



A Rhodamine-B Catalyzed Visible-Light-Mediated Benign Synthetic Route for 4,5-Dihydro-1*H*-pyrazoles

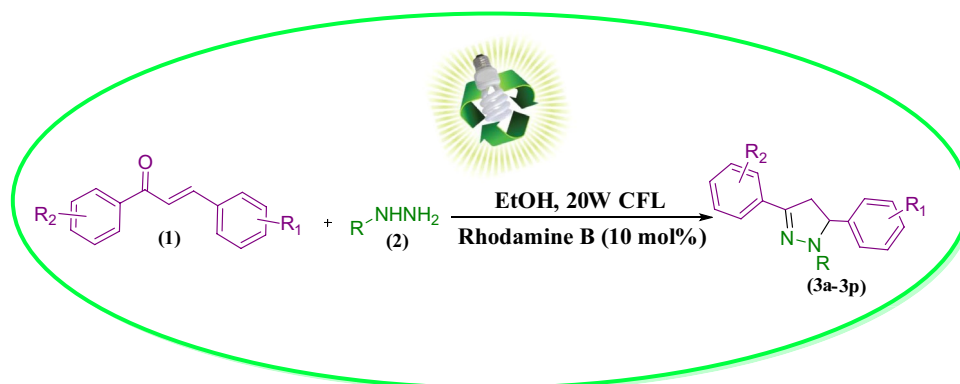
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Abstract

Herein, an apposite and straightforward methodology has been established for the synthesis of 4,5-dihydro-1*H*-pyrazole and its derivatives by using Chalcones and Hydrazines as substrates in EtOH under 20W CFL irradiation at room temperature. The distinctive trait of this protocol is the utilization of an efficient, green, highly water soluble organophotoredox catalyst “Rhodamine B”, a simple red xanthene dye, to create C–N bonds via formation of free radicals and eventually terminating with intramolecular cyclization. Short reaction time, environmentally benign approach, cost effectiveness, feasibility and adaptability with respect to a wide range of substrates and good to excellent yield of the product supplements the synthesis.

Graphical Abstract



Keywords Visible-light-assisted protocol · Benign synthesis · Rhodamine B · Room temperature · 4,5-dihydro-1*H*-pyrazoles

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1 Introduction

For last few decades, the scientific communities have together augmented their voice about the impact of our acts on the environment, putting pressure on the authorities and looking for explications to address the issue. Amongst them, chemistry has received foremost attention, as many conventional chemical procedures are not sustainable over long periods of time, with disastrous outcomes for the environment and human well-being. Within this frame of reference, the concept ‘Green Chemistry’ is slowly but continuously attaining popularity [1, 2].

Visible-light photoredox catalysis has been experiencing a resurgence as a consequence of the rising interest in renewable energy and green chemistry [3–5]. On considering recent environmental concerns which necessitates the development of sustainable methodologies over the conventional practices, visible light procedures are a judicious choice to explore the full possibility of this protocol. In the last few years, visible light triggered transformations have captured a notable attention from scientists and organic chemists in the area of environmentally benign synthesis with various advantages like eco-sustainability, ubiquity, operational feasibility, mild reaction conditions, non-hazardous nature and thus have emerged as a valuable approach for a myriad of organic synthesis [6, 7].

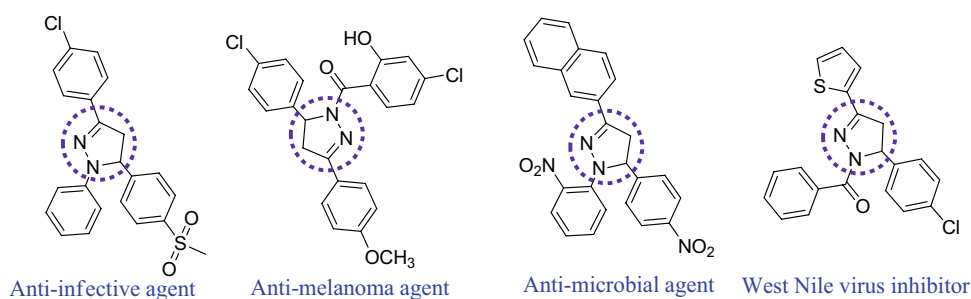
Although, some organic compounds do not undergo the required reaction due to their incapability to absorb visible light. To overcome this constraint, chemists use transition metals, nanoparticles and organic dyes as photo catalysts [8–11]. In this regard, a highly water soluble and simple

