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Organocatalytic Oxidative Synthesis of C2-Functionalized Benzoxazoles, Naphthoxazoles, Benzothiazoles and Benzimidazoles

Dhananjaya Kaldhi,[a] Nagaraju Vodnala,[a] Raghuram Gujjarappa,[a] Subhashree Nayak,[b] V. Ravichandiran,[c] Sreya Gupta,[c] * Chinmoy K. Hazra,[d] * Chandi C. Malakar [a] *

[a]*Department of Chemistry, National Institute of Technology Manipur, Imphal - 795004, Manipur, India*
[b]*Department of Chemistry, National Institute of Science Education and Research (NISER), Jatani, Odisha -752050, Bhubaneswar, India*
[c]*Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Kolkata, Chunilal Bhawan, 168, Maniktala Main Road, Kolkata – 700054, India*
[d]*King Abdullah University of Science and Technology, KAUST Catalysis Center, Thuwal-23955-6900, Saudi Arabia*

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ABSTRACT

An efficient organocatalyzed method is described for the cyclization of *o*-aminophenols, 1-amino-2-naphthol, *o*-aminothiophenol and *o*-phenylenediamine with alcohols to yield the corresponding benzoxazoles, naphthoxazoles, benzothiazoles and benzimidazoles under aerobic oxidative conditions. This method relies on the use of 3-nitropyridine as a sole catalyst for the *in situ* transformation of benzyl alcohols or cinnamyl alcohol to corresponding aldehydes under aerobic conditions. The developed protocol excludes the use of expensive metals like Ru, Pd, and Cu as catalyst and harsh oxidizing agents. A large number of substituted *o*-aminophenols, 1-amino-2-naphthol, *o*-aminothiophenol and *o*-phenylenediamine were tolerated under the optimized reaction conditions to give analogous benzoxazoles, naphthoxazoles, benzothiazoles and benzimidazoles. A mechanistic proposal has been drawn based upon the control experiments. It was demonstrated that under the influence of aerobic conditions the catalytic amounts of ^{t}BuOOH can be generated by auto-oxidation of *tert*-butoxide base which plays a decisive role towards successful completion of the developed approach. The described method was extended to yield a wide range of derivatives with the isolated yields up to 96%.

Introduction

The effective synthesis of biologically active small molecules and organic intermediates can be achieved by various novel methods.[1] Among these methods, organocatalysis is one of the key synthetic tools used in drug discovery research. The advantages are not only restricted to its synthetic range but also extended to the economic point of view. Therefore, in recent years, organocatalysis is recognized as one of the fascinating research topics in advanced organic chemistry which has been found as the best alternative to the prevalent transition metal catalytic system.[2] The metal free approach in organocatalysis brings an indisputable advantage considering both the principles of "green chemistry" and the economic point of view.[3] In addition, the concept of organocatalytic aerobic oxidation has provided a surrogate and sustainable platform towards oxidative transformation.[4] Hence, there is a decent demand towards the development of novel organocatalytic system in the multidisciplinary fields of research. Here, we have demonstrated that a combination of 3-nitropyridine and NaO^{t}Bu under aerobic conditions can serve the access of diverse heterocycles from simple substrates. N-heterocyclic skeletons are the key structural units in the field of drug discovery and medicinal chemistry due to their wide occurrence in biologically active compounds.[5] Among these molecules, five membered N-heterocycles such as benzoxazoles, naphthoxazoles, benzothiazoles and benzimidazoles are found as the major components in natural products,[6] and bioactive compounds.[7]

