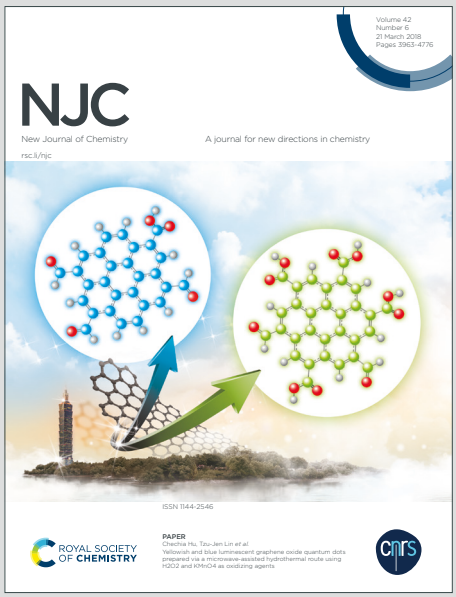
NJC

New Journal of Chemistry

A journal for new directions in chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. K. Sharma, A. JAISWAL, A. Mishra, J. Tiwari, D. Jaiswal, S. Singh, J. Singh and J. Singh, *New J. Chem.*, 2020, DOI: 10.1039/D0NJ02714F.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

Visible-Light-Induced Radical Cascade Cyclization of Pyrazoles bearing a coumarin unit

Amit Kumar Sharma,[a] Anjali Jaiswal,[a] Anu Mishra,[a] Jyoti Tiwari,[a] Deepali Jaiswal,[a] Shailesh Singh,[a] Jaya Singh[b] and Jagdamba Singh[a]*

[a]*Environmentally Benign Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad-211002 (India); Tel: +919415218507; E-mail: dr.jdsau@gmail.com*

[b]*Department of Chemistry, LRPG College, Sahibabad, Ghaziabad-201005 (India)*

Abstract

Herein, we have described an efficient, eco-friendly, metal free, visible light catalysed synthesis of coumarin based pyrazoles under an open atmosphere condition involving a photoredox catalyst, which is an inexpensive organic dye. The present strategy is the first example of visible light promoted, aerobic, oxidative cyclization of pyrazoles bearing a coumarin unit via the formation of C–C, C–O and C-N bonds to afford excellent yield of the products in a simple one-pot operation under mild reaction conditions. The major advantages of the present methodology include short reaction time, cost effectiveness, easy work-up, broad substrate scope and high atom economy.

Keywords: Visible Light, Photoredox Catalysis, Multicomponent, Pyrazoles bearing a coumarin unit.

Introduction

In the last few era, visible-light-mediated photoredox catalysis,[1-3] for single electron transfer (SET) has been arisen as a substitute, versatile, economical and green implement for imperative organic transformations such as oxidation/reduction, C-C/ C-X bond formation in the heterocyclic compounds.[4-6] Organo-photoredox catalyst has an unique characteristic as it can stimulate atmospheric oxygen, a green and natural oxidizing agent, in presence of visible-light for organic transformations involving SET.[7,8] In contrast, the transition metal based photocatalysts such as iridium, ruthenium and polypyridyl complexes have been associated with many drawbacks such as being highly expensive, low sustainability, low toughness, potential toxicity and being problematic during separation.[9-11] Metal-free organic dye, primarily Eosin Y has been utilized as it is an economically and environmentally better option than metal-based photo-redox catalyst.[12,13] The photochemistry of Eosin Y has been very much

analyzed upon excitation by visible light and it has been shown that Eosin Y experiences quick intersystem crossing to the lowest energy triplet state.[14,15]

Now a days, multicomponent reactions (MCRs) are turning out to be an influential and competent strategies for the development of heterocycles in modern organic and medicinal chemistry since they permit multistep synthesis to be led in a single procedural step to give novel and highly functionalized biologically active heterocyclic compound from conveniently available starting materials. Multicomponent reactions (MCRs) have been linked to remarkable synthetic efficiency, reduce the generation of chemical waste, Easy purification and high atom economy.[16-18]

Pyrazole nucleus is a well-recognized to be an essential core of numerous agrochemicals and pharmaceuticals. They demonstrate wide spectrum of biological activities for example, antitubercular,[19] anti-hyperglycemic,[20] antioxidant,[21] Pharmacological Activities,[22] kinase inhibitors,[23] anti-AIDS,[24] anti-anxiety,[25] corrosion inhibition,[26] insecticidal agents,[27] and Antimicrobial.[28] Coumarin also constitute another essential nucleus frequently occurring in various natural products, pharmaceuticals, agrochemicals, dyes and functional materials.[29-32] Due to the significance of these two auxiliary structures, the development of a basic methodology for the synthesis of the target compound containing both the pyrazole and coumarin nucleus by utilizing biodegradable material as a catalyst and green solvent is still desirable and challenging task (**Figure 1**).[33,34]

