# Eosin Y catalysed visible-light mediated aerobic oxidation of tertiary amines

Vishal Srivastava, Pravin K. Singh, Praveen P. Singh

PII: S0040-4039(19)30798-1
DOI: https://doi.org/10.1016/j.tetlet.2019.151041
Reference: TETL 151041

To appear in: *Tetrahedron Letters*

Received Date: 1 July 2019
Revised Date: 9 August 2019
Accepted Date: 11 August 2019

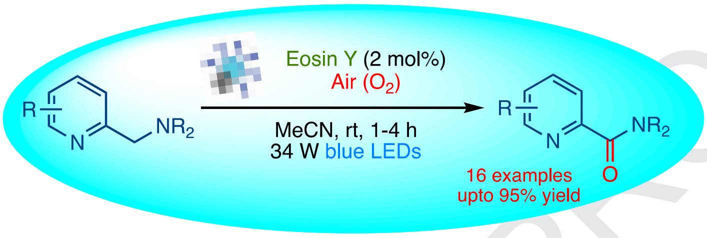
Please cite this article as: Srivastava, V., Singh, P.K., Singh, P.P., Eosin Y catalysed visible-light mediated aerobic oxidation of tertiary amines, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151041

## Graphical Abstract

### Eosin Y catalysed visible-light mediated aerobic oxidation of tertiary amines

Leave this area blank for abstract info.

Vishal Srivastava[a] Pravin K. Singh[a] and Praveen P. Singh*[b]



Tetrahedron Letters
journal homepage: www.elsevier.com

# Eosin Y catalysed visible-light mediated aerobic oxidation of tertiary amines

Vishal Srivastava[a] , Pravin K. Singh[a] and Praveen P. Singh[b,] ∗

[a]*Department of Chemistry, CMP Degree College, University of Allahabad, Prayagraj 211002, India*
[b]*Department of Chemistry, United College of Engineering & Research, Naini, Prayagraj 211010, India*

ARTICLE INFO

*Article history:*
Received
Received in revised form
Accepted
Available online

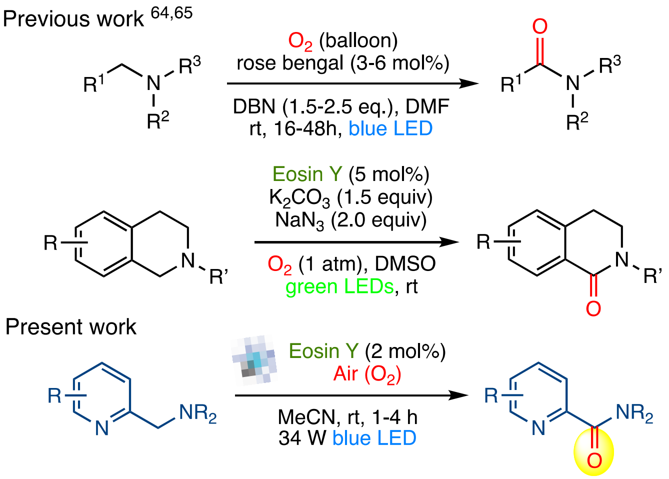
*Keywords:*
Visible light
Eosin Y
Aerobic oxidation
Pyridine

ABSTRACT

A mild and efficient one-pot visible light-induced method has been developed for the aerobic oxidation of saturated carbon conjugated with pyridine moiety with an important conversion in medicinal and synthetic organic chemistry. This eosin Y based organic transformations, exhibit a novel approach towards site selective functionalization of pyridine with enhance integrity and capability. This novel synthetic route may hold great potential for diverse functionalization of a wide range of pyridine moiety with an economical and sustainable manner.

