Visible light promoted formation of N-S bond catalysed by photocatalyst Eosin Y

Ankit Verma[a], Arjita Srivastava[b], Saurabh K Tiwari[a], Neetu Yadav[a], Mohd Danish Ansari[a], Vijay B Yadav[a], Hozeyfa Sagir[c], Ibadur R Siddiqui*[a]

[a] Ankit Verma, Saurabh K. Tiwari, Neetu Yadav, Mohd. Danish Ansari, Vijay B. Yadav and Prof. Ibadur R Siddiqui
Laboratory of Green Synthesis
Department of Chemistry
University of Allahabad
Prayagraj
E-mail: dr.irsiddiqui@gmail.com
[b] Dr. Arjita Srivastava
Department of Chemistry
CMP Degree College, Prayagraj
A Constituent PG College of University of Allahabad
[c] Dr. Hozeyfa Sagir
Department of Chemistry
Paliwal PG College
Shikohabad

Abstract: A novel efficient protocol for the synthesis of 5-imino-1,2,4-thiadiazole motif in open air and visible light has been reported. The reaction involves Eosin Y as photocatalyst which is a cost-effective organic dye. The designed protocol represents a novel, mild, metal free, green strategy for the construction of 1,2,4-thiadiazole nucleus by intramolecular cyclization via N-S bond formation. The reaction has been carried out under visible light exposure in ethanol: water (4:1) mixture using 2-aminopyridine and isocyanate as reactants.

Introduction

The development of sustainable stratagems for chemical synthesis as alternative to conventional synthetic methodologies has acknowledged a widespread cumulative consideration from the synthetic research community[1-3]. Among such pursuits, the selective activation of chemical bonds via visible light mediated chemical reactions as a synthetic tool has witnessed a prominent emergence during the last few decades.[4] The application of this synthetic tool for the eco-compatible synthesis of heterocyclic compounds has also risen prominently.[5] Literature survey suggests that many visible-light photo-redox catalysts, based on metal or non-metal complexes, have been used for chemical transformations in organic synthesis by number of research groups[6]. In this perspective, a well-known organic dye eosin Y (EY), a typical photoredox catalyst, has been used and reported as a remarkable substitute to typical inorganic transition metal photocatalysts[7]. Photoredox catalysis has proven to be an optimum strategy for fulfilling the current mandate in finding the sustainable synthetic methodologies and newer alternative energy sources. The prominent biological activity of N-heterocyclic compounds has encouraged the research community to establish convenient methods for the synthesis of theses structure through N-C, N-N, N-S and N-O bond formation strategies. Among these, 1,2,4-thiadiazoles, a fore-runner core structures of significant medicinal concern, are widely associated with a broad spectrum of biological activity comprising antiulcerative[8], antibacterial[9], antidiabetic[10], anti-inflammatory[11], antirheumatic[12], and antimicrobial agents[13]. For instance, cefozopran, a 1,2,4-thiadiazole nucleus based drug, are available for commercial purpose as an antibiotic drug.[14] In recent years, 1,2,4-thiadiazole derivatives are widely studied as potential drugs for the treatment of human leukemia[15]. However, other fascinating biological effects are as cathepsin B inhibitors[16], as allosteric modulators binding at secondary binding site of biomolecules[17], non-ATP competitive GSK-3 inhibitors[18] and as dual 5-lipoxygenase and cyclooxygenase inhibitors[19]

1,2,4-thiadiazoles have been synthesized by various methods, like copper-catalyzed reaction of amidine hydrochlorides with isothiocyanates,[20] from aryl nitriles in 1-butyl-3-methylimidazolium bromide,[21] molecular iodine catalyzed N-S bond formation,[22] copper-catalyzed aerobic oxidative annulation,[23] and electrochemical intermolecular dehydrogenative S-N coupling.[24] Despite these interesting reports for synthesis of these moieties, visible light promoted methods for synthesis of 1, 2, 4-thiadiazoles remains a relatively unexplored area. Accordingly, in persistence of our current research attention on the incorporating the newer alternatives to access biologically vital heterocyclic moieties in an eco-friendly green method,[25-27] in present study, we herein devise a novel, photocatalysed, metal-free, clean and efficient synthesis of 1,2,4-thiadiazoles nucleus using organic dye eosin Y as a photoredox catalyst **(Scheme 1)**.