View Article Online
DOI: 10.1039/D0NJ02714F

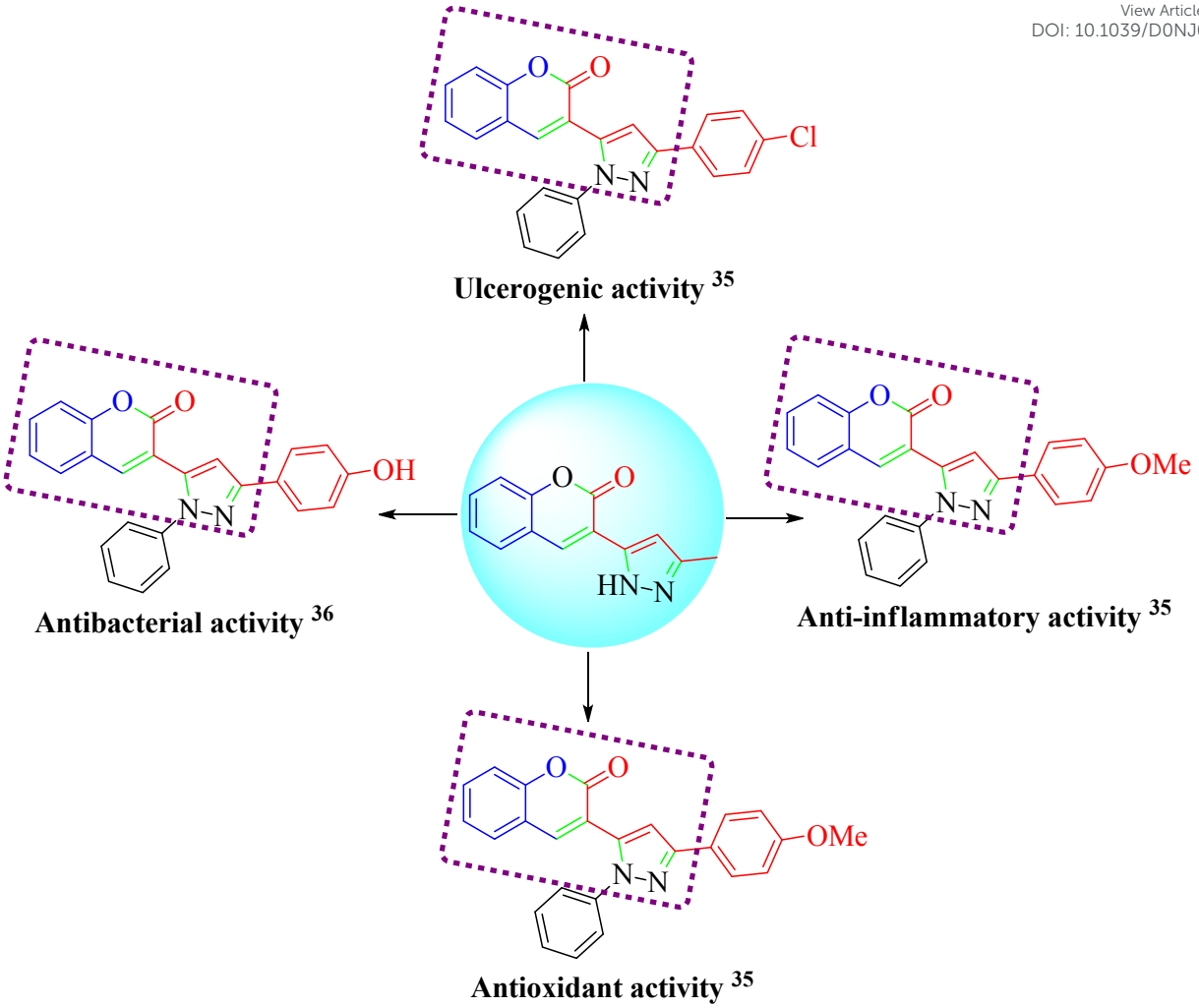
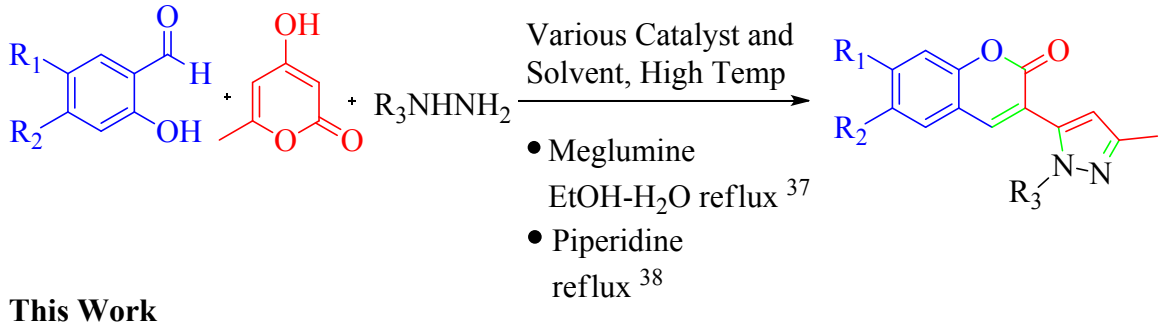
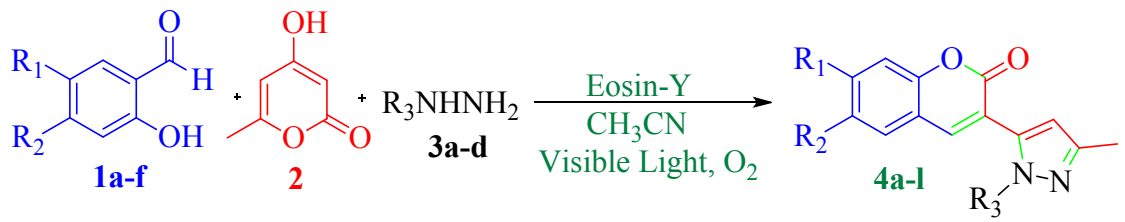