The direct functionalization of pyridine using metal catalysts or photocatalysts has been studied extensively, [1-4] due to it's convenient and cost-effective access to core structures of many privileged heterocycles, which are important in materials science [5,6] and medicinal chemistry. [7,8] The direct functionalization of pyridine moiety remains a difficult challenge for organic chemists, however few synthetic methods [9-14] have been developed for alkylation of pyridine. In recent years, one of the biggest challenges in the field of chemistry has been the utilization of green energy and renewable processes for photocatalytic conversion of organic compounds to provide ideal candidates for a variety of environment benign organic transformations. [15] Developing safe, accessible, and low cost oxygen utilization for aerobic oxidation systems to access structurally diverse oxygenated compounds is a challenging task in catalytic chemistry. [16,17] Recently, visible-light photocatalysis reactions have provided an attractive and energy-saving platform for developing diverse aerobic chemical transformations under mild conditions. [18,19] A number of researchers have utilized and focused on photocatalytic induced oxidation as an emerging strategy for many types of reactions, [20-27] which have been successfully oxidized at atmospheric pressure. The utilization of inexpensive molecular oxygen as an environmentally friendly oxidant to develop efficient and green protocols for visible light promoted aerobic oxidations is of great interest in organic transformations, with high advantage area of research. [28-30]

Harnessing visible light as a safe, renewable, and inexpensive source of chemical energy to facilitate the construction of complex organic molecules has emerged recently as a powerful theme in organic chemistry. [31-34] This is because solar energy (visible light) is clean, easy to handle and an unlimited energy source having great prospects for the development of sustainable and eco-friendly protocols for organic synthesis. [35] Some pioneering researchers have dedicated to converting solar energy into chemical energy for chemical transformations [36,37] which includes a promising strategy for the application of photoredox catalysts to initiate single electron transfer (SET) processes. [38,39] Visible light photoredox catalysis has recently received much attention in organic synthesis owing to ready availability, sustainability, non-toxicity and ease of handling. [40–45]



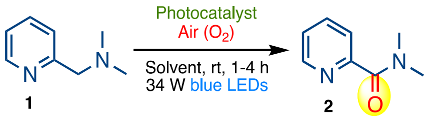
**Scheme 1.** Photocatalysed aerobic oxidation of tertiary amines

---

∗ Corresponding author. e-mail: ppsingh23@gmail.com

Recently, a superior alternative to transition metal photoredox catalysts, especially metal-free organic dyes such as eosin Y, fluorescein, rose bengal, nile red, perylene and rhodamine B have been used as economically and ecologically superior surrogates for Ru(II) and Ir(II) complexes in visible-light promoted organic transformations involving SET. [46–48] These organic dyes have great potential for applications in visible-light-mediated organic synthesis [49–52] which fulfils the basic principle of green chemistry. In continuation of our work on development of environmentally benign synthesis [53-63] herein we report a simple, visible light irradiated, efficient green protocol for the eosin Y catalysed aerobic oxidation of tertiary amines conjugated with pyridine moiety **(Scheme 1)**.

**Table 1.** Optimization of reaction conditions.[a]



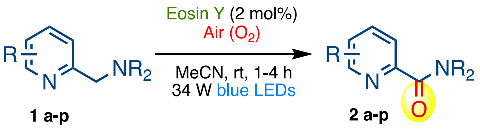
| Entry | Photocatalyst | Catalyst loading (mol%) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Eosin Y | 2 | MeCN | 1 | 93 |
| 2 | 4CzIPN | 2 | MeCN | 1 | 90 |
| 3 | Rose Bengal | 2 | MeCN | 1 | 87 |
| 4 | Fluorescein | 2 | MeCN | 1 | 81 |
| 5 | Nile Red | 2 | MeCN | 1 | 79 |
| 6 | Perylene | 2 | MeCN | 1 | 77 |
| 7 | Rhodamine B | 2 | MeCN | 1 | 80 |
| 8 | Quinones | 2 | MeCN | 1 | 84 |
| 9 | Benzophenones | 2 | MeCN | 1 | 74 |
| 10 | Eosin Y | 2 | EtOH | 1 | 63 |
| 11 | Eosin Y | 2 | DMF | 1 | 78 |
| 12 | Eosin Y | 1 | DMSO | 1 | 86 |
| 13 | Eosin Y | 1 | MeCN | 1 | 67 |
| 14 | Eosin Y | 3 | MeCN | 1 | 92 |
| 15 | Eosin Y | 2 | MeCN | 4 | trace[c] |
| 16 | Eosin Y | 2 | MeCN | 4 | trace[d] |
| 17 | - | - | MeCN | 4 | n. d.[e] |
| 18 | Eosin Y | 2 | MeCN | 4 | trace[f] |
| 19 | Eosin Y | 2 | MeCN | 4 | 58[g] |
| 20 | Eosin Y | 2 | MeCN | 1 | 92[h] |
| 21 | Eosin Y | 2 | MeCN | 1 | 89[i] |

