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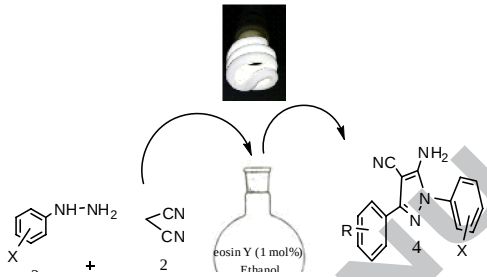

Atmospheric oxygen mediated synthesis of pyrazole under visible irradiation

Snehalata Yadav, [a] Pratibha Rai, [a] Madhulika Srivastava,[a] Jaya Singh,[b]Kamala Prasad Tiwari[a] and Jagdamba Singh[a]*

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ABSTRACT

A novel protocol has been reported for synthesis of pyrazoles by visible light irradiation in presence of eosin Y, an organophotocatalyst under atmospheric oxygen. We have successfully carried out a visible light induced Michael addition followed by intramolecular cyclization reactions for the formation of heterocyclic ring. The present the method in incoprate advantages such as being eco-friendly, invoving metal free condition, reporting excellent yield, using minimum reaction time, making use of an easily available catalyst and eliminating the use of column chromatography.

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Now the chemists are adopting new trends in organic synthesis. Amongst them the solar energy is the most readily available and a good source of visible light. 1a-b Visible light photoredox processes provide a wide platform for researchers which satisfy all parameters of green chemistry-like mild reaction conditions, easy availability of solar energy, easy handling and non toxicity. Since reaction takes place at room temperature and atmospheric pressure so the use of thermal energy is not required to initiate the reaction1c-e. The fact that molecular oxygen is easily available in the atmosphere allows this method to outweigh traditional methods2. There are certain organic molecules which are not able to absorb the broad range of visible light3a.. To overcome this hurdle we make of use photo sensitizers and photo catalysts. Generally photo catalysts are smoothly reduced as well as oxidized in excited state, hence can be used both as electron donor and electron acceptor [3b]. A number of methods have been reported which include the use of organanometallic photo catalysts[4a-k]. However we have incorporated the use of eosin Y [2-(2, 4,5,7-tetrabromo-6-hydroxy-3-oxo-3H-xanthen-9-yl)benzoic acid] as a photoredox catalyst due to its high reactivity and sufficient stability under irradiation with visible light. Eosin Y has been used frequently as a photo catalyst in visible light photoredox reactions. In the presence of visible light eosin Y undergoes excitation to a triplet state, which is more oxidizing and reducing as compared to the previous state. In addition, the photo excited state of eosin Y also plays a role in energy transfer [4h]. This outweighs the use of transition metal photo catalysts due to the former being more cost effective and being easily available. Furthermore analogous to excited Ru^{2+} the excited eosin Y also undergoes both reductive and oxidative quenching. It has been used in place of Ru^{2+}, and Ir^{2+} complexes in visible light catalyzed reaction involving single electron transfer[5]. Pyrazole nucleus form an elite class of hetero scaffold. In recent years they have been used as ligands[6a], chiral catalysts[6b] and moieties to increase regioselectivity and stereoselectivity. In addition they have also been used for the preparation of dyes[6c], couplers for photographic substances[6d] and materials used in florescence, luminescence and herbicides[6e]. They also find wide application in pharmaceutical industries since they form the central nucleus of many commercially available drugs e.g. Celebrex, Zometapina, Viagara, and Acomplia. (Figure 1)

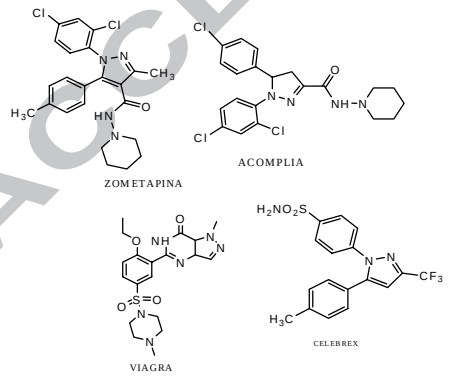
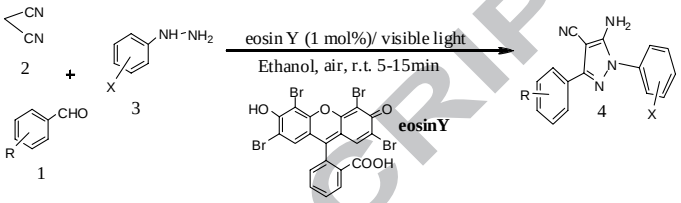