Figure 1. Examples of some biologically active pyrazoles bearing a coumarin unit

Previous Work



This Work



View Article Online
DOI: 10.1039/D0NJ02714F

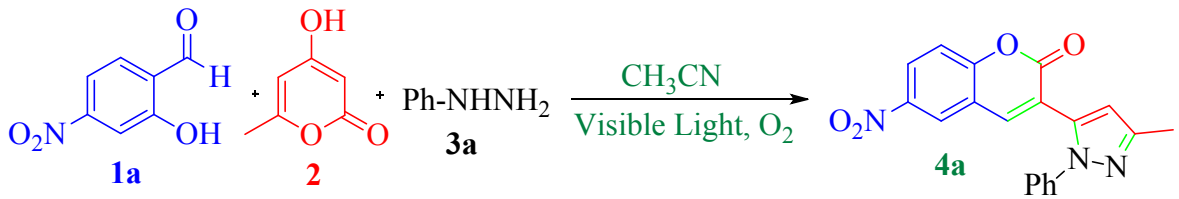
Scheme 1. Comparison of proposed protocol with previously reported methods

Evidently this moiety has never been synthesized via visible-light pathway initiated by photoredox catalyst. Therefore, visible light was chosen as an efficient promoter for the synthesis of coumarin containing pyrazoles using Eosin-Y as a photoredox catalyst at room temperature (**Scheme 1**). This new approach for the synthesis of coumarin based pyrazole and its derivatives is mechanistically attractive because it involves through visible light photoredox catalysis.

Results and discussion

In order to check the credibility of our proposed protocol, we instigated our study by utilizing 4-Nitrosalicylaldehyde (**1a**), 1,4-hydroxy-6-methyl-2H-pyran-2-one (**2**) and phenylhydrazine (**3a**) as model substrates for the synthesis of target compound. We commenced with the optimisation of the reaction conditions by using varied catalyst (**Table 1**). To begin with, reaction is carried out in the absence of photocatalyst at room temperature under CFL (23W) irradiation, product could not be obtained even after 24 h of irradiation (Table 1, entry 1). Subsequently, we performed our reaction in the presence of photocatalysts. We used Eosin Y (2 mol%) as a catalyst which afforded 84 % yield of the product within 24 h (Table 1, entry 4). A series of other organic photocatalysts such as Methylene Blue, Rose-Bengal and Rhodamine-B, and (Table 1, entries 6−8) were explored. Although, Rhodamine-B gave good yield but amongst all the catalysts screened, Eosin Y was outstanding. In the case of methylene blue, no product was formed and Rose-Bengal gives trace in yield. Decreasing the amount of Eosin Y had a significant effect on the yield of the product, whereas increasing the amount of Eosin Y did not affect the yield of product (Table 1, entries 3 and 5). Repeated experiments led to the conclusion that organic dye and visible light are obligatory components for this novel transformation (Table 1, entries 1 and 2).

Table 1. Optimization of organic photoredox catalysts[a]

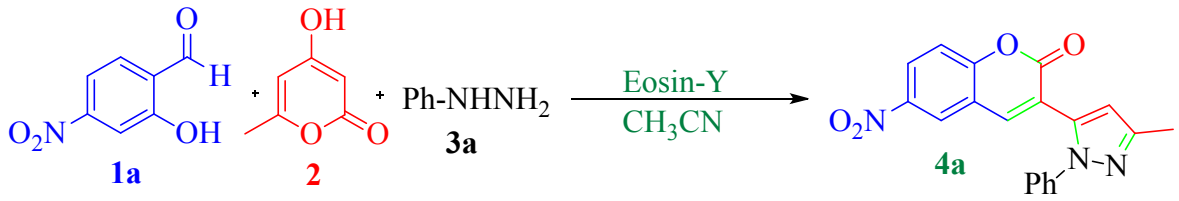


Entry	Photocatalyst (mol %)	Time (hour)	Yield (%)[b]
1	None[c]	24	NR[d]
2	Eosin Y (2)[e]	24	NR[d]
3	Eosin Y (1)	24	64
4	Eosin Y (2)	24	84
5	Eosin Y (4)	24	84
6	Methylene Blue	24	NR[d]
7	Rose Bengal	24	Trace
8	Rhodamine B	24	75

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol), CH_3CN (3 mL), 23W CFL irradiation under an open atmosphere at room temperature; [b] Isolated yield of product; [c] Without catalyst; [d] NR = no reaction; [e] Without irradiation.

Encouraged by favourable results, we performed our model reaction with different intensities of light source (CFL 18W, 23W, 27W, Green LED, blue LED and white LED) (Table 2, entries 1-6) and observed that CFL (23W) is the ideal source of visible light for the present protocol (Table 2, entry 2). Moreover, the reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (2.0 mmol), clearly indicate that reaction proceed through a free radical pathway (Table 2, entry 9).[39, 40]

Table 2. Optimization of visible-light source[a]



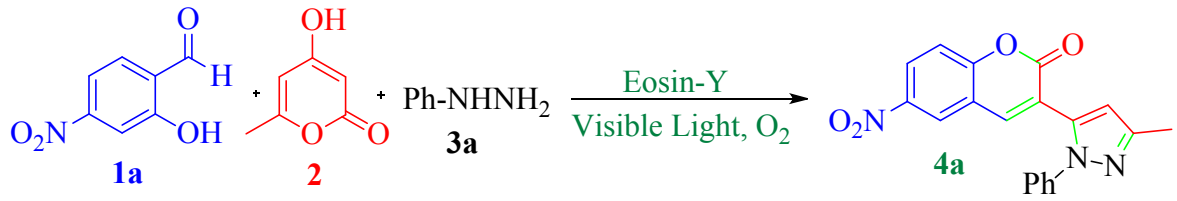
Entry	Visible - light source	Time (h)	Yield (%)[b]
1	CFL (18 W)	24	70
2	CFL (23 W)	24	84
3	CFL (27 W)	24	84
4	Green LED (2.5W)	36	20
5	Blue LED (6W)	36	15
6	White LED (9W)	36	10
7	CFL (23 W) TEMPO	24	NR[c, d]
8	Daylight	24	NR[d]

9	Dark	24	NR[d]
10	Nitrogen atm	24	NR[d]

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol), CH_3CN (3 mL), in different light source under an open atmosphere at room temperature; [b] Isolated yield of product; [c] Reaction was quenched with TEMPO (2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl) (2.0 equiv.); [d] NR = no reaction.

