Research Article

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Visible-light-assisted base-catalyzed, one-pot synthesis of highly functionalized cinnolines

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Abstract: The synthesis of cinnolines has found great interest due to their diverse biological and industrial potency. Yet, the reported synthetic protocols for their synthesis showed limitations that involve harsh reaction conditions such as strong acidic or basic medium, low reaction yields, and using expensive and high loading catalysts. The C–H functionalization has been recognized as intriguing synthetic approach for the synthesis of aromatic/heteroaromatic scaffolds over the past two decades. Here, we reported a novel metal-catalyzed free photocatalytic synthesis of polyfunctionally substituted cinnolines. When ethyl 1-aryl-5-cyano-4-methyl-6-oxo-1,6-dihydropyridazine-3-carboxylates and nitrostyrene derivatives are irradiated with white light (LED 30 W) in ethanol in the presence of piperidine (30 mol%) in open air for 8 h at room temperature, the corresponding polyfunctionally substituted cinnolines are obtained in excellent yields (90–95%) via C–H activation of pyridazine methyl group and nitrostyrene (–N═O) function. Several merits were achieved, which are as follows: (1) the reaction is metal-free; (2) the reaction proceeds with increasing energy efficiency; (3) diversity of functionally substituted cinnolines; (4) high EcoScale value, which reflects the greens of the reaction; and (5) ease handling either in conducting the reaction or in the isolation of products.

Keywords: C–H functionalization, visible-light, metal-catalyst free, one-pot synthesis, polyfunctionally substituted cinnolines

1 Introduction

Nitrogen-containing heterocycles are ubiquitous in pharmaceutical and biologically active scaffolds [1,2]. In this regard, cinnoline and its derivatives as aromatic bicycles contain two adjacent nitrogen atoms in the same six-membered ring, which represent an interesting and important class of heterocycles that constitute the core structure of numerous dyes [3,4], drugs [5–7], natural products [8], materials [9] as well as optical [10] and luminescent reagents [11]. Also, they exemplified intriguing anti-inflammatory [12], analgesic [13], antimicrobial [14,15], antimalarial [16], and anticancer [17–20] potencies owing to their ability to interact with several molecular receptors and enzymes [21–23]. The examples of biologically active cinnolines are illustrated in Figure 1.

Cinnoline was first synthesized in 1883 by Von Richter [24] via the ring closure of *in situ* formed phenyldiazonium ions onto ortho alkyl function in the presence of hydrochloric or hydrobromic acid. Other classical methods were followed, involving the cyclization of aryl hydrazines [25], aryl hydrazones [26,27], triazines [28], and phenyl diazonium salts [29].

Several disadvantages were associated with these protocols involving harsh reaction conditions such as strong acidic or basic ones, elevated temperatures, as well as low reaction yields, formation of side products, and limited scope. In this regard, atom economical efficient approaches for cinnoline synthesis have been achieved via the transition metal-catalyzed methodologies.

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Transition metal-catalyzed reactions have recently recognized as an efficient and reliable strategy for carbon–carbon and carbon–heteroatom bond formation [30]. In recent years, green and atom economical approaches for cinnoline synthesis have been realized using the transition metal-catalyzed conditions. A novel two-step copper-catalyzed synthesis to build this interesting scaffold was developed by Willis's group [31] via intermolecular annulations of aryl-alkenyl dihalides and *N*,*N*-disubstituted hydrazines. Ge et al. [32] have developed appealing work for cinnoline synthesis via the aerobic copper-catalyzed dehydrogenative cyclization of *N*-methyl-*N*-phenylhydrazones. A novel cascade copper-catalyzed radical cyclization of arylsulfonylhydrazones derived from ortho-alkynyl arylketones was recently reported by Wang's group [33] to afford the corresponding cinnolines in good yields.

A novel cross-dehydrogenative coupling reaction of *N*-phosphorylhydrazones using copper catalyst has been reported – for the first time – to afford the corresponding cinnoline derivatives in good to excellent yields [34]. Rh-catalyzed tandem redox-neutral annulation C–H and C–N formation has been reported by Lin's group [35] starting from azo and diazo precursors. The process revealed a diversity of substrate scope. Very recently, Pd(II)-catalyzed cross-dehydrogenative regioisomeric coupling of 1-aryl-indazolones and subsequent [4 + 2] annulations using allenoate precursor was reported by Sakhuja et al. [36] to afford either internal or exocyclic double-bond cinnoline derivatives depending on the applied reaction conditions. Despite the merits of using transition metals in cinnoline synthesis, sometimes they are expensive and potentially toxic and their selectivity is difficult to be controlled.

