conditions, costly reagents, repetitive workup, low yield, prolonged reaction time, and environmental hazards.

Due to the aforementioned challenges and our concern for ecologically benign procedures, most scientists have been intrigued by the quest for easy, efficient, and environmentally safe methods that may enhance organic reactions under green conditions. Considering the above concerns, it is critical to investigate environmentally safe catalysts under green conditions for the correct synthesis of nitrogen heterocyclic complexes. This research establishes a novel function for the utilization of a nonmetallic dye, Na₂ eosin Y, in the aforementioned photochemical synthesis process. The Biginelli reactivity³⁷ involving β -ketoesters, arylaldehyde derivatives, and urea/thiourea in ethanol at room temperature and in an air environment is facilitated by visible light. This is a successful one-pot reaction carried out under very efficient, moderate, and simple conditions.

Table 1. Optimization Table of Photocatalysts for the Synthesis of 4a^a


entry	photocatalyst	solvent (3 mL)	time (min)	yields (%) ^b
1		EtOH	60	trace
2	Na ₂ eosin Y (0.2 mol %)	EtOH	20	78
3	Na₂ eosin Y (0.5 mol %)	EtOH	10	94
4	Na ₂ eosin Y (1 mol %)	EtOH	10	94
5	rhodamine B (0.5 mol %)	EtOH	10	67
6	9H-xanthen-9-one (0.5 mol %)	EtOH	10	61
7	fluorescein (0.5 mol %)	EtOH	10	75
8	acenaphthenequinone (0.5 mol %)	EtOH	10	69
9	erythrosin B (0.5 mol %)	EtOH	10	58
10	riboflavin (0.5 mol %)	EtOH	10	72
11	Alizarin (0.5 mol %)	EtOH	10	45
12	xanthene (0.5 mol %)	EtOH	10	41
13	rose bengal (0.5 mol %)	EtOH	10	74
14	phenanthrenequinone (0.5 mol %)	EtOH	10	52

^aReaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) in EtOH (3 mL), white LED (18 W), and various photocatalysts at rt. ^bIsolated yield.

Table 2. Optimization Table of Solvent and Visible Light for the Synthesis of 4a^a


entry	light source	solvent (3 mL)	time (min)	yields (%) ^b
1	white light (18 W)	H ₂ O	10	65
2	white light (18 W)		20	73
3	white light (18 W)	EtOH	10	94
4	white light (18 W)	MeOH	10	69
5	white light (18 W)	EtOAc	10	61
6	white light (18 W)	H ₂ O/EtOH (1:1)	10	77
7	white light (18 W)	H ₂ O/EtOH (1:2)	10	82
8	white light (18 W)	H ₂ O/EtOH (2:1)	10	74
9	white light (18 W)	DMSO	25	38
10	white light (18 W)	CH ₃ CN	20	56
11	white light (18 W)	CHCl ₃	40	19
12	white light (18 W)	CH ₂ Cl ₂	40	15
13	white light (18 W)	DMF	35	26
14	white light (18 W)	THF	25	23
15	white light (18 W)	toluene	25	42
16	white light (10 W)	EtOH	10	75
17	white light (12 W)	EtOH	10	82
18	white light (20 W)	EtOH	10	94
19		EtOH	45	<5
20	green light (18 W)	EtOH	10	88
21	blue light (18 W)	EtOH	10	81