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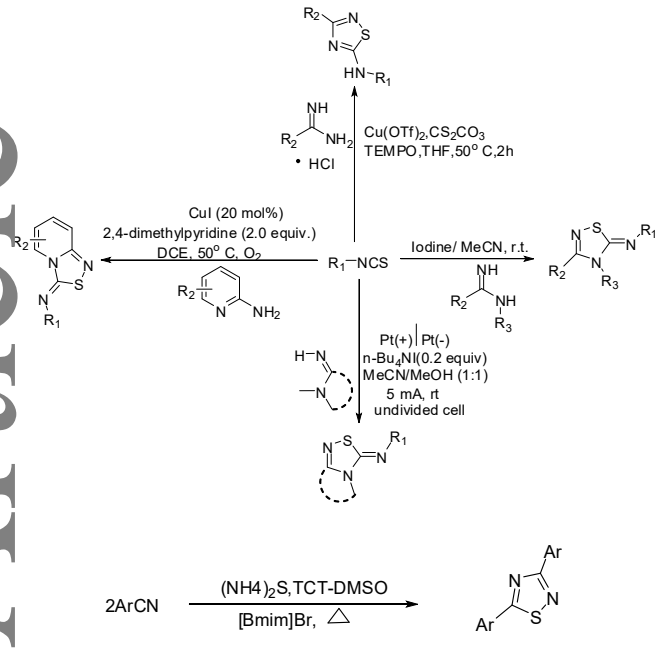
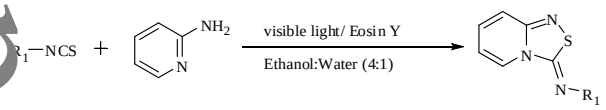
Previous works



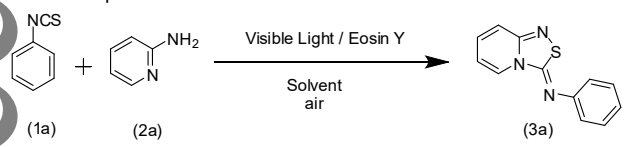
This work: Scheme 1



Results and Discussion

Initially we carried out a reaction with phenyl isothiocyanate (1a) with 2-aminopyridine (2a), in DCM and exposed to the light of a household 22 W fluorescent lamp for tabulated time at room temperature. The desired product was obtained in considerable yields **(Table 1, Entry 1)**.

Table 1: Optimization of solvent[a]



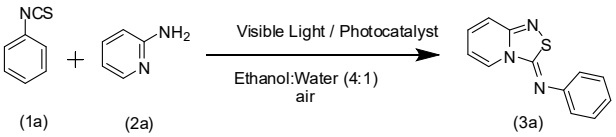
Entry	Solvent	Time (h)	Yield (%)[b]
1	DCM	4	50
2	Toluene	4	trace
3	Benzene	4	10
4	THF	4	21
5	DMSO	4	48
6	MeOH	4	40
7	EtOH	4	80
8	H_2O	4	20
9	EtOH: H_2O (1:1)	4	88
10	EtOH: H_2O (2:1)	3	91
11	EtOH: H_2O (4:1)	1	95

[a]**Reaction conditions**: Phenyl isothiocyanate (3 mmol), 2-aminopyridine(3mmol), under 22W CFL irradiation at room temperature. [b] Isolated yields.

In an attempt to obtain better yields and reaction optimisation, the reaction was carried out in different solvents like toluene, benzene, THF, DMF, MeOH, EtOH and H_2O **(Table 1, Entries 1-8)**. It was noted that polar solvents furnished better yields in comparison to non-polar ones. EtOH was found to be the most effective solvent for the reaction **(Table 1, Entry 7)**. The desired product was obtained in poor yields using water as a solvent, probably because of the low solubility of isothiocyanate in water **(Table 1, Entry 8)**. The increase of reaction time did not affect the yields of the product in any case. A mixed solvent system consisting of ethanol and water was then utilized to minimize the amount of volatile organic solvent for the reaction **(Table 1, Entries 9-11)**. It was noticed that EtOH:H_2O solvent system was better for enhancing the yield and reducing the reaction time for corresponding product. In this way we reduced the tedious workup, waste and cost of the overall process. Later, different ratios of ethanol: water were evaluated and the analysis revealed that the use of 4:1 ratio of ethanol to water proved to be the optimum solvent system for this reaction **(Table 1, Entry 11)**.

Our next step was optimisation of the catalyst in the reaction. In a control experiment performed without any photocatalyst, no yield of the desired products was obtained **(Table 2, Entry 1)**.