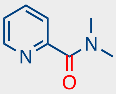
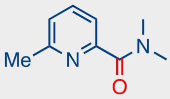
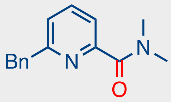
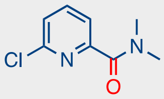
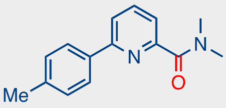
(a) Reaction conditions: **1** (1.0 mmol), catalyst (mol%), in 3 mL solvent irradiated using high power blue LEDs [34 W] under an air atmosphere at rt for 1–4 h.
(b) Another one Isolated yield of the pure product **2**.
(c) Reaction was performed under nitrogen.
(d) Reaction was performed in the dark.
(e) Reaction was carried out without catalyst.
(f) Reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl(TEMPO) (1.0 mmol).
(g) 34 W CFL (compact fluorescent lamp, Philips) was used.
(h) $O_2$ balloon was used.
(i) The reaction was quenched with DABCO (1.0 mmol).

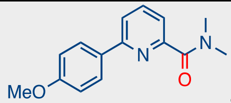
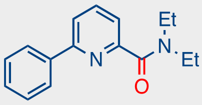
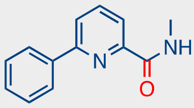
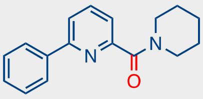
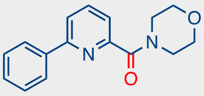
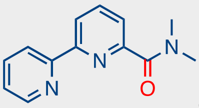
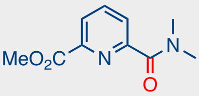
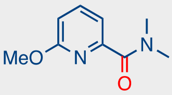
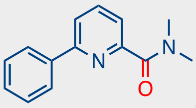
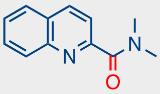
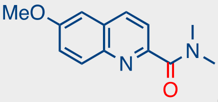
In order to realise our idea and optimise the reaction conditions, the key reaction of substituted pyridinyl methanamine **1a** with catalytic amount of eosin Y in a solvent under irradiation with blue LEDs [34 W, λ = 470 nm] in open air (**Table 1**). We were delighted to get the desired product substituted alkyl picolinamide **2a** in 94 % yield (**Table 1, entry 1**). Then, the control experiments were carried out, which show that eosin Y, air ($O_2$) and visible light are essential for the reaction, because in the absence of any of the reagents/reaction parameters either the product was not detected (n. d.) or formed in the traces (**Table 1, entry 1 versus 15 – 18**). The optimum amount of eosin Y required for the reaction was 2 mol%. On decreasing the amount of eosin Y from 2 mol% to 1 mol% the yield was considerably reduced (**Table 1, entry 13**), whereas the yield was not enhanced even on use of 3 mol% of eosin Y (**Table 1, entry 14**). The use of another organic photocatalyst like 4CzIPN (2 mol%), rose bengal (2 mol%), fluorescein (2 mol%), nile red (2 mol%), perylene (2 mol%), rhodamine B (2 mol%), quinones (2 mol%) and benzophenones (2 mol%), was not so effective as eosin Y (2 mol%) (**Table 1, entry 1 versus 2 – 9**). Blue LEDs [34 W, λ = 470 nm] were more effective than fluorescent light (**Table 1, entry 19**), which shows that the higher photocatalytic activity of eosin Y in presence of high intensity blue light. The presence of $O_2$ (air) is also essential for the reaction because only a trace of product formation was detected under a nitrogen atmosphere (**Table 1, entry 15**). Notably, the same result was obtained on using $O_2$ (balloon) instead of an air atmosphere (**Table 1, entry 20**). Moreover, the reaction was quenched with 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) (1.0 mmol) in standard state showing that there may be radical intermediates involved in reaction (**Table 1, entry 18**). Furthermore, the reaction did not quench in the presence of DABCO (1.0 mmol) (**Table 1, entry 21**), which indicates the involve- ment of triplet oxygen in the reaction. Since, DABCO is a good quencher of singlet oxygen and quenching was not observed, it suggests that singlet oxygen was not involved in the reaction. [66] The possibility of substituted pyridinyl methanamine as a reducing agent that undergoes oxidation to radical cation is very less because quenching of radical cation could not be done. Next, the reaction was optimized for an effective solvent system. It was found that MeCN was the best among the tested solvents EtOH, DMF, DMSO and MeCN, hence it was used throughout the present study (**Table 1, entry 1 versus 10 – 12**).