red xanthene dye, Rhodamine-B (RB), is a fascinating alternative and is being widely used as an organophotoredox catalyst for organic interconversions [12–14].

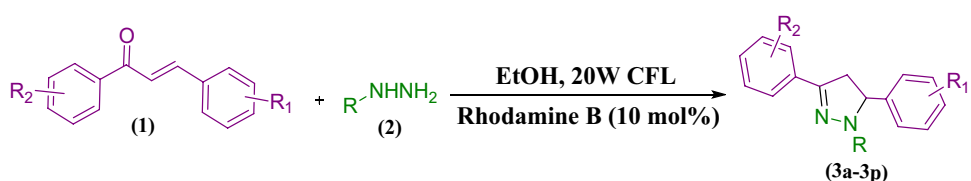
Nitrogen containing compounds symbolize an indispensable category of compounds because of their relevance to biological and medicinal significance. Within this context, a five membered nitrogen containing heterocycle, 4,5-dihydro-1*H*-pyrazole exhibits various biological and pharmaceutical properties like being anti-cancer, anti-convulsant, anti-depressant, anti-melanoma, anti-microbial and anti-infective activities [15–20], etc. (Fig. 1).

Up to now, several synthetic routes for 4,5-dihydro-1*H*-pyrazoles have been developed, but these procedures are linked with numerous disadvantages like utilization of large quantities of reagents or catalysts, long reaction time, use of inorganic bases, very high temperature, etc. [21–25]. Henceforth, the scheming of an easy and proficient method for direct formation of nitrogen comprising heterocycle, 4,5-dihydro-1*H*-pyrazole, posed as an alluring and a challenging pursuit for us. In order to expand our continuing efforts on environmentally benign synthesis [26–31] and the huge biological attributes of 4,5-dihydro-1*H*-pyrazoles, herein we have developed an easy, green, visible light driven, two component protocol for the synthesis of 4,5-dihydro-1*H*-pyrazole and its derivatives by using Rhodamine B as organophotoredox catalyst and Chalcones (1) and Hydrazines (2) as reactants in EtOH under 20W CFL irradiation at room temperature (Scheme 1).

Fig. 1 Some biologically important derivatives of 4,5-dihydro-1*H*-pyrazole



Scheme 1 Synthesis of 4,5-dihydro-1*H*-pyrazoles



2 Results and Discussion

Our initial efforts focused on the exploration of optimized reaction conditions by electing chalcone (**1a**) and phenylhydrazine (**2b**) as model substrates. The results have been abridged in (Table 1 and 2).

To begin with, we took chalcone (**1a**) and phenylhydrazine (**2b**) in toluene using 5 mol% of Rhodamine B under CFL (20 W) irradiation and found that only 25% product was formed (Table 1, entry 1). Subsequently, we have carried out this reaction with other solvents like DMF, DMSO, CH₃CN, DCM, MeOH and EtOH (Table 1, entries 2–7). Fascinatingly, it was observed that EtOH is a perfect solvent for the present methodology which afforded 85% yield of the product within 1 h (Table 1, entry 7). In an effort to further upsurge the efficacy of this reaction, we performed a number of test reactions in presence of different photocatalysts and varied sources of visible light (Table 2). We discovered that 10 mol% Rhodamine-B afforded 90% yield of the product in 1 h (Table 2, entry 5). Our next focus consisted of deciding on the appropriate photocatalyst loading (Table 2, entries 4–6). Multiple trials led us to deduce that 10 mol% Rhodamine-B is the most favorable for this protocol (Table 2, entry 5). Our next venture was to examine the varying effects of employing different intensities of visible light source (CFL) on the present procedure (Table 2, entries 5 and 7–10). In order to achieve this goal, we carried out a series of reactions by using 18 W, 20 W, 22 W CFLs, sunlight and white LED