Table 2: Optimization of catalyst[a]



Entry	Photocatalyst	Air	Time (h)	Yield (%)[b]
1	-	+	6	--
2	Eosin Y (2 mol%)	-	1	Trace
3	Eosin Y (2 mol%)	+	1	95
4	EosinY (1 mol%)	+	1	65
5	EosinY (3 mol%)	+	1.5	95
6	Eosin Y (5 mol%)	+	1	95
7	Rose Bengal (5 mol %)	+	1	24
8	**Eosin Y (2 mol%)**	**+**	**1**	**95[c]**

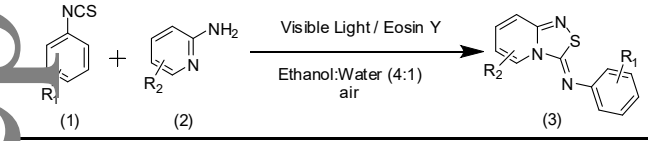
[a]**Reaction conditions**: Phenyl isothiocyanate (3 mmol), 2-aminopyridine(3mmol), in 8 ml EtOH: H_2O (4:1) solvent, under 22W CFL irradiation at room temperature. [b] Isolated yields, [c] **Gram scale synthesis--** Phenyl isothiocyanate (12 mmol, 1.62g), 2-aminopyridine(12mmol, 1.12g), in 20 ml EtOH: H_2O (4:1) solvent, under 22W CFL irradiation at room temperature, product 3a-95%, 2.60g

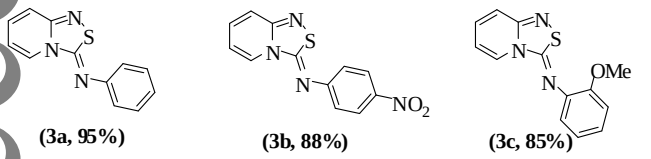
The reaction was then carried out in the presence of 2 mol% Eosin Y, keeping other reaction conditions the same. Role of air was also checked during the process and it was observed that absence of air resulted in only trace amounts of the desired product **(Table 2, Entry 2)**. Interestingly, on adding Eosin Y as the photocatalyst (2 mol%) in the presence of visible light and air, the desired 1,2,4-thiadiazole **3a** was obtained in 95% yield. Optimum catalyst loading was found to be 2 mol% **(Table 2, Entry 3)**. On lowering the catalyst loading from 2 mol% to 1 mol%, there was a significant decrease in the yield **(Table 2, Entry 4)**;

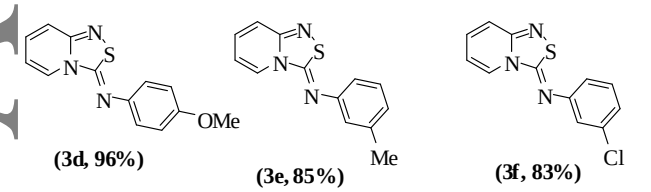
while an increase in the catalyst loading from 2 mol% to 3 mol% and 5 mol% did not improve the yield **(Table 2, Entries 5 & 6)**. The reaction was also carried out using Rose Bengal as the photocatalyst, which did not provide satisfactory results **(Table 2, Entry 7)**. In order to demonstrate the practical applicability of this protocol, a gram scale reaction was also performed and excellent results were obtained **(Table 2, Entry 8)**. These results indicate that the photocatalyst, visible light, and air all are essential for the reaction and support the photocatalytic model for the reaction.

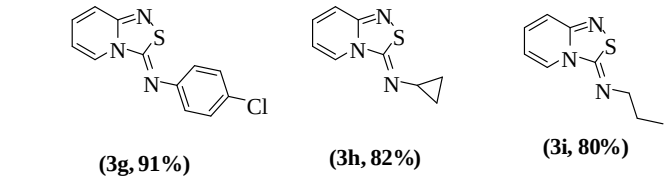
In prolongation of our effort to find out adequate reaction conditions for our model reaction, we next moved our attention to enquire the adaptability of different substrates for projected reaction conditions **(Scheme 2)**. The effect of various substituents at different positions of arylisothiocyanate was checked in our protocol. One noteworthy finding was that arylisothiocyanates with strong electron withdrawing groups as well as electron donating groups were well endured under given reaction conditions, and N-fused 1,2,4-thiadiazole products were obtained in good to excellent yields **(3b-3g)**. However, it was seen that arylisothiocyanates containing electron donating groups such as methoxy and methyl at different positions gave better reactivity and provided the corresponding products in good to excellent yields **(3c)** 85%, **(3d)** 96% and **(3e)** 85% respectively. Conversely, arylisothiocyanates with electron-withdrawing groups such as chloro at para- and meta-positions equipped corresponding products in moderate to good yields, i.e. **(3f)** 83% and **(3g)** 91% respectively.