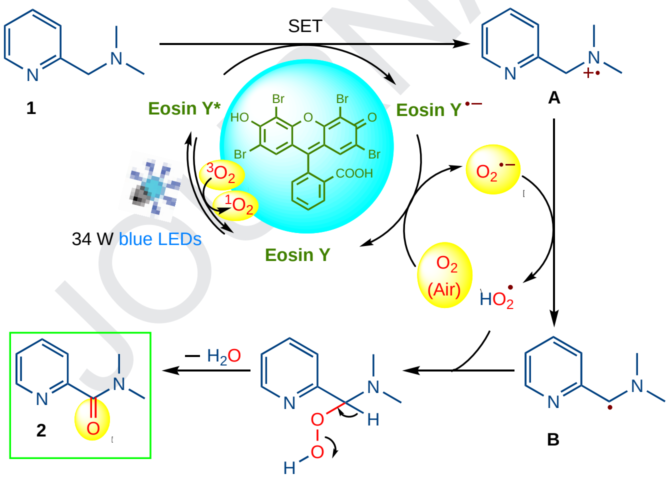
The scope of the present protocol across a range of substituted pyridinyl methanamine incorporating various substituents. It was found that pyridinyl methanamine with an electron-donating group on the aromatic ring appear to react faster and afford marginally higher yields in comparison to those bearing an electron-withdrawing group. **(Table 2)**

**Table 2.** Scope of the reaction.



| S.N | Product | Yield |
|---|---|---|
| 1 |  **2a** | 93 |
| 2 |  **2b** | 94 |
| 3 |  **2c** | 90 |
| 4 |  **2d** | 77 |
| 5 |  **2e** | 85 |

| | | |
|---|---|---|
| 6 |  **2f** | 87 |
| 7 |  **2g** | 88 |
| 8 |  **2h** | 86 |
| 9 |  **2i** | 72 |
| 10 |  **2j** | 70 |
| 11 |  **2k** | 76 |
| 12 |  **2l** | 78 |
| 13 |  **2m** | 95 |
| 14 |  **2n** | 87 |
| 15 |  **2o** | 87 |
| 16 |  **2p** | 89 |



**Scheme 2.** Plausible mechanism for the aerobic oxidation of tertiary amines

On the basis of our observations and the literature reports [65,67] a plausible mechanistic pathway is depicted in **Scheme 2.** 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). $^3$EY* may undergo both reductive and oxidative quenching. [68-72] A SET from substituted pyridinyl methanamine **1** to the excited state of eosin Y (EY*) generates aminyl cation radical **A** and $EY^{\cdot -}$. Furthermore, the reaction between oxygen and $EY^{\cdot -}$ results in the formation of a superoxide radical anion ($O_2^{\cdot -}$), which could then react with aminyl cation radical **A** to afford intermediate **B**. Followed by a reaction with the hydroperoxyl radical ($HOO^{\cdot}$), results the desired product **2** with elimination of water molecule. The formation of superoxide radical anion ($O_2^{\cdot -}$) during the reaction was confirmed by the detection of the resulting $H_2O_2$ using KI/starch indicator. [73]

In conclusion, we have developed a novel, one-pot photocatalysed aerobic oxidation of tertiary amines conjugated with pyridine moiety. This protocol utilizes atmospheric oxygen along with visible light as the cheapest and eco sustainable reagents as well as eosin Y as an organophotoredox catalyst at room temperature. Thus, it is a superior alternative to the existing method with respect to green and sustainable chemistry (better atom and step-economy). The proposed method exhibits a new approach towards site-selective functionalization of pyridine derivatives and will expand the medicinal chemist toolbox for accessing valuable privileged scaffolds.