as a source of visible light and observed that 20 W CFL is the most appropriate for the present protocol (Table 2, entry 5). Further, to get an insight into the mechanism of proposed synthetic route, we used a radical scavenger “TEMPO” [(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl] and established that the reaction was inhibited which directs towards the participation of radicals in the reaction [32] (Table 2, entry 12).

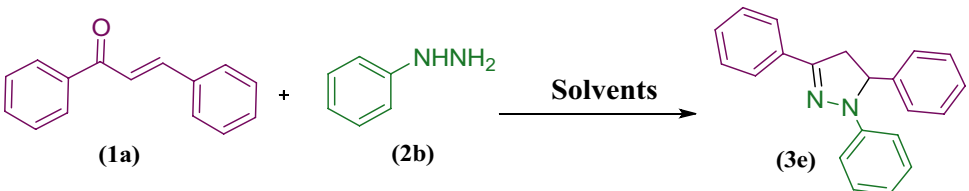
Eventually, we succeeded in establishing the finest reaction conditions for this procedure with model substrates and succeeded; Rhodamine-B (10 mol%) catalyzed, visible-light-facilitated synthetic route for 4,5-dihydro-1*H*-pyrazoles in EtOH under 20 W CFL irradiation with 90% optimal yield of the product in 1 h.

As soon as the optimal reaction conditions were deciphered, we were enthused about the evaluation of the possibilities and restrictions of this reaction pathway with various derivatives of chalcone (**1**) and hydrazine (**2**). To our delectation, reactants containing electron withdrawing group or electron donating group, both were well abided by and provided substantial yield of the product (Scheme 2).

2.1 Gram Scale Synthesis

We have also executed the above experimentation on a large scale to corroborate the practicability of the proposed transformation. For this, we took EtOH in a round bottom flask and added Chalcone (**1a**, 10 mmol, 2.0826 g), phenylhydrazine (**2b**, 10 mmol) in presence of Rhodamine B (10 mol%) under 20 W CFL irradiation at room temperature and

Table 1 Optimization of solvents^a

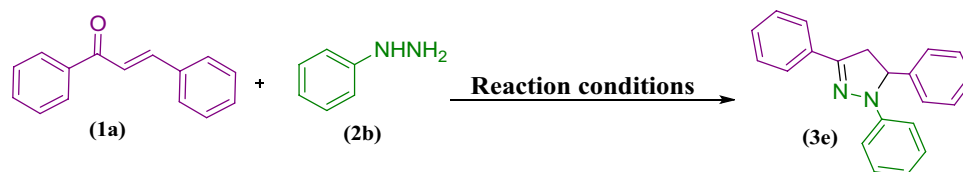


Entry	Solvent	Time (hour)	Yield (%) ^b
1	Toluene	1	25
2	DMF	1	30
3	DMSO	1	20
4	CH ₃ CN	1	75
5	DCM	1	40
6	MeOH	1	50
7	EtOH	1	85

DMF Dimethylformamide, DMSO Dimethylsulfoxide, DCM Dichloromethane

^aReaction conditions: **1a** (1.0 mmol), **2b** (1.0 mmol) in different solvents and 5 mol% of rhodamine-B using 20W CFL irradiation under an open atmosphere at room temperature

^bIsolated yield of product

Table 2 Optimization of reaction conditions^a

Entry	Photocatalyst (mol %)	Time (hour)	Yield (%) ^b
1	Eosin Y (10)	1	75
2	Eosin Y (5)	1	60
3	Eosin Y (20)	1	75
4	Rhodamine B (5)	1	85
5	Rhodamine B (10)	1	90
6	Rhodamine B (20)	1	90
7	Rhodamine B (10) ^c	1	81
8	Rhodamine B (10) ^d	1	90
9	– ^e	1	20
10	Rhodamine B (10) ^f	1	57
11	Rhodamine B (10)+TEMPO ^g (2 mmol)	1	Trace