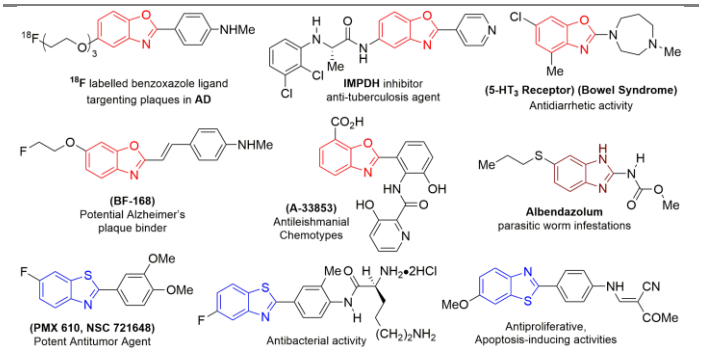
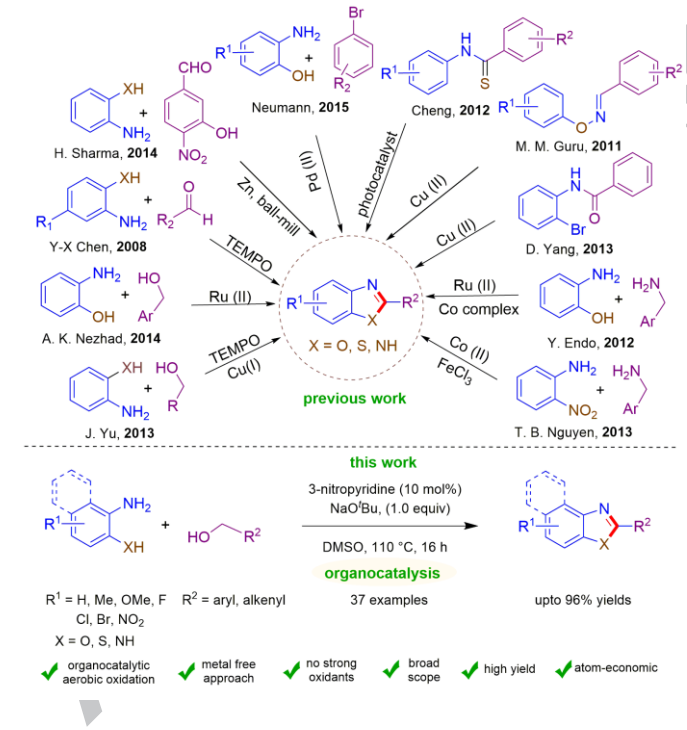


Figure 1. Medicinal impact of azole derivatives.

Moreover, due to their esteemed pharmacological profiles, these scaffolds received immense attention in marketed pharmaceuticals and the molecules under clinical trial.[8-10] These scaffolds have found enormous applications in the pharmacology such as ^{18}F-Labeled benzoxazole derivatives are recognized as potential positron emission tomography probes for imaging of cerebral β-amyloid plaques in Alzheimer's disease.[11] These molecules are also used as anti-tuberculosis agent,[12] anti-leishmanial chemotypes[13] and anti-diarrhetic agent.[14] Subsequently, the benzothiazoles are present in many pharmaceuticals that exhibit remarkable biological and therapeutic activities. For example, benzothiazoles exhibit potent anti-tumor activity[15] (PMX 610, NSC 721648), anti-bacterial activity,[16] anti-microbial activity,[17] anti-proliferative and apoptosis inducing activity.[18] On the other hand, the substituted benzimidazole derivatives have found application in diverse therapeutic areas including anticonvulsant, anti-ulcer, anti-hypertensive, anti-histaminic,[19–23] and anti-tumor activity.[15a,b]

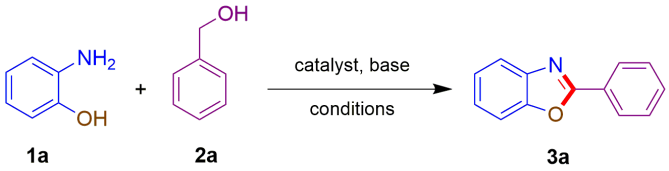


Scheme 1. Approaches for the synthesis of azoles.

The selected scaffolds are presented in Figure 1 along with their immense biological importance. In the past years, several useful approaches have been developed for the preparation of these molecules. The straightforward methods include the condensation reactions of *o*-aminophenols, *o*-aminothiophenol and o-phenylenediamine with either carboxylic acids/derivatives (nitriles, imidates, orthoesters)[24] or aldehydes[25] using strong dehydrating agents. Additionally, these scaffolds can be synthesized efficiently using intramolecular cyclization of 2-haloanilides/derivatives[26] or 2-hydroxyanilides,[27] with suitable reaction partners under the influence of transition-metal catalysis.[28] However, the transformations rely on strong acidic or oxidative conditions[25f,29–33] using $Pb(OAc)_4$,[34] $Na_2S_2O_5$,[35] $(NH_4)_2S_2O_8$,[36] DDQ,[37] MnO_2,[38] oxone,[39] and H_2O_2.[40] Despite the traditional condensation approaches which being most widely explored, the oxidative condensation using alcohols remains more attractive.[41] In recent years transition metal catalyzed transformations using Pd, Co, Cu, Rh, Ru, Fe, and Zn have also