Although these reactions have their achievements, the need for novel, greener, efficient, and atom-economical procedures using available precursors and simple reaction courses to access polyfunctionally substituted cinnolines is highly desirable.

Given the increased requests for atom-economic, green, and sustainable chemical transformations, visible-light photocatalysis are emerging strategies that can meet such demand. Such process continuously using photons as a green energy source. The inexpensive, practical nature selectivity, and ease handle of visible light to conduct chemical transformations have attracted extensive attention, and immense development was achieved in the past few years [37]. It is worth mentioning that visible light has lower energy than ultraviolet traditionally applied for photocatalysis. In recent years, the metal-free photocatalysis transformation has become one of the highly demanding strategies in chemical processes [38].

As a part of our continuing efforts to develop green and efficient methodologies for the synthesis of biologically relevant heterocycles [39–45], we report herein, for the first time, the visible light-promoted synthesis of polyfunctionally substituted cinnolines via the metal-free reaction of ethyl 1-aryl-5-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-carboxylates **3a–d** with nitrostyrenes **4a–f** in ethanol (EtOH) containing a catalytic amount of piperidine at room temperature (Scheme 1).

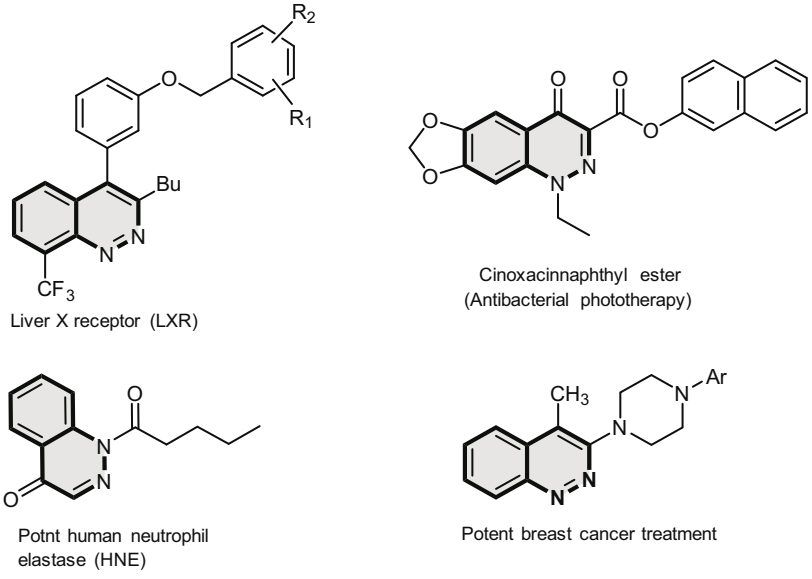
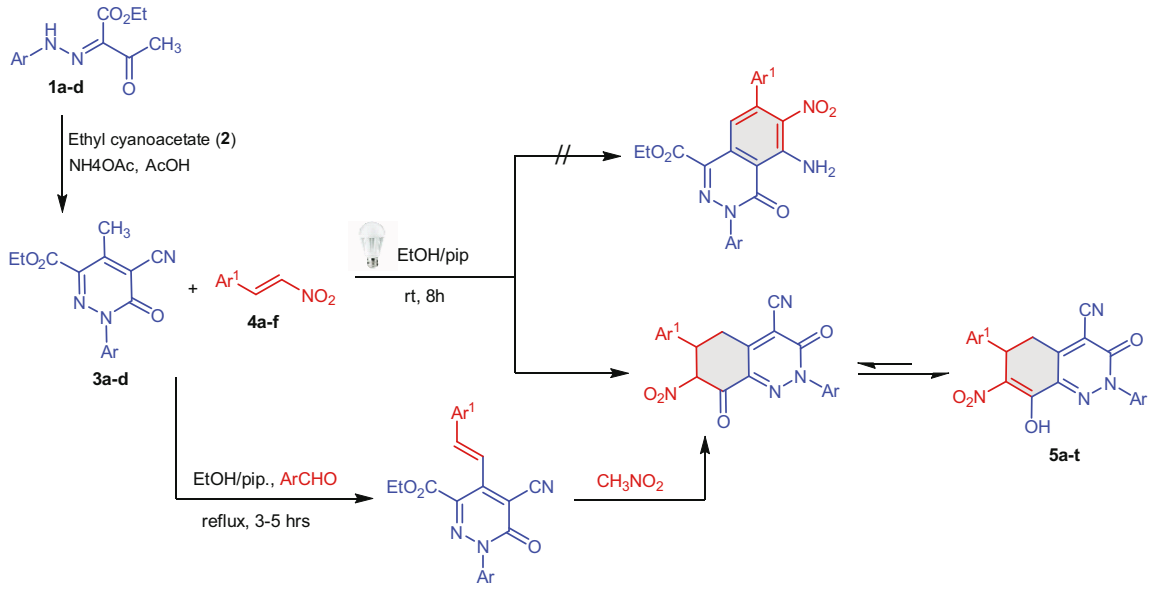
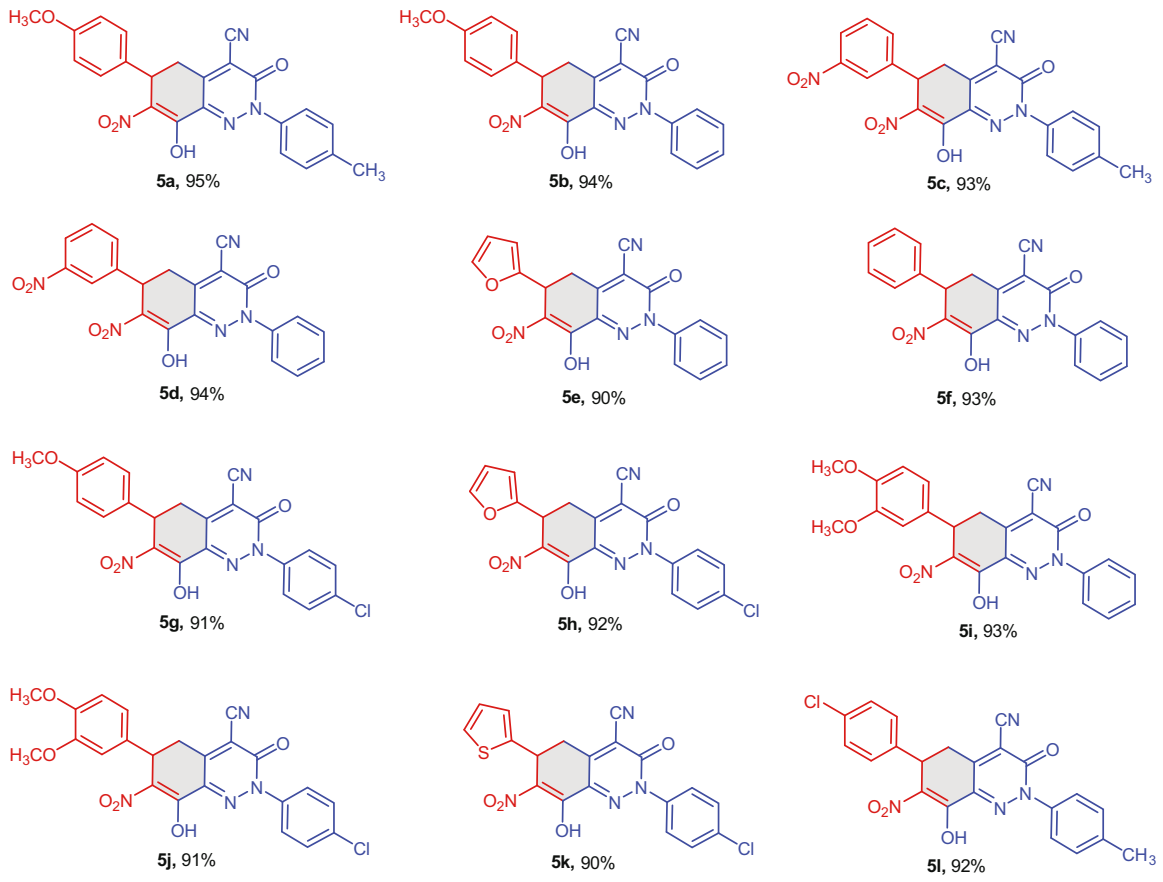