^aReaction conditions: **1a** (1.0 mmol), **2b** (1.0 mmol) in EtOH (10 mL) using 20W CFL irradiation under an open atmosphere at room temperature

^bIsolated yield of product

^cCFL (18 W)

^dCFL (22 W)

^eSunlight

^fWhite LED

^g(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl

product 4,5-dihydro-1*H*-pyrazole (**3e**) was formed within 1 h in 90% yield by employing common laboratory glasswares (Scheme 3).

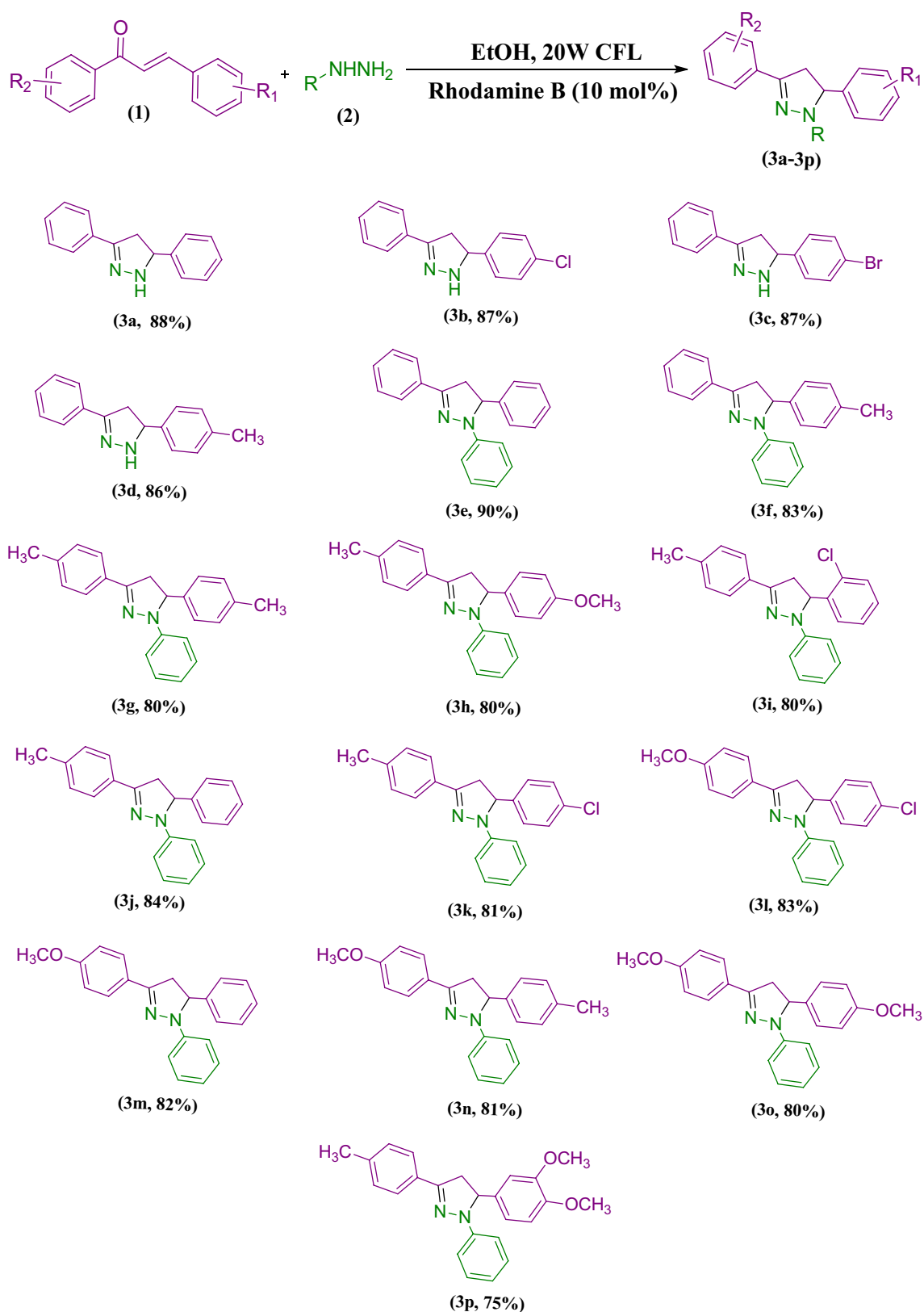
2.2 Mechanism

On the basis of above experimental results and literature studies, [13, 14, 26, 27, 29, 33] a proposed mechanism has been discussed thoroughly in scheme 4. In presence of light, on photo-absorption, Rhodamine B goes to its excited state (**RB***) and a single electron transfer (**SET**) takes place which converts chalcone (**1**) and phenyl hydrazine (**2**) into their corresponding radical-anion (**A**) and radical-cation (**B**), respectively. Simultaneously, Rhodamine B radical-cation and Rhodamine B radical-anion that are formed in the first step get quenched by oxygen and this completes the photocatalytic cycle of Rhodamine B. [13, 14] Thereafter, coupling of the radical-anion (**A**) and radical-cation (**B**) takes place and results into intermediate (**C**). Now, the homolytic cleavage of N–H bond and C=C bond of intermediate (**C**) occurs which results into intermediate (**D**). Eventually, the

biradical coupling of intermediate (**D**) followed by dehydration results into the desired product (**3**).