After the finalization of the best photocatalyst and light source, we next screened different solvent to further optimize the reaction conditions (**Table 3**). Firstly, we used 2 mL of tetrahydrofuran (THF) or in 2 ml of dimethyl sulfoxide (DMSO), separately and the reaction mixture was irradiated under compact florescent lamp (CFL) with 2 mol% Eosin Y for 24 h in an open pot at room temperature. The expected product could not be detected and the substrate was recovered completely unreacted (Table 3, entries 1 and 2). Next, we carried the reaction in various solvents and neat condition (Table 3, entries 3-8) and observed that the acetonitrile has been found to be most impressive, convenient and efficient for the desired transformation.

Table 3. Optimization of solvents.[a]



Entry	Solvent	Time (hour)	Yield (%)[b]
1	THF	24	NR[c]
2	DMSO	24	NR[c]
3	CH_3CN	24	84
4	DMF	24	NR[c]
5	DCE	24	52
6	EtOH	24	40
7	Toluene	24	25
8	Neat	24	10

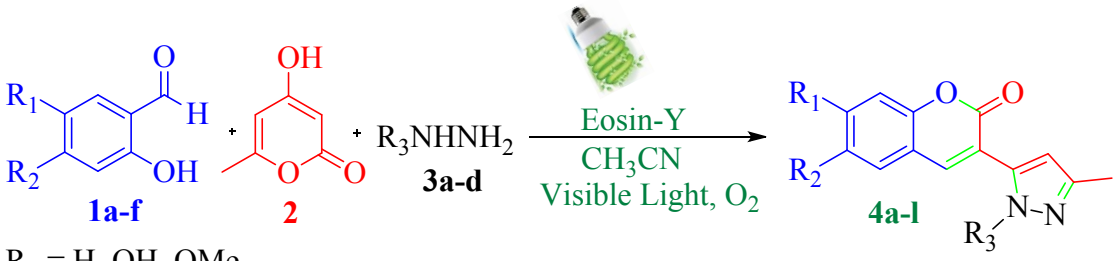
[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol), in different solvent using 23W CFL irradiation under an open atmosphere at room temperature; [b] Isolated yield of product; [c] NR = no reaction. DMF= DiMethylFormamide, DCE= DiChloroEthane

Under the established reaction conditions, we next explored the substrate scope of the present strategy. The results of our investigation are listed in (**Table 4**). Explicitly, salicylaldehyde

bearing either electron-withdrawing or electron-donating groups (such as -OMe, -OH, -Cl, -Br, $-NO_2$) are well tolerated and furnished the target compound and its derivatives afforded excellent **(4a-4f)** 92−75% yields.

Inspired by these results, we next explored the other substrate, arylhydrazine containing electron-withdrawing and electron-releasing group and observed that all afforded excellent **(4g−4i)** 83−73% yields. However, it was established that arylhydrazine containing electron-releasing group is more efficient product formation.

Table 4. Substrate scope.[a,b]



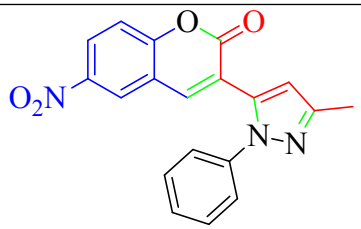
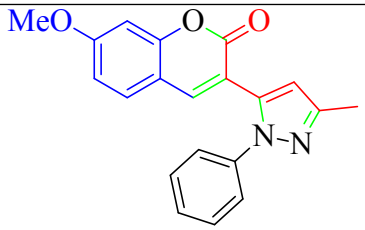
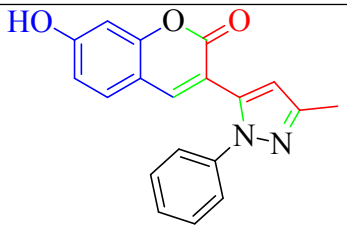
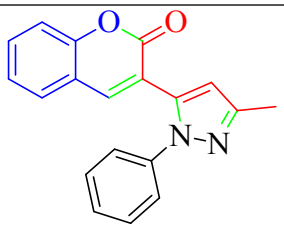
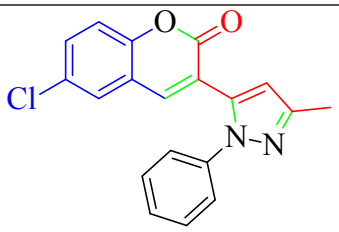
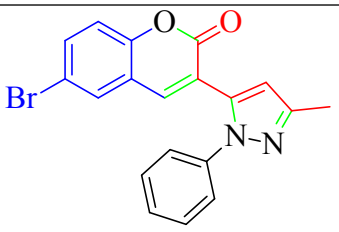
R_1 = H, OH, OMe