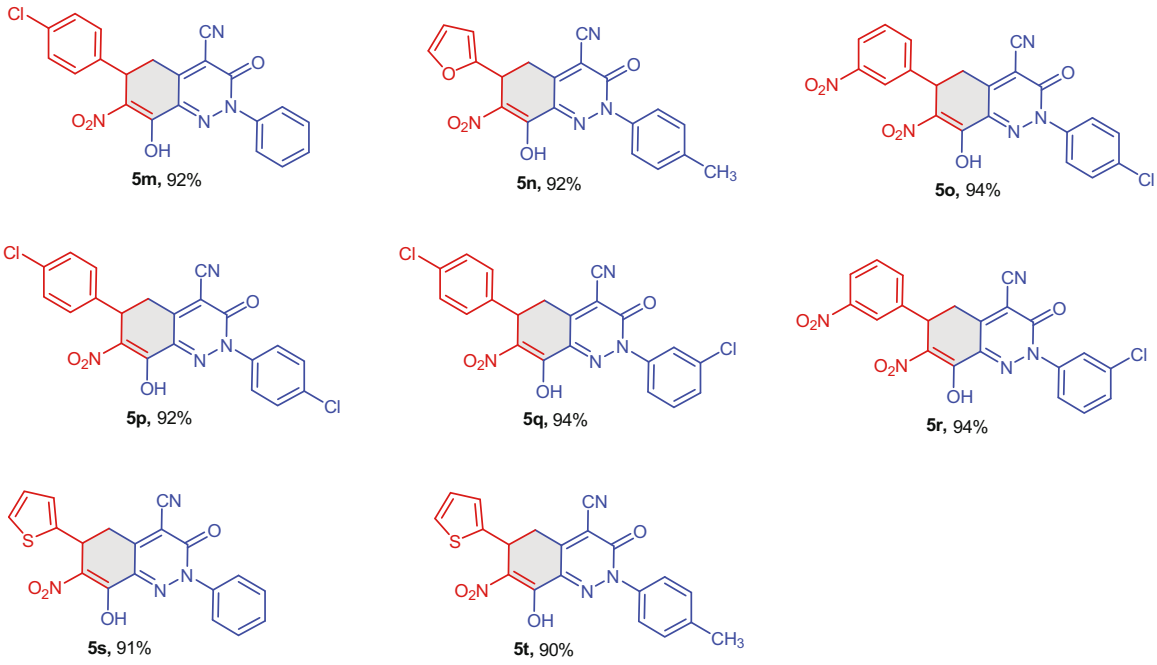
Figure 1: Examples of biologically relevant cinnolines.



1a, Ar= C_6H_5; **1b**, Ar= 4-$CH_3C_6H_4$; **1c**, Ar= 4-Cl-C_6H_4; **1d**, Ar= 3-Cl-C_6H_4. **3a**, Ar= C_6H_5; **3b**, Ar= 4-$CH_3C_6H_4$; **3c**, Ar= 4-Cl-C_6H_4; **3d**, Ar= 3-Cl-C_6H_4. **4a**, Ar^1= 4-$OCH_3C_6H_4$; **4b**, Ar^1= 3-$NO_2C_6H_4$; **4c**, Ar^1= furan-2-yl; **4d**, Ar^1= thiophen-2-yl; **4e**, Ar^1= 3,4-$(OCH_3)_2C_6H_3$; **4f**, Ar^1= 4-Cl-C_6H_4.



Scheme 1: Synthesis of cinnoline derivatives **5a–t**.



Scheme 1: (*Continued*)

2 Materials and methods

2.1 Chemistry

All chemicals and solvents were purchased from Aldrich or Merck companies. Melting points were recorded using open capillaries in a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were run in a Bruker (600 MHz) for ^{1}H NMR and (150 MHz) for ^{13}C NMR spectrometer; using dimethyl sulfoxide-d_6 as a solvent and tetramethylsilane as internal standard, and the chemical shifts are expressed in δ ppm. Mass spectra were measured on a VG Autospec-Q MS 30 with electron ionization (70 eV) mode. All reactions were monitored by thin-layer chromatography (TLC) on aluminum sheets pre-coated with silica gel and were carried out until starting materials were completely consumed. The reaction mixture was placed in open air under irradiation from white LED lamp (30 W) at room temperature. Microanalytical data were obtained from the Microanalytical Data Unit at Kuwait University.