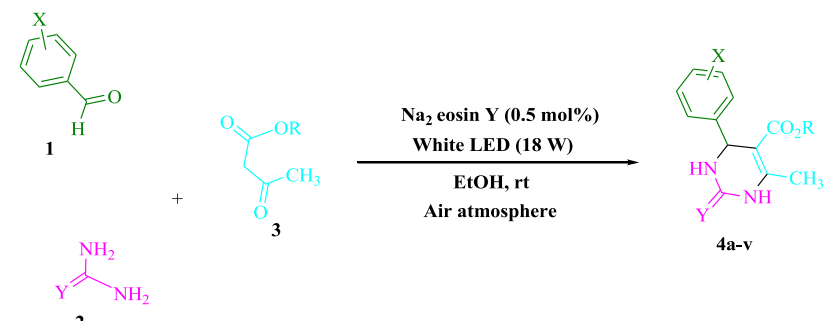
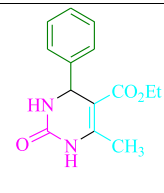
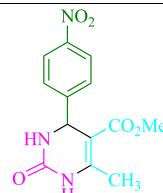
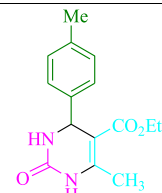
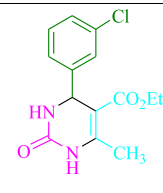
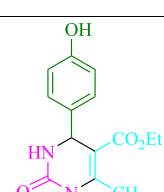
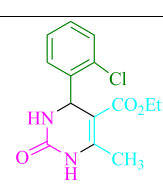
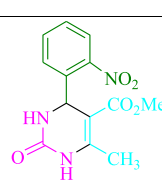
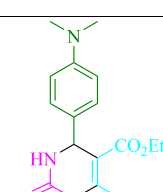
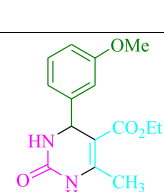
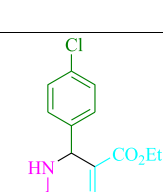
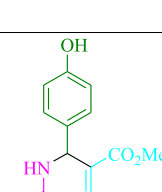
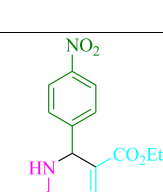
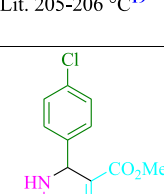
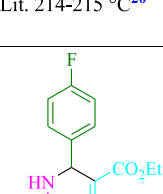
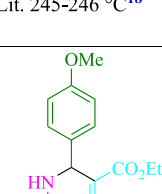
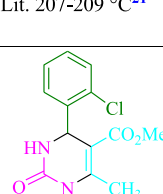
^aReaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol), and Na₂ eosin Y (0.5 mol %) at rt. ^bIsolated yield.

RESULTS AND DISCUSSION

To begin with, Table 1 summarizes the findings of an investigation into the reactivity of benzaldehyde (1.0 mmol),

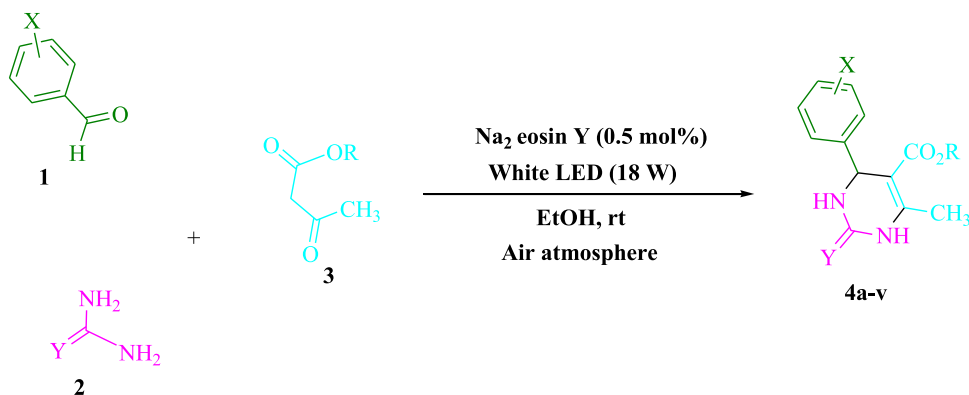
urea (1.5 mmol), and ethyl acetoacetate (1.0 mmol) in EtOH (3 mL) enhanced by irradiation at ambient temperature. With no photocatalyst, a trace quantity of 4a was detected at room

Table 3. Photoexcited Na₂ Eosin Y as a Photocatalyst for the Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones/thiones