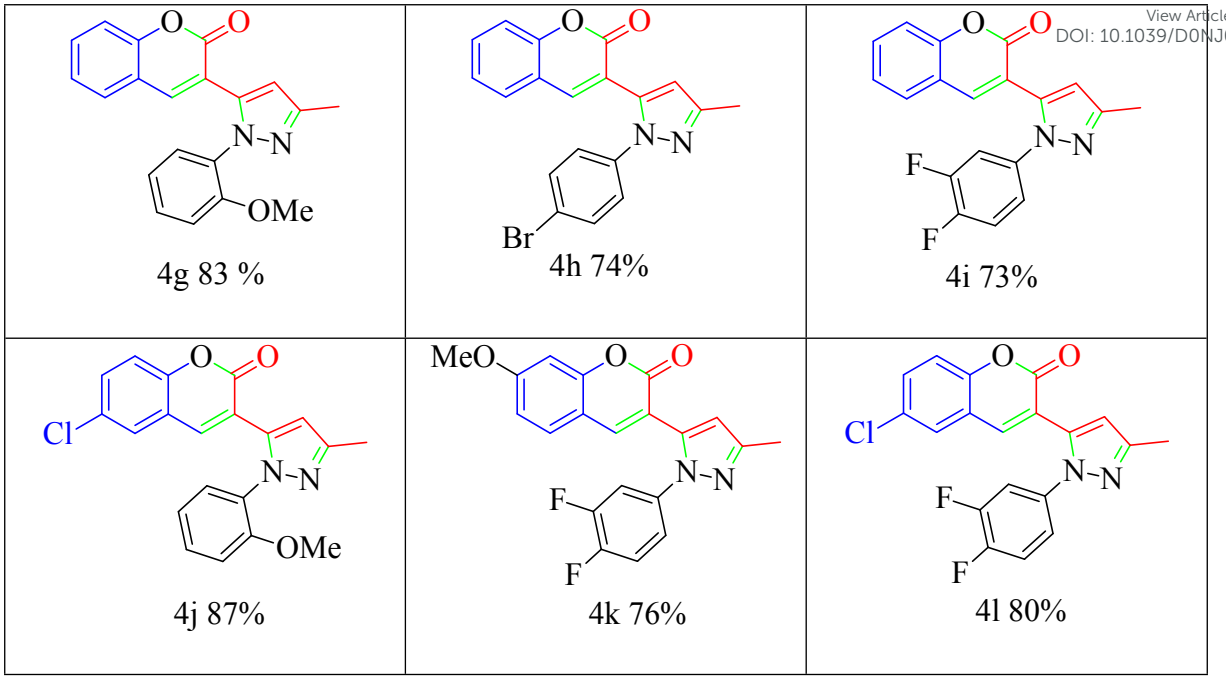
R_2 = H, Cl, Br, NO_2

R_3 = Ph, 2-OMe-Ph, 4-Br-Ph, 3,4-$(F)_2$-Ph

12-Molecules

73-92%

 4a 84%	 4b 77%	 4c 75 %
 4d 78 %	 4e 88%	 4f 92%



[a] Reaction conditions: **1a-f** (1.0 mmol), **2** (1.0 mmol), **3a-d** (1.0 mmol), CH_3CN (3 mL), 23W CFL irradiation under an open atmosphere at room temperature; [b] Isolated yield of product.

Mechanism

Examine by the control experiments and literature reports,[41-45] the following plausible mechanism using the model substrates has been suggested (**Figure 2 and 3**). The pyrone radical (**5**) is generated smoothly by the HAT through light-activated *Eosin Y (**I**) and pyrone (**2**).[44] Pyrone radical (**5**) react with salicylaldehyde (**1**) to produce another radical (**6**). Now the reverse hydrogen atom transfer (RHAT) between radical **6** and eosin Y-H (**II**) regenerates ground state Eosin Y and intermediate (**8**). Similarly, in the same way, HAT between light-activated *Eosin Y (**I**) and intermediate (**8**) to produce radical (**9**)**.** In this step, eosin Y-H undergoes aerial oxidation to regenerate the ground state Eosin Y and forms a $HO_2^{\bullet}$ radical, which further undergoes disproportionation to give oxygen and hydrogen peroxide.[46,47] Thus, formed H_2O_2 was distinguished by starch and potassium iodide as indicator.[48] After that radical (**9**) undergoes an intramolecular cyclization by free radical addition of enolate oxygen to carbonyl group as well as ring opening to afford the compound (**10**) and then compound (**11**) by abstraction of $H^{\bullet}$ radical from water molecule. A homolytic cleavage of compound (**11**) and phenyl-hydrazine (**3**) followed by free radical addition between compound (**12**) and phenyl-hydrazine radical (**3**) gives compound (**13**). After that compound (**13**) undergoes dehydration to form the compound (**14**)**.** Finally, homolytic cleavage of N-H bond and carbonyl carbon followed by radical coupling of the compound (**14**) gives the desired product (**4**)**.**