2.2 General procedure for the synthesis of cinnoline derivatives 5a–t

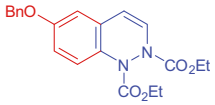
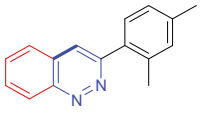
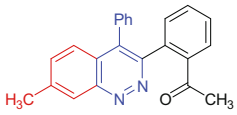
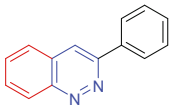
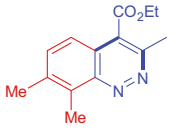
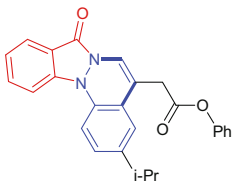
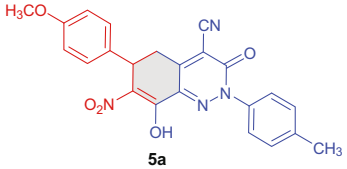
Method (A) (visible light): To a suspension of **3a–d** (1 mmol) and nitrostyrenes **4a–f** (1 mmol) in absolute EtOH (10 mL),

Table 1: Different reaction conditions screened to get the best yield of products*

Entry	Solvent	Base	LED (yield%)	Conventional heating (yield%)
1	THF	Na_2CO_3	65	60
2	THF	$NaHCO_3$	60	55
3	THF	Et_3N	70	64
4	THF	Piperidine	73	68
5	DMF	Na_2CO_3	78	73
6	DMF	$NaHCO_3$	76	72
7	DMF	Et_3N	80	75
8	DMF	Piperidine	80	77
9	CH_3CN	Na_2CO_3	80	75
10	CH_3CN	$NaHCO_3$	77	70
11	CH_3CN	Et_3N	86	80
12	CH_3CN	Piperidine	89	83
13	EtOH	Na_2CO_3	85	80
14	EtOH	$NaHCO_3$	80	75
15	EtOH	Et_3N	88	80
16	**EtOH**	**Piperidine**	**95**	**82**
17	EtOH	—	NR	NR
18	Dioxane	Na_2CO_3	82	79
19	Dioxane	$NaHCO_3$	75	70
20	Dioxane	Et_3N	82	78
21	Dioxane	Piperidine	86	80

*Optimized reaction conditions: open air and irradiation of visible light with 30 W white LED; 4-methyl-pyridazine **3a** and nitrostyrene (**4a**), equimolar amounts, base (30 mol%), solvent (10 mL), temperature (rt, 25°C), and time (8 h).

Table 2: Comparison of EcoScale of literature reported synthesis of cinnoline derivatives

Product	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)	EcoScale
	Dioxane	CuI/DMEDA/K_2CO_3	90	18	86	77 [31]
	DMF	Py/CF_3SO_3H (3.5:01), O_2 (1 atm)	110	14	96	82 [32]
	DCE/ CH_3OH (3:1)	$Cu(OAc)_2$, (5 mol%), TBHP (3.0 equiv), K_2CO_3 (1.0 equiv)	40, N_2	5	86	73 [33]
	Toluene	$Cu(OAc)_2.H_2O$	110	11	94	81 [34]
	PivOH/DCE	$[RhCp^*Cl_2]_2/AgSbF_6$	50	24	93	79 [35]
	Dioxane	$Pd(OAc)_2$ (15 mol%), NaOAc (100 mol%)	100	5	87	76 [36]
 5a	**Ethanol**	**Piperidine (30 mol%)**	**Rt**	**8**	**95**	**96**

piperidine (30 mol%) was added. The reaction mixture was irradiated with LED white lamb (30 W) in open air for 8 h, and the reaction progress was monitored by TLC. The resulting solid product was collected by filtration, washed with EtOH, dried, and recrystallized from EtOH.

Method (B) (Conventional heating): A suspension of **3a–d** (1 mmol), **4a–f** (1 mmol), and piperidine (30 mol%) in absolute EtOH was heated under reflux for 3–5 h (monitored by TLC). After concentration and cooling to room temperature, the precipitated solid product was collected by filtration, washed with EtOH, dried, and recrystallized from EtOH.