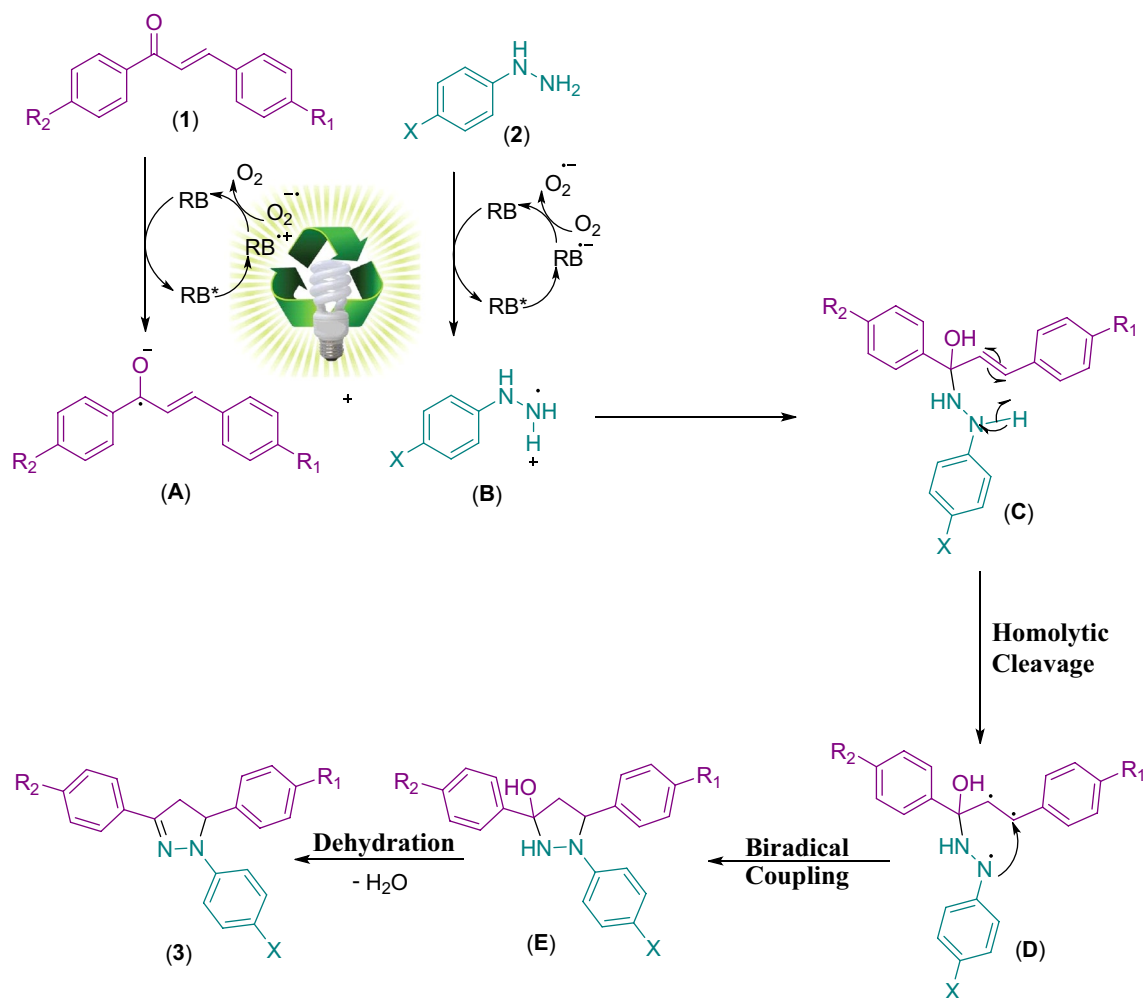
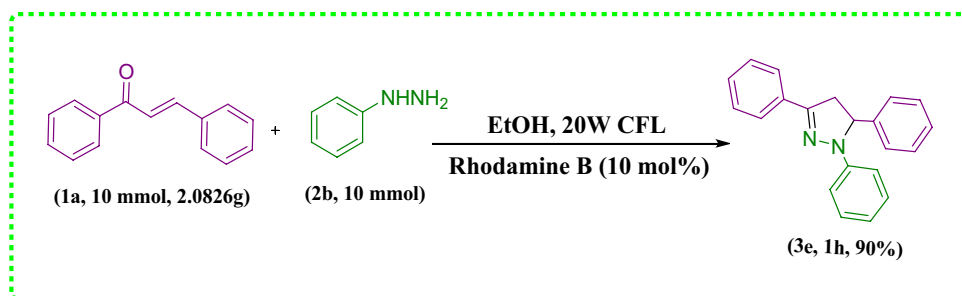
3 Conclusion

In conclusion, we have efficaciously developed a visible-light-triggered, eco-efficient and facile synthetic route for 4,5-dihydro-1*H*-pyrazoles using Rhodamine B as a photoredox catalyst and Chalcones (**1**), Hydrazines (**2**) as substrates in EtOH under 20W CFL irradiation at room temperature. Rhodamine B is a water soluble, cost effective and easily obtainable organic dye and has proven to be the most effective photocatalyst for this procedure. To the best of our knowledge, this is the first visible-light-driven synthetic route starting from Chalcones (**1**) and Hydrazines (**2**) which exhibits hallmarks like being straightforward, simplistic and green to synthesize a series of 4,5-dihydro-1*H*-pyrazoles and its derivatives with good to excellent yields of the product in short reaction time. Practicability, mild reaction conditions, broad substrate scope, utilization of CFL and low-priced organic dye unveils this method as more interesting



Scheme 2 Substrate scope for 3. Reaction conditions: 1 (1.0 mmol) and 2 (1.0 mmol) in EtOH (10 mL) using rhodamine B (10 mol%) under 20W CFL irradiation in an open atmosphere at room temperature for 1–2 h

Scheme 3 Gram scale synthesis



Scheme 4 Proposed mechanism for 4,5-dihydro-1H-pyrazoles (3)

and performable with respect to the aforementioned reported methods. Besides, it is an effortless and environmentally benign method which can be profitable for chemical and therapeutical industries.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10562-024-04591-4>.

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