been developed towards synthesis of these scaffolds.[26c-d,42-48] (Scheme 1). In addition, recently the photo-catalyzed reactions have been utilized as efficient synthetic tools[49] for the preparation of azole derivatives using easy available substrates. Besides the number of advantages, these methods suffer in terms of non-renewable metal waste, hazardous and toxic oxidants. Hence, the development of novel and facile methods for the synthesis of these molecules remain desirable. More recently, the development of organocatalysts has rarely received attention for the synthesis of these scaffolds.[50] Albeit, a large number of efficient methods have been devised, and the further development of novel organocatalytic protocols could serve the purpose of surrogate efficient protocols. We developed a more facile and mild organocatalytic system comprises 3-nitropyridine as organocatalyst and NaO^{t}Bu as a base to serve the synthesis of benzoxazoles, naphthoxazoles, benzothiazoles and benzimidazoles.

Table 1. Initial screening of the conditions for the reaction between **1a** and **2a**.[a]



1a **2a** **3a**

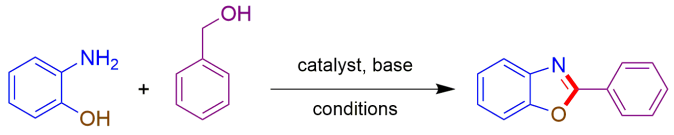
Entry	Catalyst [Mol %]	Additive [equiv.]	Temp [°C]	Time [h]	3a, Yield %[b]
1	-	NIS (3)	50	16	NR[c]
2	-	TBAI (3)	100	16	NR
3	TBAI (10)	TBHP (3)	100	16	60
4	Iodine (50)	TBHP (3)	100	16	42
5	Iodine (50)	$K_2S_2O_8$ (2)	100	12	33
6	Iodine (50)	H_2O_2 (2)	100	12	71
7	Pyridine N-oxide (10)	NaO^{t}Bu (0.2)	120	16	14
8	TEMPO (10)	NaO^{t}Bu (1)	120	16	47
9	2-Picolinic acid (10)	TBAI (0.3)	120	16	NR
10	2-Picolinic acid (10)	Iodine (0.3)	120	16	NR

[a]Unless otherwise indicated, all reactions were performed using 1.0 mmol **1a** and 1.0 mmol **2a** in 2 mL DMSO under aerobic conditions. [b]Isolated yields. [c]Reaction was carried out using 2 mL THF as solvent.

Having various thoughts towards developing the organocatalytic system which can deal with the aerobic oxidation protocol for the synthesis of azole derivatives, we carried out several initial screening reactions between *o*-aminophenol **1a** and benzyl alcohol **2a**, (Table 1) in the presence of mild oxidizing agents. Formation of the product **3a** was not observed when the reaction was carried out in presence of NIS as oxidizing agent in THF as solvent at 50 °C (Entry 1). However, the outcome remains unnoticeable when NIS was replaced with TBAI as oxidizing agent in DMSO as solvent at 100 °C (Entry 2). Interestingly, the 2-arylated benzoxazole **3a** was obtained in 60% yield, when the reaction was carried out using 10 mol% TBAI and 3.0 equiv. TBHP in DMSO as solvent at 100 °C for 16 hours (Entry 3). Next it was observed that the yield of the product **3a** was reduced considerably, when TBAI was replaced with catalytic amounts of iodine (Entry 4). Then, the feasibility for the formation of desired product **3a** was verified using equivalent amounts of alternative oxidants such as $K_2S_2O_8$ and H_2O_2 in presence of iodine as catalyst (Entries 5-6). It was found that among the oxidants attempted for the reaction between **1a** and **2a**, using 50% of iodine and 2.0

equiv. H_2O_2 delivered the highest yield of the expected product **3a** (Entry 6). Although, the satisfactory yield of the product **3a** was obtained, nevertheless the development of the novel organocatalytic conditions have been intended for the reaction between **1a** and **2a**.