			
 4a (10 min, 94%) Mp. 202–204 °C Lit. 200–202 °C ²¹	 4b (10 min, 91%) Mp. 213–215 °C Lit. 214–216 °C ²¹	 4c (10 min, 96%) Mp. 205–207 °C Lit. 204–205 °C ¹⁹	 4d (20 min, 89%) Mp. 192–194 °C Lit. 191–193 °C ¹⁸
 4e (20 min, 85%) Mp. 228–230 °C Lit. 230–232 °C ²²	 4f (15 min, 86%) Mp. 222–224 °C Lit. 220–223 °C ¹⁸	 4g (10 min, 94%) Mp. 275–277 °C Lit. 274–277 °C ²³	 4h (15 min, 89%) Mp. 255–257 °C Lit. 255–257 °C ²⁰
 4i (15 min, 91%) Mp. 206–208 °C Lit. 205–206 °C ¹⁹	 4j (20 min, 85%) Mp. 212–214 °C Lit. 214–215 °C ²⁰	 4k (20 min, 88%) Mp. 246–248 °C Lit. 245–246 °C ¹⁸	 4l (10 min, 93%) Mp. 206–208 °C Lit. 207–209 °C ²¹
 4m (20 min, 86%) Mp. 203–205 °C Lit. 205–206 °C ²⁵	 4n (10 min, 96%) Mp. 175–177 °C Lit. 174–176 °C ²²	 4o (15 min, 89%) Mp. 201–203 °C Lit. 202–203 °C ²⁰	 4p (15 min, 88%) Mp. 250–252 °C Lit. 248–252 °C ¹⁸

temperature for 60 min in 3 mL of EtOH (Table 1, entry 1). To promote the reaction, various organic photocatalysts (Figure 2) were examined in similar scenarios. Acceptably, the evolution of

this reaction was observed in 41–94% yields (Table 1) while obtaining the matching product 4a. As per our results, Na₂ eosin Y performed better than other eosins in this process. By adding

Scheme 3. Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones/thiones

0.5 mol % Na_2 eosin Y, the yield was improved to 94% (Table 1, entry 3). Additionally, a poor product yield was observed in dimethyl sulfoxide (DMSO), CH_3CN , CHCl_3 , CH_2Cl_2 , dimethylformamide (DMF), tetrahydrofuran (THF), and toluene (Table 2). As the reaction progressed slowly in H_2O ,

no solvent, EtOH, MeOH, EtOAc, and $\text{H}_2\text{O}/\text{EtOH}$, the yield and rate of the reaction increased (Table 2). The reaction proceeded extremely well in EtOH, yielding 94% under similar circumstances (Table 2, entry 3). The yield was tested using a variety of illuminations, showing that it increased somewhat in