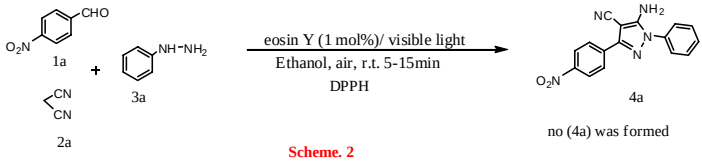
Figure 1 biologically active drug with pyrazole nucleus

Knoevengel condensation occurs between an aldehyde and malanonitrile and the adduct form is used as an intermediate for the synthesis of substituted alkenes and coumarin derivatives which has been found useful in perfume and in cosmetic industries. In addition it also has wide application in bioactive compounds and pharmacological industries[7]. Literature survey has revealed that a number of methods have been reported for the synthesis of pyrazole nucleus (i). B.A. Bhat et.al synthesized pyrazole nucleus with use of chalcones[8a] (ii) Xinting Zhang and co-workers also synthesized pyrazole[8b] (iii) Piyush N. Kalaria used l-Proline for synthesis of pyrazole nucleus[8c]. In continuation of our previous work[9] we have developed a visible –light-mediated, one pot synthesis of highly funtionalized pyrazole derivatives from easily available and simple starting materials involving aldehyde **(1)**, malononitrile **(2)**, and phenylhydrazine **(3)** and employing eosin Y as an organophotoredox catalyst and atmospheric air (O_2) as an oxidant. This strategy is significant due to the involvement of a highly eco-friendly approach. (Scheme 1). The reported method outweighs previously used methods since it eliminate the use of thermal energy, involves short reaction time, does not require quenching and involves simple work up.



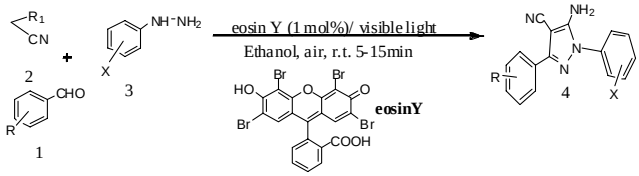
Scheme1**.** Synthesis of target compound (4)

In our initial attempt we carried out reaction of aldehyde **(1a)** 1mmol, malononitrile **(2a)** 1mmol, and phenyl hydrazine **(3a)** 1mmol in ethanol in presence of 1 mol% of eosin Y and air. The reaction mixture was irradiated in presence of simple household compact fluorescent light (CFL, 22W) at room temperature. The desired product was obtained in high yield with excellent purity. This encouraged us to perform a series of experiments to assure the necessity of several reaction conditions such as catalyst, solvent, light, time and air to increase the yield of the product. Our next Endeavour was to employ the best reaction conditions with respect to the amount of catalyst and solvent so that it not only contributed to the increase in yield but also decreased the overall reaction time. We discovered that the ideal amount of eosin Y is 1 mol% (**Table 1, entry 1**) for the model reaction. When we increase the amount of catalyst beyond 1mol% , it did not affect the yield of the product **(Table1, entry 7, 8).** But decrease in the amount of catalyst from 1mol% to 0.2 mol%

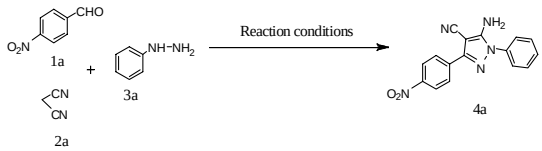


Scheme. 2

resulted in a decrease in the amount of product **(Table 1, entry 9).** We concluded that ethanol is the best solvent for the reaction because its use not only enabled a good yield but also provide easy workup.