3 Results and discussions

Initially, visible-light-assisted reaction of ethyl 5-cyano-4-methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-3-carboxylate (**3a**), which prepared via the reaction of ethyl 3-oxo-2-(2-phenyl-hydrazineylidene)butanoate (**1a**) with ethyl cyanoacetate (**2**) in the presence of ammonium acetate/acetic acid and heating under microwave irradiation at 70°C for 3 min. [46], and nitrostyrene **4a** was chosen as a model to optimize the reaction conditions. The reaction was conducted by reacting 1 mmol of **3a** and nitrostyrene **4a** in ethanol as a solvent and catalytic amount of piperidine in a system open to air. Irradiation was carried out by white LED (30 W) for 8 h. We are delighted to achieve excellent yield (95%) of the corresponding cinnoline derivative **5a** (entry 16). As shown in Table 1, when several solvents including tetrahydrofuran (THF), dimethylformamide (DMF), acetonitrile (CH_3CN), and dioxane, with piperidine were used as a catalyst, a lower yield was achieved (Table 1). Other bases, such as sodium carbonate (Na_2Co_3), sodium bicarbonate ($NaHCO_3$), and triethylamine (Et_3N), were examined, and piperidine proved to be the best catalyst, affording the best yields. No reaction occurred in the absence of basic catalyst, suggesting its involvement in some

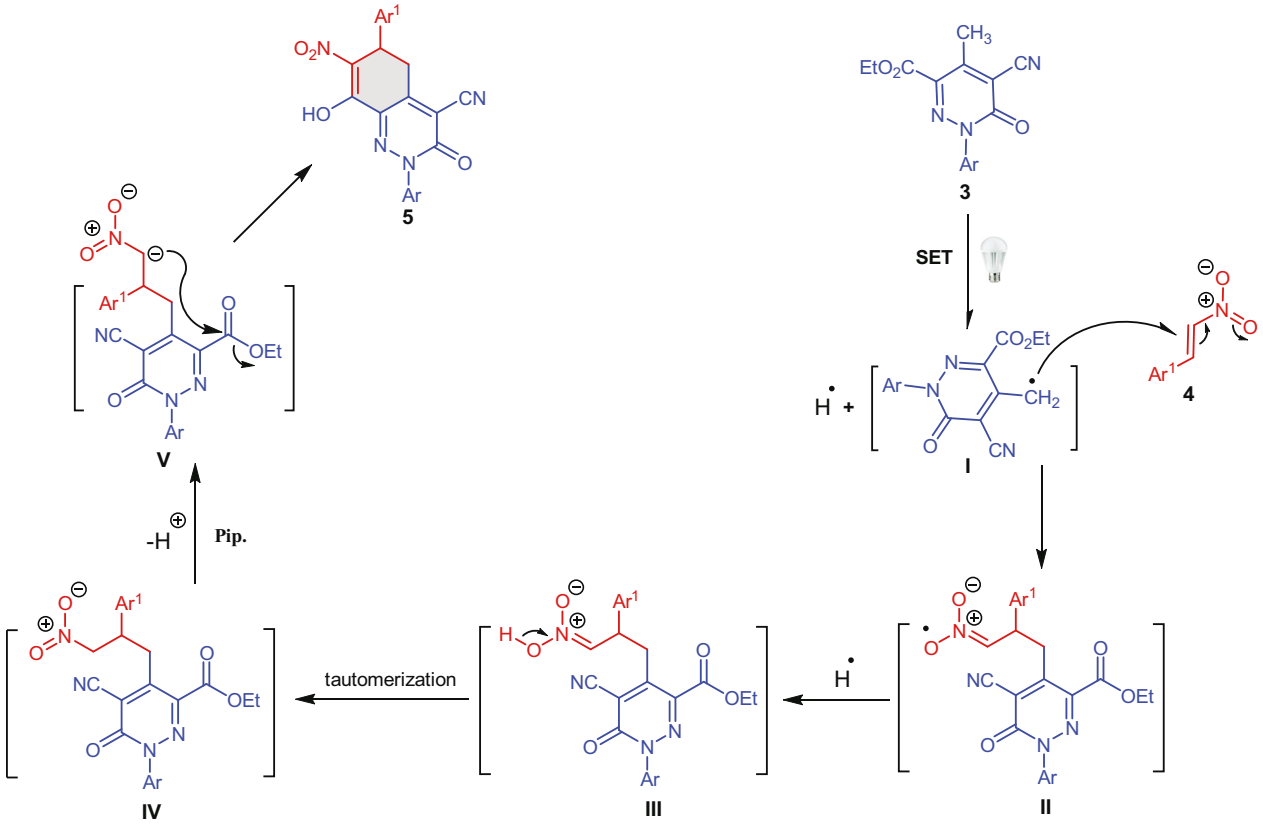
steps (entry 17). When the reaction was carried out under nitrogen or argon atmosphere, only a trace amount of **5a** was detected with nitrogen; however, no product was observed in argon atmosphere, which both serve as a protective shield to prevent air oxygen, implying that the presence of O_2 (air) is essential for the reaction. Besides, performing the reaction under blue or green LED lights affords no product, and the reactants were recovered almost unchanged even after exposure to light for a longer time (12 h). This could be rationalized for the energy of these photons at these wavelengths, which is insufficient to reach the threshold energy of the reaction. In order to determine the exact pathway, either thermal or photochemical, the reaction mixture was monitored by inserting thermometer in the reaction mixture. The temperature reached during light exposure did not exceed the room temperature (25°C), which ruled out the possibility of thermal reaction pathway.