Scheme 4. Proposed Mechanistic Route

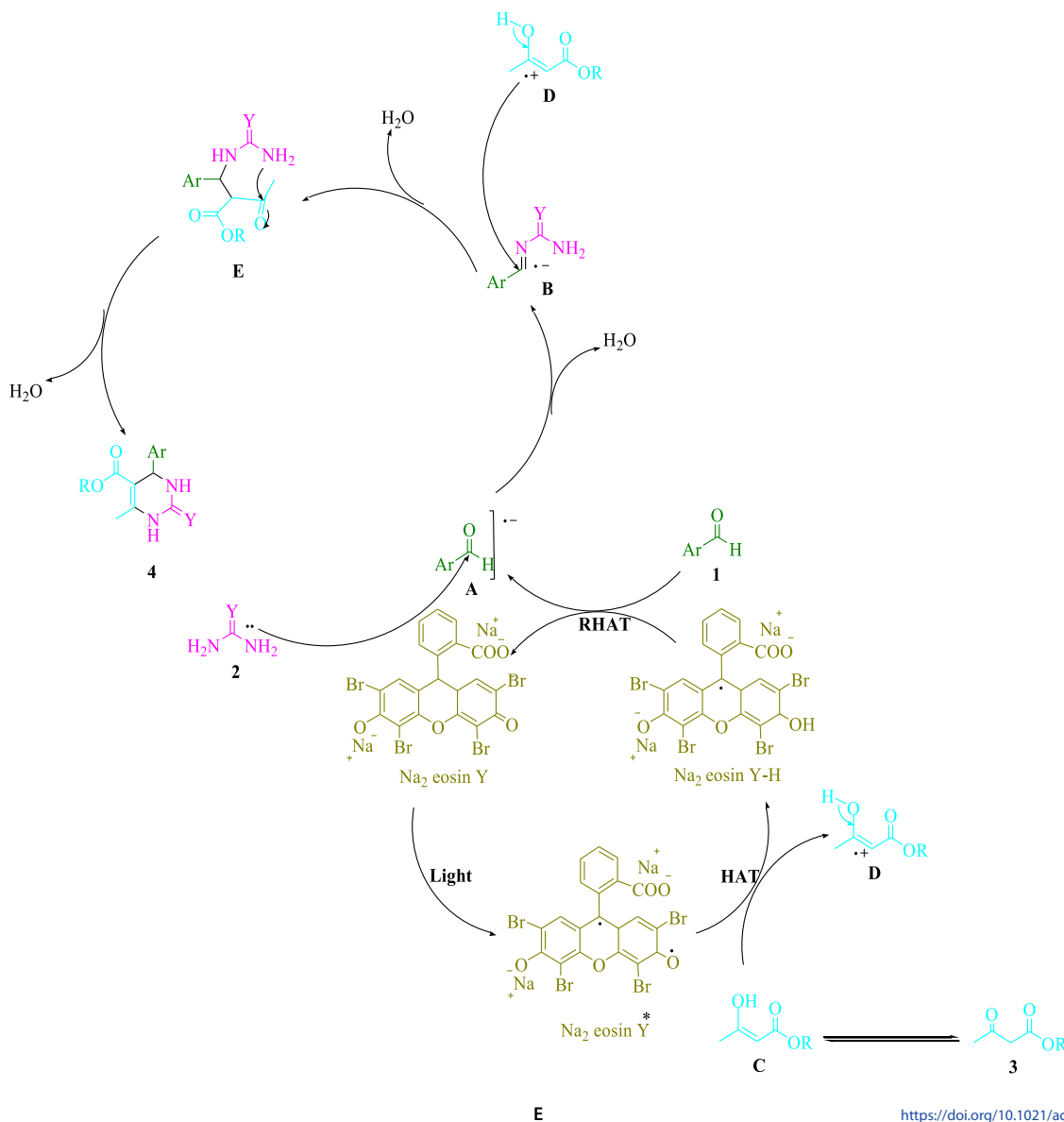


Table 4. Calculated Values of Turnover Number (TON) and Turnover Frequency (TOF)

entry	product	TON	TOF	entry	product	TON	TOF
1	4a	188	18.8	12	4l	186	18.6
2	4b	182	18.2	13	4m	172	8.6
3	4c	192	19.2	14	4n	190	19
4	4d	178	8.9	15	4o	178	11.8
5	4e	170	8.5	16	4p	176	11.7
6	4f	172	11.4	17	4q	184	12.2
7	4g	188	18.8	18	4r	174	11.6
8	4h	178	11.8	19	4s	182	18.2
9	4i	182	12.1	20	4t	172	8.6
10	4j	170	8.5	21	4u	180	12
11	4k	176	8.8	22	4v	174	11.6

response to white light (Table 2, entry 3). Based on the test control, there was a minuscule of 4a without utilizing the light source. Moreover, the enhanced settings were defined by irradiation of various intensities of a white light-emitting diode (LED). As seen in Table 2, the best results were obtained when white 18 W LED irradiation was used. It was revealed that this method can work with different substrates (Table 3, Scheme 3).

Table 4 incorporates information on TON and TOF. The lesser amount of catalyst used, the greater the yield, the higher the TON and TOF numerical values, and as the esteem increments, the catalyst will get more successful.