## Acknowledgments

We sincerely thank Emerging Science Society for financial support as well as SAIF, CDRI, Lucknow and IISc Bangalore for providing microanalyses and spectra.

## References

1. S. Han, P. Chakrasali, J. Park, H. Oh, S. Kim, K. Kim, A. K. Pandey, S. H. Han, S. B. Han, I. S. Kim, Angew. Chem., Int. Ed. 57 (2018) 12737.
2. A. J. Boyington, M.-L. Y. Riu, N. T. Jui, J. Am. Chem. Soc. 139 (2017) 6582.
3. P. S. Fier, J. Am. Chem. Soc. 139 (2017) 9499.
4. J. P. Lutz, S. T. Chau, A. G. Doyle, Chem. Sci. 7 (2016) 4105.
5. J.-N. Desrosiers, X. Wei, O. Gutierrez, J. Savoie, B. Qu, X. Zeng, H. Lee, N. Grinberg, N. Haddad, N. K. Yee, F. Roschangar, J. J. Song, M. C. Kozlowski, C. H. Senanayake, Chem. Sci. 7 (2016) 5581.
6. F. Raoof, M. Boostanizadeh, A. R. Esmaeilbeig, S. M. Nabavizadeh, R. B. Aghakhanpour, K. B. Ghiassi, M. M. Olmstead, A. L. Balch, RSC Adv. 5 (2015) 85111.
7. E. Vitaku, D. T. Smith, J. T. Njardarson, J. Med. Chem. 57 (2014) 10257.
8. K.-H. Lam, C.-H. Chui, R. Gambari, R. S.-M. Wong, G. Y.-M. Cheng, F.-Y. Lau, P. B.-S. Lai, S.-W. Tong, K.-W. Chan, W.-Y. Wong, A. S.-C. Chan, J. C.-O. Tang, Eur. J. Med. Chem. 45 (2010) 5527.
9. X. Ma, S. B. Herzon, J. Am. Chem. Soc. 138 (2016) 8718. (b) X. Ma, H. Dang, J. A. Rose, P. Rablen, S. B. Herzon, J. Am. Chem. Soc. 139 (2017) 5998.
10. W. Jo, J. Kim, S. Choi, S. H. Cho, Angew. Chem., Int. Ed. 55 (2016) 9690.
11. M. Nagase, Y. Kuninobu, M. Kanai, J. Am. Chem. Soc. 138 (2016) 6103.
12. X. Zhang, A. McNally, Angew. Chem., Int. Ed. 56 (2017) 9833.
13. R. D. Dolewski, P. J. Fricke, A. McNally, J. Am. Chem. Soc. 140 (2018) 8020.
14. M. C. Hilton, R. D. Dolewski, A. McNally, J. Am. Chem. Soc. 138 (2016) 13806.
15. I. R. Shaikh, J. Catal. (2014) 1.
16. J. Liu, X. Zhang, H. Yi, C. Liu, R. Liu, H. Zhang, K. Zhuo, A. Lei, Angew. Chem., Int. Ed., 54 (2015) 1261.
17. S. E. Allen, R. R. Walvoord, R. P. Salinas, M. C. Kozlowski, Chem. Rev. 113 (2013) 6234.
18. B. Xu, J.-P. Lumb, B. A. Arndtsen, Angew. Chem., Int. Ed. 54 (2015) 4208.