In order to evaluate the privilege of visible-light-induced reaction, the reaction of **3a** with **4a** in EtOH/piperidine under conventional heating for 3–5 h was examined. The desired product **5a** was obtained in lower yield (83%) than the corresponding visible-light methodology. (Table 1).

The structure of **5a** was established based on its analytical and spectral data. ^{1}H NMR revealed the absence of ethoxy (OC_2H_5) pyridazine function at C-5, which showed the involvement of this group in the cyclization step, in addition to the doublet signal at δ = 2.98 ppm and the triplet signal at δ = 5.69 ppm assigned for cinnoline C-5 and C-6 protons, respectively. ^{13}C NMR and mass spectrum were in agreement with the proposed structure (Supplementary Information). Using optimized visible light, the photocatalytic reaction variety of pyridazine derivatives **3a–d** and nitrostyrenes **4a–f** was screened, and the results revealed the accessibility of our protocol to achieve excellent yields irrespective of the nature of pyridazine or nitrostyrene aryl group either electron-donating or electron-attracting (Scheme 1).

After synthesizing the diversity of cinnoline derivatives, some controlled experiments were performed to clarify the mechanism. The standard reaction under dark or open-air conditions at ambient temperature was conducted, and no product was obtained even after prolonged reaction time up to 24 h, which revealed that the radical pathway is involved in the reaction course [47].

EcoScale [48] is a novel semi-quantitative tool to evaluate the greenest of a particular reaction based on yield, cost, safety, technical steps, temperature, ease of workup, and purification. It is assigned by a range of penalty points of such metrics subtracted from the total of 100 points.



Scheme 2: Plausible mechanism to account for the formation of the cinnoline derivatives **5a–t**.

The EcoScale of compound **5a** has been calculated and compared with other key methods in order to evaluate the greens of our protocol. We found that our methodology has a value of 96 in terms of EcoScale, which is the highest among others (Table 2).

In order to obtain insights into the reaction mechanism, control experiment was conducted via adding 1.0 mol% of 1,4-benzoquinone inhibitor to the reaction mixture under optimized conditions. After 8 h, no product was detected, indicating that radical intermediates are involved in the product formation. It is worth to mention that in visible-light-driven catalyst-free synthesis, at least one of the starting materials can absorb the light and activates the single electron transfer pathway to generate radical substrate [49].

A plausible mechanism to account for the formation of the reaction products **5a–t** is depicted in Scheme 2. First, pyridazine **3** with its active methyl function acts as a light-absorbing molecule that undergoes catalyst-free single electron transfer providing pyridazine radical **I** and followed by coupling of radical **I** with nitrostyrene **4** forming intermediate **II**, which abstracts hydrogen radial introducing intermediate **III**, which undergoes tautomerization to afford the corresponding intermediate **IV**. Abstraction of hydrogen proton from methylene moiety adjacent to nitro group in **IV** by base gives intermediate **V**. The latter intermediate **V** undergoes intramolecular cyclization via the attack of carbanion to ester carbonyl group followed by the loss of one molecule of EtOH to give the final isolable product **5**.

4 Conclusion

We have developed a highly efficient atom economical and environmentally friendly metal-free visible-light aerobic photocatalytic one-pot synthesis of polyfunctionally substituted cinnolines in excellent yields. The method showed diverse advantages such as inexpensive and laboratory available starting materials, simple workup of the reaction, and good functional group tolerance. The use of visible light instead of thermal heating constitutes a green and trending synthesis of great interest. The mechanism to account for the formation of end product was demonstrated to go through a free radical process. Moreover, the presence of base is crucial for the final cyclization step leading to the final end product.

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Conflict of interest: The authors state no conflict of interest.

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on a reasonable request.

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