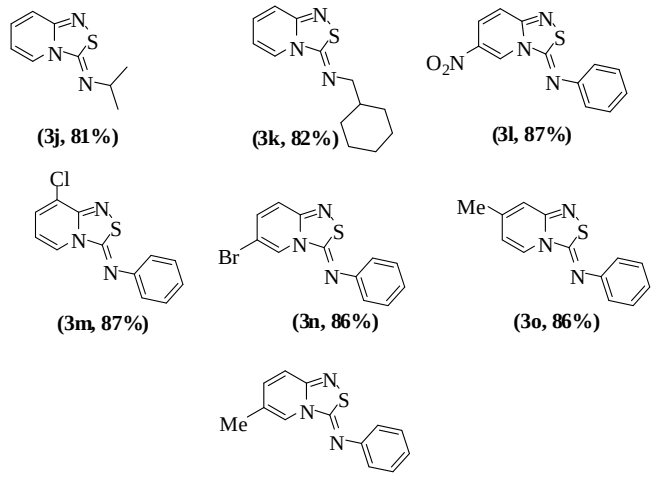
Substrate scope for the synthesis of 3, 4-Disubstituted 5-amino-1,2,4-thiadiazoles- Scheme 2[a]









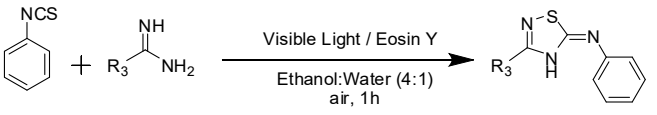


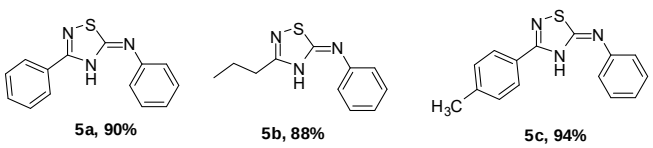
[a]Reaction conditions: Phenyl isothiocyanate (3 mmol), 2-aminopyridine(3mmol), in 8 ml EtOH: H_2O (4:1) solvent, under 22W CFL irradiation at room temperature. [b] Isolated yields.

An alicyclic isothiocyanate such as cyclopropyl isothiocyanate was also tolerated under these reaction conditions, and the corresponding product 3h was isolated in 82% yield. Other aliphatic isothiocyanates including, propyl, isopropyl and cyclohexyl methyl groups were also used to give the corresponding products in good yields **(3i−3k)**. To further examine the scope and generality of the reaction, various 2-aminopyridine derivatives were studied in proposed protocol. When a strong electron-withdrawing nitro group was used, the desired product **(3l)** was obtained in 87% yield **(3l)**. Electron-withdrawing groups such as choro and bromo were compatible and gave the equivalent products **(3m)** and **(3n)** in 87 and 86% yield. Methyl-substituted 2-aminopyridine was well tolerated, and the position of the methyl substituent at 4 and 5 did not bear any significant effect on the reaction yield of **(3o)** and **(3p)** respectively.

In order to further explore the generality of this protocol, the reaction of phenyl isothiocayante was carried out with a few amidine **(4)** substrates **(Scheme 3)**. Good to excellent yields of the desired product were obtained **(5a-5c)**.