View Article Online
DOI: 10.1039/D0NJ02714F

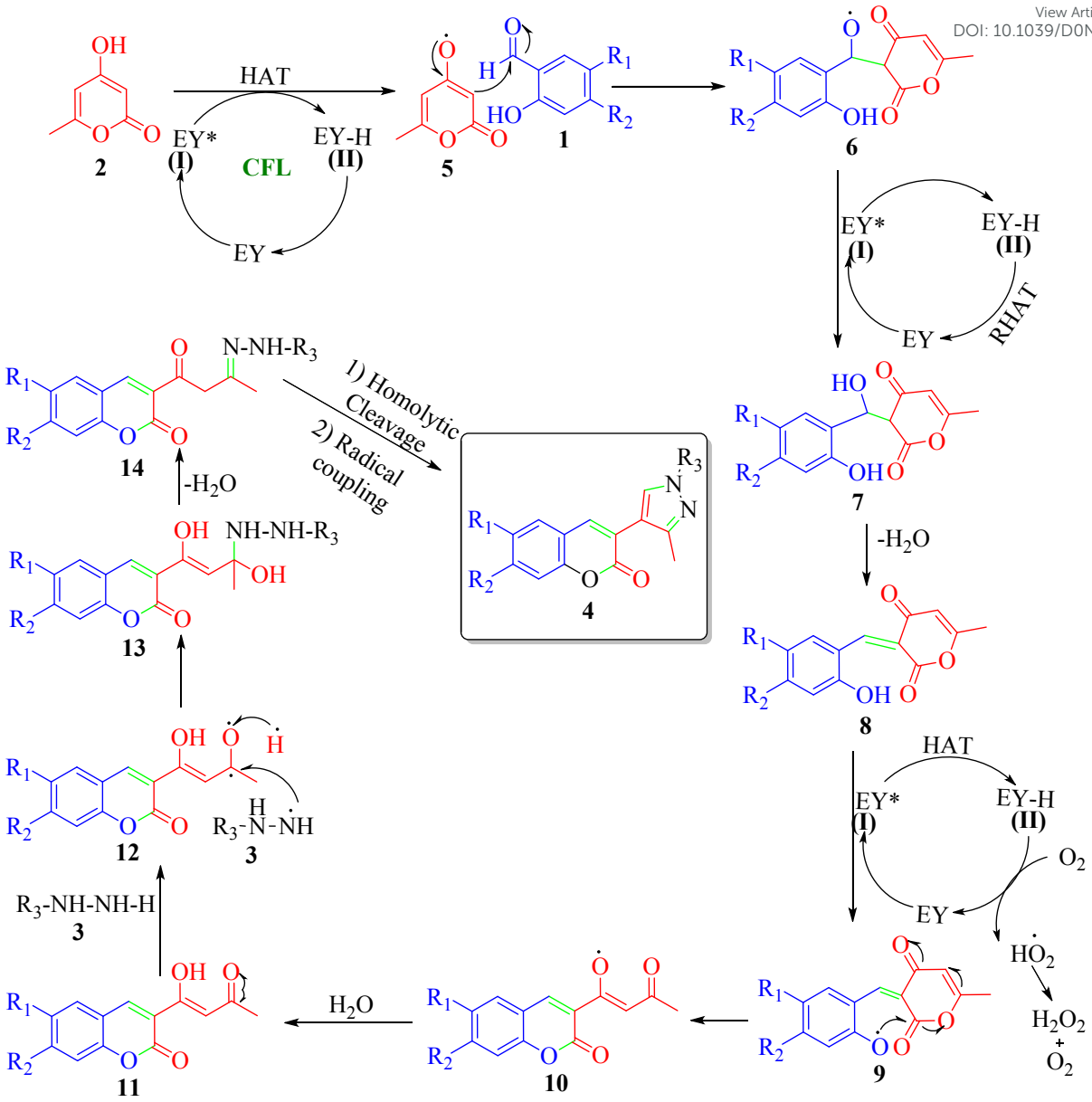


Figure 2. Probable mechanism

View Article Online
DOI: 10.1039/D0NJ02714F

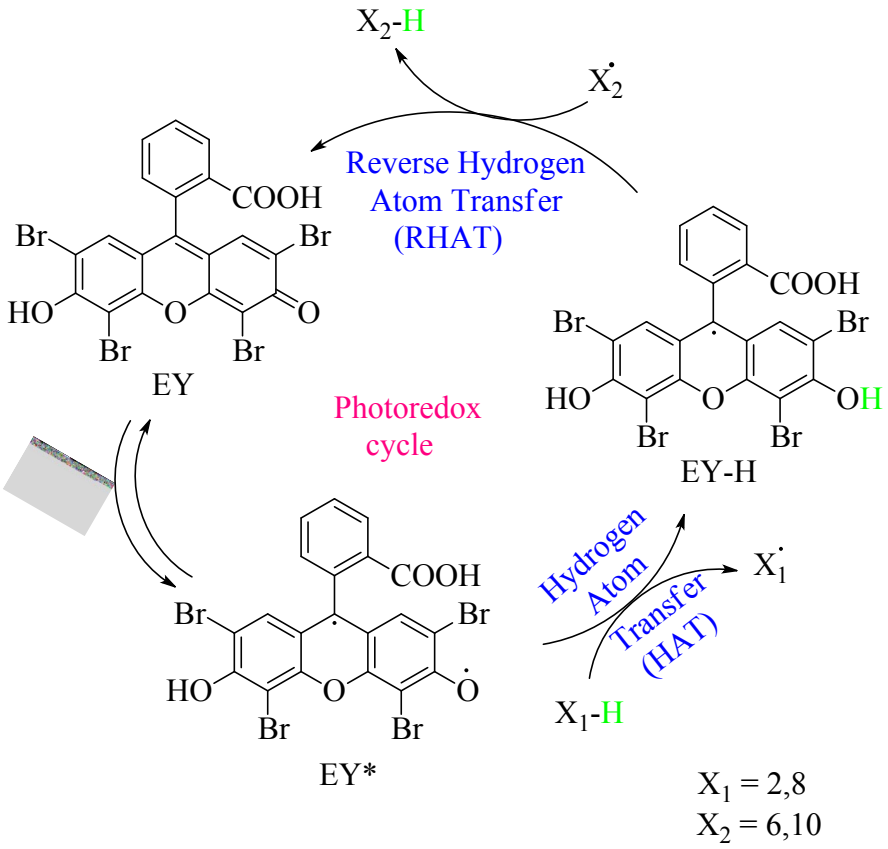


Figure 3. Photoredox cycle of Eosin Y[44]

Conclusions

In conclusion, we have successfully developed a novel and an effective synthetic pathway for coumarin based pyrazole and its derivatives via one-pot-three-component reaction of salicylaldehydes (**1**), 4-hydroxy-6-methyl-2H-pyran-2-one (**2**) and phenylhydrazines (**3**) in acetonitrile by utilizing air and Eosin Y as an inexpensive, biodegradable photoredox catalyst. The present method incorporates broad range of substrate scope applicability. Most important highlights of the proposed protocol are that it is accessible, greener, experimentally feasible, cost-effective and during the product formation air is used as a sole green oxidant.