Water and ethanol mix due to hydrogen bonding such that the product separates very easily. With the above optimized condition in hand we continue our optimization for the best solvent under the established condition and results were tabulated in **Table (1)**. A series of control experiment were further



performed which showed that absence of florescent light, photocatalyst or air, reduced the yield of the product considerably (**Table2, entry6, 7, 8, 9).** These results indicate that the reaction

condition (photo catalyst, visible light and air) all are essential In order to observe the electronic effect of the substituent on the reactant the reaction was performed with different types of aldehydes. Result shows that aldehydes with electron withdrawing group (EWG) provided better result as compared to aldehydes with electron releasing group (ERG). The product formation takes place via a knoevenagel condensation[7a,10] followed by a 1, 2 type addition,[11] intramolecular cyclization and air oxidation.

for present protocol. These result indicate that fluorescent light and air both are essential for the present protocol

Table 1 Optimization of solvent and amount of catalyst

Reaction conditiona : aldehyde (1a) 1mmol, malanonitrile (2a) 1mmol, and phenyl hydrazine (3a) 1mmol, ethanol(5ml), 22W CFL(compact fluorescent lamp) in presence of given amount of catalyst eosin Y. In condition (b) The yields are for pure, isolated products

Table-2 Optimization of reaction condition

.

Reaction condition : aldehyde **(1a)** 1mmol, malanonitrile **(2a)** 1mmol, and phenyl hydrazine **(3a)** 1mmol, ethanol(5ml), 22W CFL(compact fluorescent lamp) in presence of given amount of catalyst eosin Y. In condition (b) the yields are for pure, isolated products (c) desired product not formed.* only aldehyde with electron withdrawing substituent gives sufficient yield

Entry	Visible light	EosinY (mol%)	Solvent	Time(min.)	Yield[b] (%)
1	22WCFL	1	Atm.O_2	5	95
2	22WCFL	-	Atm.O_2	8	68
3	Dark	1	Atm.O_2	5	trace
4	Daylight	1	Atm.O_2	6	70
5	22WCFL	1	N_2	10	60*
6	Dark	1	N_2	15	-[c]
7	Daylight	1	N_2	12	27
8	Daylight	-	N_2	15	-[c]
9	Dark	-	N_2	20	-[c]

.

Table 3 Scope of aldehyde and active mehylene group

Entry	EosinY(mol%)	Solvent	Time(min)	Yield[b]
1	1	EtOH	5	95
2	1	CH_3CN	6	72
3	1	DMSO	8	77
4	1	CH_3NO_2	7	65
5	1	DCM	6	62
6	1	MeOH	5	80
7	2	EtOH	5	95
8	3	EtOH	5	95
9	.2	EtOH	12	80

Reaction condition[a] aldehyde **(1a)** 1mmol, malononitrile **(2a)** 1mmol, and phenyl hydrazine **(3a)** 1mmol, in ethanol in presence of given amount of catalyst in condition. [b]The yields are for pure, isolated products

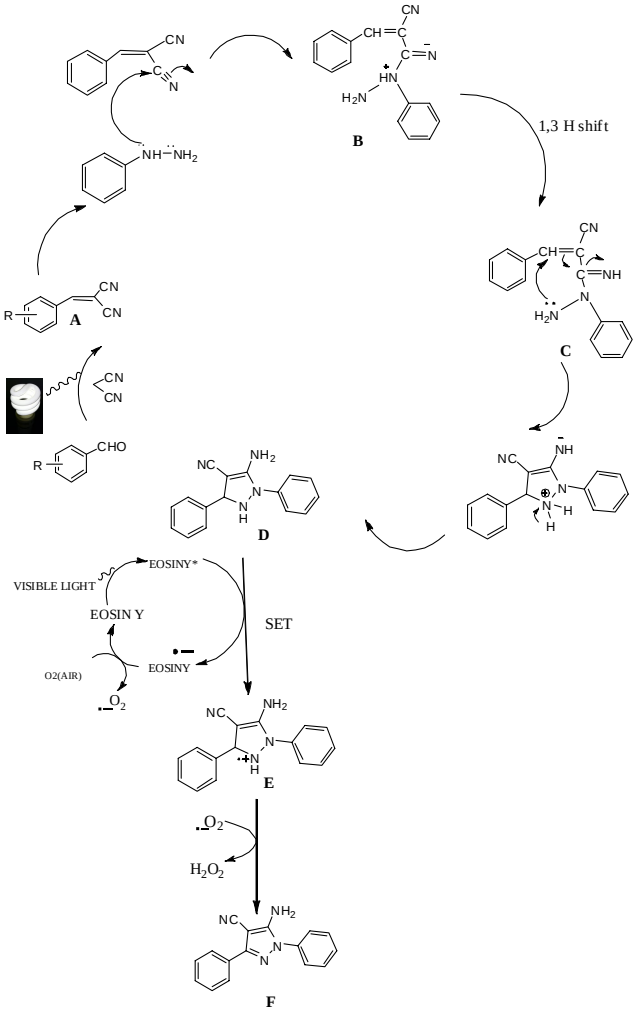
1. On the basis of our investigation and literature survey a plausible mechanism of the reaction is shown in scheme (**3**) which seems to follow radical pathway because it is quenched by the addition of DPPH (scheme 2). It was further proven by experiment that the reaction was not quenched either in presence of DABCO (2 mol%) or 2,3 dimethyl-2-butyl (2mol%). It s obvious that singlet oxygen is not utilized in the reaction mechanism. Presence of triplet oxygen is a characteristic feature of radical reaction. EY, an organophotoredox catalyst is excited to its singlet state ^{1}EY* on absorption of visible light which further convert in to its more stable triplet state ^{3}EY* via Inter System Crossing and undergoes single electron transfer (SET). ^{3}EY* may undergo both oxidative[12] and reductive quenching[13]. Aldehyde (1) reacts with malanonitrile (2) to give Knoevengel product (A) which undergoes 1, 2-addition with phenyl hydrazine (3) resulting in the formation of (B). In our next step (B) undergoes 1, 3 H shift forming (C) which further undergoes intramolecular cyclization resulting in the formation of (D). A SET from D to ^{3}EY* generates radical cation (E) which gives desired product (F) by attack of $O_2^{\cdot-}$ Generation of superoxide radical anion $O_2^{\cdot-}$ during the reaction was proven by conforming the resulting hydrogen peroxide using KI/starch indicator.[14]