19. X. Sun, X. Li, S. Song, Y. Zhu, Y.-F. Liang, N. Jiao, J. Am. Chem. Soc. 137 (2015) 6059.
20. Xu Zhang, K. P. Rakesh, Xu Zhang, K. P. Rakesh, Green Chemistry 20 (2018) 4790.
21. T. Chatterjee, G. Roh, M. A. Shoaib, C. H. Suhl, J. S. Kim, C. G. Cho, E. J. Cho, Org. Lett. 19 (2017) 1906.
22. S. Higashimoto, K. Okada, M. Azuma, H. Ohue, T. Terai, Y. Sakata, RSC Adv. 2 (2012) 669.
23. X. Lang, H. Ji, C. Chen, W. Ma, J. Zhao, Angew. Chem., Int. Ed. 123 (2011) 4020.
24. S. Furukawa, T. Shishido, K. Teramura, T. Tanaka, ACS Catal. 2 (2011) 175.
25. Z. Li, C. Liu, H. Abroshan, D. R. Kauffman, G. Li, ACS Catal. 7 (2017) 3368.
26. L. E. Hofmann, L. Mach, M. R. Heinrich, J. Org. Chem. 83 (2018) 431.
27. Y. Nagasawa, Y. Matsusaki, T. Hotta, T. Nobuta, N. Tada, T. Miura, A. Itoh, Tetrahedron Lett. 55 (2014) 6543.
28. A. N. Campbell, S. S. Stahl, Acc. Chem. Res. 45 (2013) 851.
29. E. Roduner, W. Kaim, B. Sarkar, V. B. Urlacher, S. Laschat, ChemCatChem 5 (2013) 82.
30. W. Wu, H. Jiang, S. Adimurthy, Acc. Chem. Res. 45 (2012) 1736.
31. J. W. Tucker, C. J. R. Stephenson, J. Org. Chem. 77 (4) (2012) 1617.
32. D. R. Heitz, K. Rizwan, G. A. Molander, J. Org. Chem. 81 (16) (2016) 7308.
33. F. X. Felpin, S. Sengupta, Chem. Soc. Rev. 48 (2019) 1150.
34. H. Chen, L. Guo, Yu Shouyun, Org. Lett. 20 (19) (2018) 6255.
35. X. Sala, I. Romero, M. Rodriguez, L. Escriche, A. Llobet, Angew. Chem. Int. Ed. 48 (16) (2009) 2842.
36. D. Mandler, I. Willner, J. Am. Chem. Soc. 106 (18) (1984) 5352.
37. O. Ishitani, S. Yanagida, S. Takamuku, C. Pac, J. Org. Chem. 52 (13) (1987) 2790.
38. A. Inagakia, M. Akita, Coord. Chem. Rev. 254 (2010) 1220.
39. C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Chem. Rev. 113 (7) (2013) 5322.
40. D. A. Nicewicz, T. M. Nguyen, ACS Catal. 4 (1) (2014) 355.
41. J. Xie, H. Jina, P. Xu, C. Zhu, Tetrahedron Lett. 55 (1) (2014) 36.
42. X. Lang, X. Chen, J. Zhao, Chem. Soc. Rev. 43 (1) (2014) 473.
43. J. Hu, J. Wang, T.H. Nguyen, N. Zheng, Beilstein J. Org. Chem. 9 (2013) 1977.
44. D. Rovelli, M. Fagnoni, A. Albini, Chem. Soc. Rev. 42 (1) (2013) 97.
45. T. P. Yoon, M. A. Ischay, J. J. Du, Nat. Chem. 2 (7) (2010) 527.
46. X. J. Yang, B. Chen, L. Q. Zheng, L. Z. Wu, C. H. Tung, Green Chem. 16 (2014) 1082.
47. K. Fidaly, C. Ceballos, A. Falguières, M. S. I. Veitia, A. Guy, C. Ferroud, Green Chem. 14 (2012) 1293.
48. D. T. Yang, Q. Y. Meng, J. J. Zhong, M. Xiang, Q. Liu, L. Z. Wu, Eur. J. Org. Chem. 33(2013) 7528.
49. Y. Q. Zou, J. R. Chen, X. P. Liu, L. Q. Lu, R. L. Davis, K. A. Jørgense, W. J. Xiao, Angew. Chem. Int. Ed. 51 (2012) 784.