Experimental Section

General Remarks

All chemicals were reagent grade and purchased from Aldrich, Alfa Aesar, Merck, Spectrochem and Qualigens and were used without purification. The reactions were monitored using pre-coated TLC plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60 F-254). NMR spectra were recorded on a Bruker Avance Neo 500FT spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C) in $CDCl_3$ using TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Mass Spectra (ESIMS) were obtained

on Micromassquadro II spectrometer. Melting points were determined by open glass capillary method and were uncorrected.

General Experimental Procedure

In a tube equipped with a magnetic stirrer bar salicylaldehyde (**1**, 1 mmol), 1,4-hydroxy-6-methyl-2H-pyran-2-one (**2**, 1 mmol) and phenylhydrazine (**3**, 1 mmol), were added in 3 mL acetonitrile and Eosin Y (2 mol%). The resulting mixture was stirred under irradiation with 23W CFL at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched with cold water (3 ml) and compound was dissolved in EtOAc. The EtOAc layer was separated and the aqueous fraction was extracted with EtOAc (3X3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and the crude product was purified by silica gel chromatography (100-200 mesh silica gel; EtOAc/Hexane) to obtain the pure product **4a-l**. All the products are well known which were characterized by the comparison of their spectra and melting point with those reported in the literature.[37,38]

Supporting Information Summary

General experimental, General procedure for the synthesis of pyrazoles bearing a coumarin derivatives and Characterization data of products.

Acknowledgements

The authors are thankful to SAIF, PU, Chandigarh for spectral data. The authors Amit Kumar Sharma, Anu Mishra and Anjali Jaiswal thanks to UGC, New Delhi for the award of SRF and JRF respectively. Prof. Jagdamba Singh acknowledges the financial support from UGC, New Delhi in the form of BSR Faculty Fellowship (Fellowship No. 201819-BSRFACULTY-10074-3). We are also thanks to Dr. Anil K. Singh, Associate Prof. department of physics, ECC PG college, University of Allahabad, for their valuable support.

References

1 N. A. Romero and D. A. Nicewicz, *Chem. Rev*., 2016, **116**, 10075-10166.

2 A. Savateev, I. Ghosh, B. Konig and M. Antonietti, *Angew. Chem. Int., Ed*.,10.1002/anie.201802472.

3 I. Ghosh, R. S. Shaikh and B. Konig, *Angew. Chem. Int. Ed*., 2017, **56**, 1-7.

4 M. A. Ansari, D. Yadav, S. Soni, A. Srivastava and M. S. Singh, *J. Org. Chem.*, 2019, **84,** 5404-5412.

5 K. Wang, L. Meng and L. Wang, *J. Org. Chem.*, 2016, **81**, 7080-7087.

6 K. Muralirajan, R. Kancherla and M. Rueping, *Angew. Chem. Int. Ed*., 2018, **57**, 14787-14791.

7 X. Lang, J. Zhao, and X. Chen, *Angew. Chem. Int. Ed*., 2016, **55**, 4697-4700.

8 R. S. Rohokale B. Koenig and D. D. Dhavale, *J. Org. Chem.*, 2016, **81**, 7121-7126.

9 S. D. Tambe, M. S. Jadhav, R. S. Rohokale and U. A. Kshirsagar, *Eur. J. Org. Chem.*, 2018, 4867-4873.

10 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acenã, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116,** 422.

11 T. Xu, C. W. Cheung and X. Hu, *Angew. Chem. Int. Ed*., 2014, **53**, 4910.

12 L. Lin, X. Bai, X. Ye, X. Zhao, C. Tan and Z. Jiang, *Angew. Chem. Int. Ed.*, 2017, **56**, 13842-13846.

13 M. Majek and A. J. V. Wangelin, *Angew. Chem. Int. Ed*., 2014, **53**, 1-6.

14 L. Buzzetti, G. E. M. Crisenza and P. Melchiorre, *Angew. Chem. Int. Ed*., 10.1002/anie.201809984.

15 A. A. Soto, K. Kaastrup, S. Kim, K. Ugo-Beke and H. D. Sikes, *ACS Catal*., 2018, **8**, 6394−6400.

16 Q. Xiong, S. Dong, Y. Chen, X. Liu and X. Feng, *Nat. Commun*., 2019, **10**, 2116.

17 J. Tian, Z. Chen, R. Jiang, L. Mao, M. Liu, F. Deng, H. Huang, L. Liu, X. Zhang and Y. Wei, *Dyes and Pigments.*, 2019, **171,** 107673.

18 M. Loubidi, J. Jouha, I. Hdoufane, M. E. Hafi, Z. Tber, D. Cherqaoui and J. T. Mague, *J. Mol. Struct.,* 2020, **1201,** 127178.

19 A. A. Bekhit, A. M. M. Hassan, H. A. A. E. Razik, M. M. M. El-Miligy, E. J. El-Agroudy and A. E. A. Bekhit*, Eur. J. Med. Chem.*, 10.1016/j.ejmech.2015.02.038.