To conclude, here we have developed an eco-efficient, clean and photoredox catalyzed synthesis of highly functionalized pyrazole derivatives in good to excellent yield. The most important feature of this protocol is that it satisfies all of the parameter of green chemistry and require no further purification of the desired product.

Acknowledgement

We (authors) Pratibha Rai and Madhulika Srivastava are grateful to UGC, New Delhi, for the award of senior Research Fellowship and also to Snehlata yadav thankful to UGC, New Delhi, for the Research Fellowship.

Scheme 3 Proposed mechanism for the synthesis of pyrazole derivatives



Entry	(1)	(3)	time (min)	Yield[b] (%)
1	4-$NO_2CHOC_6H_4$	$PhNHNH_2$	5	95
2	$CHOC_6H_5$	$PhNHNH_2$	10	93
3	3-$NO_2CHOC_6H_4$	$PhNHNH_2$	6	94
4	4-OCH_3 C_6H_4	$PhNHNH_2$	12	90
5	4-$OHCC_6H_4$	$PhNHNH_2$	7	89
6	1-OH C_6H_4	$PhNHNH_2$	9	85
7	2- Cl C_6H_4	$PhNHNH_2$	6	93
8	4- Cl C_6H_4	$PhNHNH_2$	6	92
9	4-CH_3 C_6H_4	$PhNHNH_2$	15	90
10	4-F C_6H_4	$PhNHNH_2$	5	94
11	2-OCH_3 C_6H_4	$PhNHNH_2$	11	88
12	3-CN C_6H_4	$PhNHNH_2$	8	91
13	4-N-dimethylC_6H_3CHO	$PhNHNH_2$	13	89
14	3,4dimethoxyC_6H_3CHO	$PhNHNH_2$	14	89
15	C_6H_5CHO	4-Br$PhNHNH_2$	12	86
16	4-OCH_3 C_6H_4	4-Cl$PhNHNH_2$	14	85

under photocatalytic condition

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Aldehyde**1**(1.00mmol), malanonitrile **2** (1.00mmol), phenylhydrazine **3**(1.00mol) and eosinY(1mol%) in ethanol was stirred at room temperature under irradiation with 22W visible light lamp in presence of air atmosphere for 5-15 minutes. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered and resulting precipitate was washed with hot ethanol. Characterization of representative compound and all the remaining compounds match with authentic sample.

Reddish solid, melting point 165-166 ^{o}C. ^{1}HNMR (400 MHz $CDCl_3$,): δ 8.26 (d, *J* = 7.6 Hz, 2H) 8.02 (s, 1H), 7.75–7.77 (m, 3H), 7.22–7.34 (m, 2H),. 7.17 (d, *J* = 7.6 Hz, 2H), 6.97(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm), 156.49, 150.06, 145.34, 137.77, 135.35, 130.22, 130.04, 129.93, 122.77, 122.35, 123.17, 113.45, 112.76, EIMS (m/e) 305(M).$^{+}$

15.

Graphical Abstract