50. D. P. Hari, B. König, Org. Lett. 13 (15) (2011) 3852.
51. M. Neumann, S. Füldner, B. König, K. Zeitler, Angew. Chem. Int. Ed. 50 (4) (2011) 951.
52. V. Rey, S. M. S. Catro, J. E. Arguello, A. B. Peñéñory, Tetrahedron Lett. 50 (33) (2009) 4720.
53. V. Srivastava, P. K. Singh, P. P. Singh, Chem. Heterocycl. Compd. 50 (2014) 573.
54. V. Srivastava, P. K. Singh, P. P. Singh, Croat. Chem. Acta 87 (2) (2014) 91.
55. V. Srivastava, P. K. Singh, P. P. Singh, Croat. Chem. Acta 88 (1) (2015) 59.
56. V. Srivastava, P. K. Singh, P. P. Singh, Croat. Chem. Acta 88 (3) (2015) 227.
57. V. Srivastava, P. K. Singh, P. P. Singh, Asian J. Chem. 8 (10) (2016) 2159.
58. (a) V. Srivastava, P. K. Singh, S. Sinha, P. P. Singh, Rev. Roum. Chim. 61 (10) (2016) 755. (b) V. Srivastava, P. K. Singh, P. P. Singh, Croat. Chem. Acta 90 (3) (2017) 435.
59. V. Srivastava, P. P. Singh, RSC Adv. 7 (2017) 31377.
60. V. Srivastava, P. K. Singh, S. Kanaujia, P. P. Singh, New J. Chem. 42 (2018) 688.
61. P. K. Singh, P. P. Singh, V. Srivastava, Croat. Chem. Acta 91 (3) (2018) 383.
62. V. Srivastava, P. K. Singh, P. P. Singh, Tetrahedron Lett. 60 (2019) 40.
63. V. Srivastava, P. K. Singh, P. P. Singh, Tetrahedron Lett. 60 (2019) 1333.
64. Y. Zhang, D. Riemer, W. Schilling, J. Kollmann, S. Das, ACS Catal. 8 (2018) 6659.
65. K. C. C. Aganda, B. Hong, A. Lee, Adv. Synth. Catal. 361 (2019) 1124.
66. T. Keshari, V. K. Yadav, V. P. Srivastava, L. D. S. Yadav, Green Chem. 16 (2014) 3986.
67. Y. Zhang, W. Schilling, S. Das, ChemSusChem, (2019) doi.org/10.1002/cssc.201900414.
68. D. C. Neckers, O. M. Valdes-Aguilera, Adv. Photochem. 18 (1993) 315.
69. M. V. Encinas, A. M. Rufs, S. G. Bertolotti, C. M. Previtali, Polymer 50 (2009) 2762.
70. T. Lizarides, T. McCormick, P. Du, G. Luo, B. Lindley, R. Eisenberg, J. Am. Chem. Soc. 131 (2009) 9192.
71. S. H. Lee, D. H. Nam, C. B. Park, Adv. Synth. Catal. 351 (2009) 2589.
72. T. Xiao, X. Dong, Y. Tang, L. Zhou, Adv. Synth. Catal. 345 (2012) 3195.
73. G. K. Fekarurhobo, S. S. Angaye, F. G. Obomann, J. Emerg.Trends Engg. Appl. Sci. (JETEAS) 4 (2013) 394.

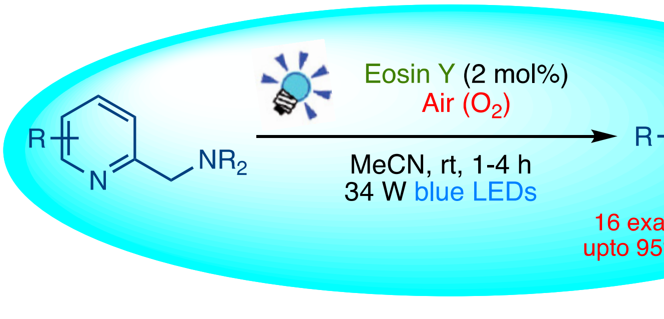
## Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

# GRAPHICAL ABSTRACT

## Eosin Y Catalysed Visible-Light Mediated Aerobic Oxidation of Tertiary Amines

Vishal Srivastava[a], Pravin K. Singh[a] and
Praveen P. Singh[b]*



# Highlights

- A mild and efficient one-pot visible light-induced method
- Metal-free organic dyes have been used
- Aerobic oxidation of saturated carbon conjugated with pyridine moiety