20 K. L. Kees, J. J. Fitzgerald, K. E. Steiner, J. F. Mattes, B. Mihan, T. Tosi, D. Mondoro and M. L. McCaleb, *J. Med. Chem*.,1996, **39***,* 3920-3928.

21 S. Durgamma, A. Muralikrishna, V. Padmavathi and A. Padmaja, *Med. Chem. Res*., 2014, **23**, 2916–2929.

22 K. Karrouchi, S. Radi, Y. Ramli, J. Taoufik, Y. N. Mabkhot, F. A. Al-aizari and M. Ansar, *Molecules.,* 2018, **23**, 134.

23 A. Dore, B. Asproni, A. Scampuddu, G. A. Pinna, C. T. Christoffersen, M. Langgard and J. Kehler, *Eur. J. Med. Chem.*, 2014, **84,** 181-193.

24 S. Jacob K. and S. Ganguly, *Int. J. Pham Pharm. Sci.,* 2016, **8**, 75-79.

25 A. Jamwal, A Javed and V. Bhardwaj, *J. Pharm. Bio Sci.,* 2013, **3**, 114-123.

26 F. Boudjellal, H. B. Ouici, A. Guendouzi, O. Benali and A. Sehmi, *J. Mol. Struct.*, 2020, **1199,** 127051.

27 S. T. Heller and S. R. Natarajan. *Org. Lett.,* 2006, **8**, 2675-2678.

28 Bayu Ardiansah, *Asian J Pharm Clin Res.*, 2018, **11**, 88-94.

29 F. G. Medina, J. G. Marrero, M. M. Alonso, M. C. Gonzalez, I. C. Guerrero, A. G. T. Garcia and S. O. Robles, *J. Name*., 2012, **00**, 1-3.

30 E. C. Gaudinoa, S. Tagliapietraa, K. Martinaa, G. Palmisanob and G. Cravotto, *J. Name*., 2013, **00**, 1-3.

31 A. K. Mourad, F. K. Mohamed and A. Y. Soliman*, Heterocycles*., 2018, **96**, 1.

32 Y. Zhao, N. Wang, H. Wu, Y. Zhou, C. Huang, J. Luo, Z. Zeng, and L. Kong, *J. Adv. Res*., 2020, **21** 57-64.

33 A. S. Al-Ayed, *Int. J. Org. Chem*., 2011, **1**, 87-96.

34 M. K. Bashir, N. A. W. Al-Omari and A. O. Omar, *International Journal of Enhanced Research in Science, Technology & Engineering.,* 2018, **7**, 2319-7463.

35 P. Aragade, R. Venkatnarayanan and P. Patil, *Drug Res.,* 2013, **63**, 28–33.

36 P. Aragade, R. V. Narayanan, V. Maddi, P. Patil, P. Shinde and M. Agrawal, *J. Enzyme Inhib. Med. Chem*., 2012, **27**, 849–853.

37 X. T. Li, Y. H. Liu, X. L. and Z. H. Zhang, *RSC Adv*., 2015, **5**, 25625-25633.

38 A. Alizadeh and R. Ghanbaripour, *Synth. Commun*., 2014, **44**, 1635-1640.

39 A. K. Yadav and L. D. S. Yadav, *Green Chem.,* 2015, **17**, 3515.

40 A. K. Yadav and L. D. S. Yadav, *Org Biomol Chem.,* 2015, **13**, 2606.

41 W. Xiao, X. Yu, Q. Zhao, J. Chen, and J Chen, *Angew. Chem. Int. Ed.,* 10.1002/anie.201809820.

42 M. A. Ansari, D. Yadav, S. Soni, A. Srivastava and M. S. Singh, *J. Org. Chem.*, 2019, **84,** 5404-5412.

43 Nathan A. Romero and David A. Nicewicz, *Chem. Rev*., 2016, **116**, 10075-10166.

44 X. Fan, P. Xiao, Z. Jiao, T. Yang, X. Dai, W. Xu, J. D. Tan, G. Cui, H. Su, W. Fang and J. Wu, *Angew. Chem. Int. Ed.,*10.1002/anie.201908556.

45 J. Zhu, W. Cui, S. Wang and Z. Yao, *Org. Lett*., 2018, **20**, 3174-3178.

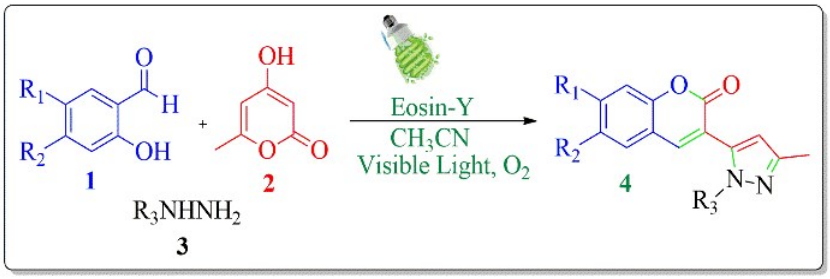
46 K. Ohkubo, K. Mizushima, R. Iwata, K. Souma, N. Suzuki and S. Fukuzumi, *Chem. Commun*. 2010, **46**, 601−603.

47 D. Ravelli, M. Fagnoni and A. Albini, *Chem. Soc. Rev*. 2013, **42**, 97−113.

48 L. Revathi, L. Ravindar, W.-Y. Fang, K. P. Rakesh and H.-L. Qin, *Adv. Synth. Catal*. 2018, **360**, 4652−4698.

View Article Online
DOI: 10.1039/D0NJ02714F

TOC



A visible light facilitated protocol for the synthesis of pyrazole and its derivatives bearing a coumarin unit in presence of Eosin Y.