The fourth scheme denotes the preferred mechanism. As previously observed,^{1a,d,4} photoexcited modes originating from Na₂ eosin Y can act as direct HAT catalysts. Regeneration of the ground-state Na₂ eosin Y and the intermediate A occurs through a reverse HAT reaction between eosin Na₂ Y–H and arylaldehydes 1. Nucleophilic addition of this radical anion A to urea/thiourea 2 results in the formation of a reactive iminium intermediate B. The cation radical D is generated through a HAT process by promoting visible light-triggered Na₂ eosin Y*. To obtain the cyclized dehydrated 4, the cation radical D attacks the iminium intermediate B (Scheme 4).

Table 5 presents the comparison between the catalytic capacity of some catalysts in this work for generating 3,4-dihydropyrimidin-2-(1H)-ones/thiones. Na₂ eosin Y may have various advantages including the utilization of a small quantity of photocatalyst, a fast reaction time, and the absence of byproducts when visible light irradiation is used. The atom-economic protocol is very successful at multigram scales and has significant industrial implications. These materials excel in terms of both efficiency and purity.

CONCLUSIONS

In conclusion, the Na₂ eosin Y-derived photoinduced states act as a HAT catalyst for photochemically synthesizing 3,4-dihydropyrimidin-2-(1H)-ones/thiones through the three-condensation domino Biginelli response of β -ketoesters, arylaldehydes, and urea/thiourea in ethanol at room temperature. This research establishes a novel function for using a nonmetallic natural dye, Na₂ eosin Y, available commercially and at a cheap cost in the photochemical synthesis using the least amount of catalyst, obtaining good results, speeding up the process, and achieving a high atom economy. This is a successful one-pot reaction carried out under very efficient, moderate, and simple conditions.

Table 5. Comparison between the Catalytic Capacity of Some Catalysts Presented in This Work^a

entry	catalyst	conditions	time/yield (%) ^{ref}
1	baker's yeast	room temperature	1440 min/84 ¹⁹
2	hydrotalcite	solvent-free, 80 °C	35 min/84 ²⁰
3	[Al(H ₂ O) ₆](BF ₄) ₃	MeCN, Reflux	1200 min/81 ²¹
4	Cu(BF ₄) ₂ ·xH ₂ O	room temperature	30 min/90 ²³
5	[Btto][p-TSA]	solvent-free, 90 °C	30 min/96 ²⁴
6	triethylammonium acetate	solvent-free, 70 °C	45 min/90 ²⁵
7	saccharin	solvent-free, 80 °C	15 min/88 ²⁶
8	caffeine	solvent-free, 80 °C	25 min/91 ²⁷
9	Na ₂ eosin Y	visible light irradiation, EtOH, rt	10 min/94 ^{this work}

^aBased on the three-component reaction of benzaldehyde, ethyl acetoacetate, and urea.

EXPERIMENTAL SECTION

General. The physical properties and infrared spectra of all substances were measured using an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. Additionally, the spectra (¹H NMR and ¹³C NMR) were recorded with nuclear magnetic resonance on a Bruker (DRX-400, DRX-300, and DRX-100) apparatus using DMSO-*d*₆ as the solvent. The mass spectra were acquired using a spectrometer from Agilent Technology (HP) operating at a 70 eV ionization potential. The elements (carbon, hydrogen, and nitrogen) were investigated using a Heraeus CHN-O-Rapid analyzer. We purchased the reagents from chemical firms Fluka, Merck, and Acros and utilized them with no further treatment.

General Procedure. Under white LED (18 W) irradiation, a combination of arylaldehyde derivatives (1, 1.0 mmol), urea/thiourea (2, 1.5 mmol), and ethyl/methyl acetoacetate (3, 1.0 mmol) in EtOH (3 mL) was added to Na₂ eosin Y (0.5 mol %) (Scheme 3) and stirred at ambient temperature. TLC was used to monitor the reaction's progress, using *n*-hexane/ethyl acetate (3:2) as the eluent. After completion of the reaction, the obtained material was screened and washed with water, and the crude solid was crystallized again from ethanol to obtain the pure substance with no further purification. After comparing spectroscopic data, the goods were categorized.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.1c05808>.

FTIR, ¹H NMR, and ¹³C NMR spectra; mass spectra; and CHN–O analysis (PDF)

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Notes

The author declares no competing financial interest.

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