Table 2. Organocatalyzed optimization of the conditions for the reaction between **1a** and **2a**[a]

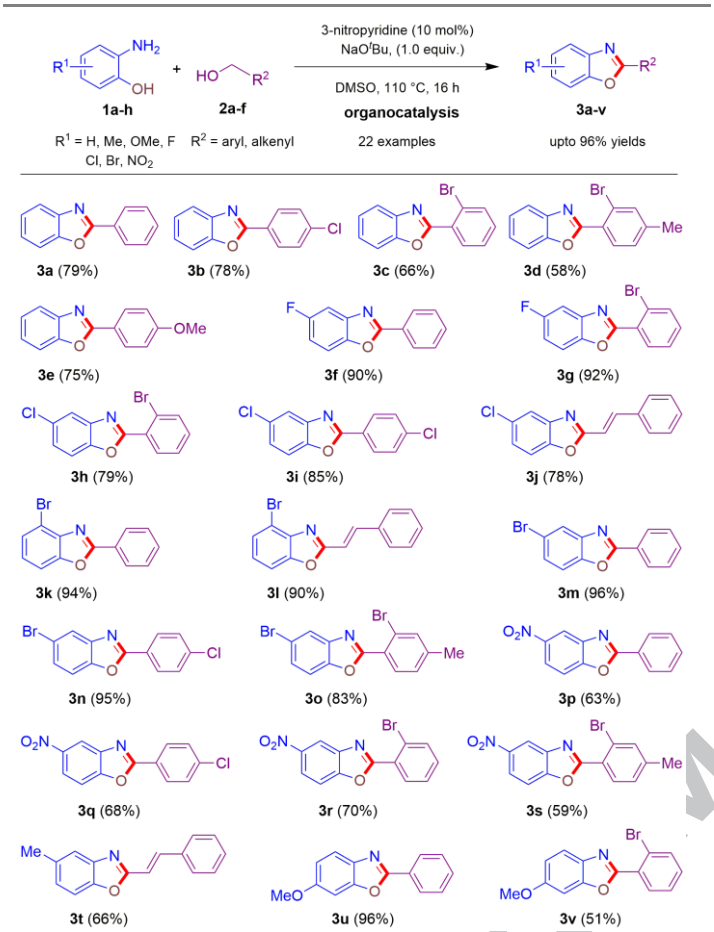


1a 2a 3a

Entry	Catalyst [Mol %]	Additive [equiv.]	Temp [°C]	Time [h]	3a, Yield%[b]
1	2-Picolinic acid (10)	NaO^{t}Bu (0.2)	120	16	23
2	Thiourea (10)	Iodine (1)	120	16	45
3	Thiourea (10)	NaO^{t}Bu (0.5)	100	16	49
4	Vitamin-B_3 (10)	NaO^{t}Bu (0.5)	100	16	42
5	3-nitropyridine (20)	TBAI (3)	120	16	67
6	3-nitropyridine (10)	NaO^{t}Bu (1)	110	16	92
7	3-nitropyridine (20)	NaO^{t}Bu (1)	110	16	89
8	3-nitropyridine (7)	NaO^{t}Bu (1)	110	16	81
9	3-nitropyridine (10)	NaO^{t}Bu (1)	120	16	87
10	3-nitropyridine (10)	NaO^{t}Bu (1)	80	16	52
11	3-nitropyridine (10)	NaO^{t}Bu (1)	110	10	69
12	3-nitropyridine (10)	NaO^{t}Bu (1)	110	24	76
13	3-nitropyridine (10)	NaO^{t}Bu (1)	110	16	< 8[c]
14	3-nitropyridine N-oxide (10)	NaO^{t}Bu (1)	110	16	85

[a]Unless otherwise indicated, all reactions were performed using 1.0 mmol **1a** and 1.0 mmol **2a** in 2 mL DMSO under aerobic conditions. [b]Isolated yields. [c]Reaction was carried out under nitrogen atmosphere.