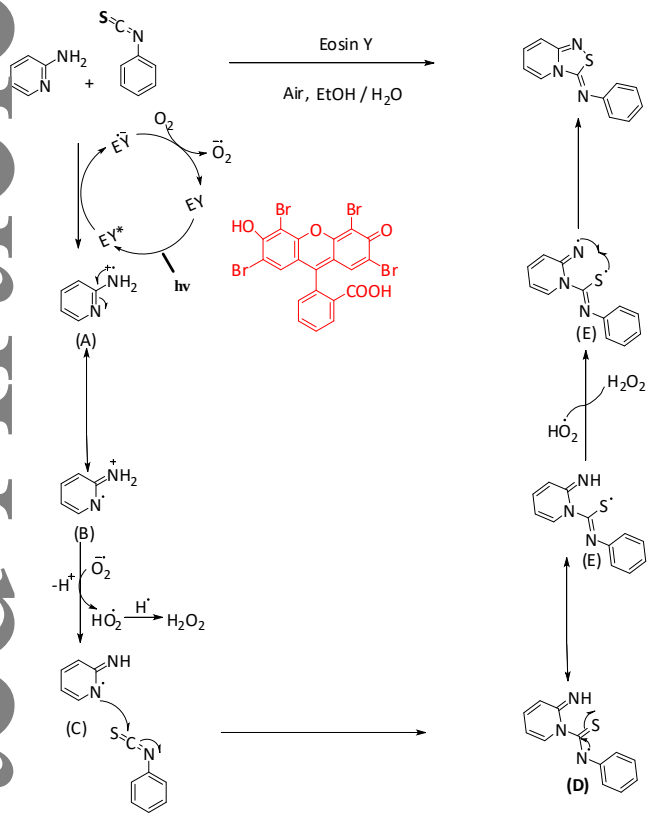
Substrate scope for the synthesis of 1,2,4-thiadiazoles- Scheme 3[a]





[a]Reaction conditions: Phenyl isothiocyanate (3 mmol), amidine substrate (3mmol), in 8 ml EtOH: H_2O (4:1) solvent, under 22W CFL irradiation at room temperature.

On the basis of the above observations and the literature precedents,[28-29] a plausible mechanism involving photo redox catalysis for the synthesis of the conveyed heterocycles is described in **Scheme 4**.



Scheme 4: Postulated mechanism for the Eosin-Y catalysed N-S bond formation.

On absorption of visible light, the organophotoredox catalyst eosin Y (EY) is excited to its singlet state ^{1}EY* which through inter system crossing (ISC) comes to its more stable triplet state ^{3}EY* and undergoes a single electron transfer (SET).[30] ^{3}EY* may undergo both reductive and oxidative quenching.[31] A SET from 2-aminopyridine to ^{3}EY* generates 2-aminopyridine radical cation **A** and radical anion of eosin Y. Radical anion of eosin Y is further returned to its ground state by electron transfer to molecular oxygen through in situ formation of superoxide radical anion. Structures **A** and **B** are resonance structures and a proton is probably abstracted from structure **B** by the superoxide anion to furnish a new intermediate **C**.

Next, intermediate **C** undergoes addition reaction with the isothiocyanate derivative resulting in the formation of new N-centered radical intermediate **D**. This intermediate **D** can easily resonate to another S-centered/thionyl radical intermediate **E**. HO_2 formed earlier now takes up hydrogen radical from intermediate **E** to produce N-centered radical species and H_2O_2 as the by-product takes place. The final cyclised product **3a** could be the result of radical coupling of the newly formed radicals. The radical pathway is supported by the fact that the presence of radical quencher TEMPO suppressed the reaction.

Conclusion

In conclusion, we have developed a novel and convenient visible light promoted method for the synthesis of N-fused 1,2,4-thiadiazole from 2-aminopyridine and phenyl isothiocyanate in a one-pot procedure by using inexpensive eosin Y as a powerful organophotoredox catalyst, at room temperature. The reaction involves a mixture of ethanol and water as the solvent system. This synthetic pathway, because of its green credentials, is an improvement over those synthetic methods which involve the use of corrosive and toxic chemicals. This synthesis widens the scope of substrates for visible light photo redox reactions. The developed synthetic approach can be easily scaled up to gram scale, thereby providing the possibility for the scaled production of diverse N-fused 1,2,4-thiadiazole. The present methodology also offers other advantages of green chemistry such as high atom economy, reduced reaction time, one-pot consolidated procedure and high efficiency.

Acknowledgements

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords: Visible Light, Eosin Y, Photocatalyst, Green Chemistry

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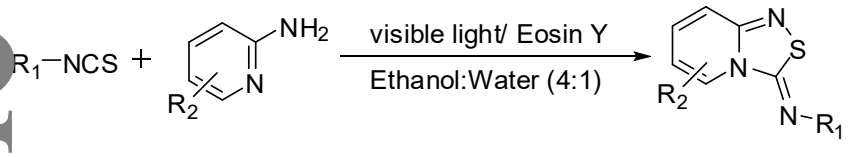

The application of visible light in combination with Eosin Y as the organic photocatalyst is being widely employed for organic syntheses. Excellent results have been obtained by using this combination for the synthesis of thiadiazole ring via an effective N-S bond formation reaction.