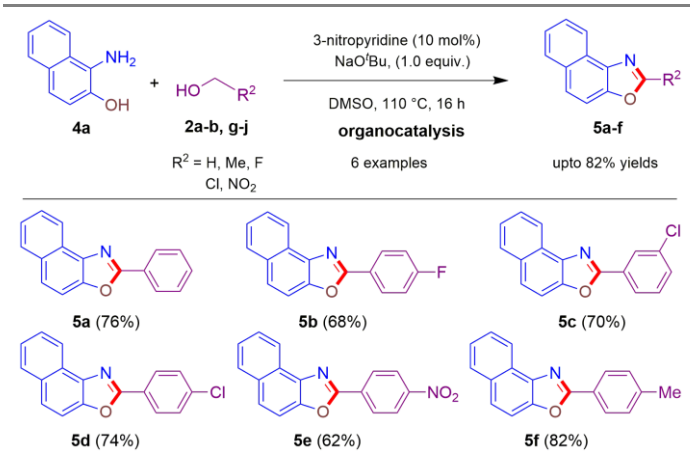
Hence, the reactions between **1a** and **2a** were realized in presence of 10 mol% Pyridine N-oxide or 10 mol% 2-picolinic acid or 10 mol% TEMPO under various reaction conditions (Entries 7-10). It was investigated that the expected product **3a** was formed in 14% and 47% yield respectively, when the reaction was carried out using 10 mol% Pyridine N-oxide or 10 mol% TEMPO as catalyst and NaO^{t}Bu as an additive in DMSO under aerobic conditions (Entries 7 and 8), whereas the transformation remains inactive when 2-picolinic acid was introduced as catalyst in the presence of TBAI and iodine as additive (Entries 9-10). Initial screening of the reaction conditions revealed that albeit, in low yield the catalytic amounts of Pyridine N-oxide influenced the formation of the product **3a** (Entry 7). Hence, in order to find the ideal organocatalytic conditions, we have attempted the further reactions between **1a** and **2a** in presence of a number of organocatalysts (Table 2). These organocatalysts include 2-picolinic acid, thiourea, vitamin-B_3, and 3-nitropyridine. Interestingly, it was observed that the catalytic amounts of 2-picolinic acid and thiourea in the presence of NaO^{t}Bu or iodine as additives delivered the desired product **3a** in yields ranging from 23-49%, when the reactions were carried out in DMSO under aerobic conditions (Entries 1- 3). Similar observation was found with vitamin-B_3 as catalyst in presence of NaO^{t}Bu as an additive (Entry 4). Next, the efficacy of 3-nitropyridine was explored as organocatalyst in the presence of TBAI or NaO^{t}Bu as additive which resulted the formation of product **3a** in high yields (Entries 5-6). Maximum yield (92%) of the product **3a** was observed, when the reaction was performed in DMSO as solvent at 110 °C using the combination of both 3-nitropyridine as catalyst and NaO^{t}Bu as additive under aerobic conditions (Entry 6). Then, the impact of the amounts of catalyst was investigated for the reaction between **1a** and **2a**.



Scheme 2. Synthesis of 2-substituted benzoxazoles under the optimized conditions.

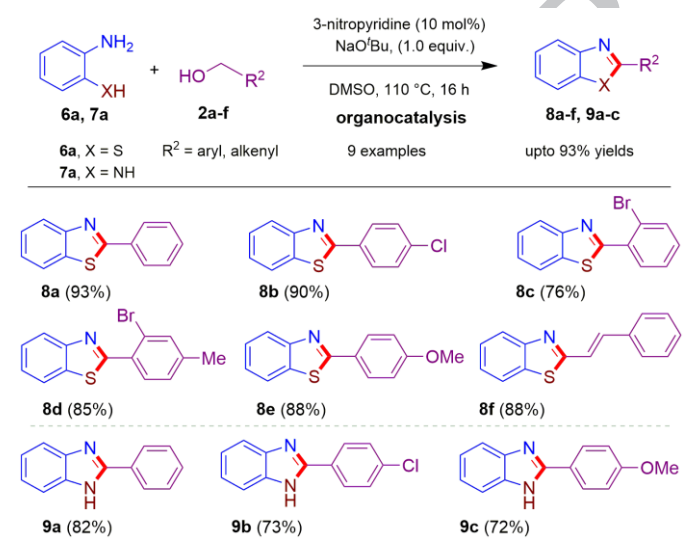
It was realized that increasing the catalyst loading, the reaction delivered the similar yield of the product **3a** (Entry 7); whereas decreasing the amounts of catalyst resulted the formation of the product **3a** in slightly lower yield (Entry 8). On the other hand, variation of reaction temperature and time did not lead to the satisfactory outcomes in terms of yield of the product **3a** (Entries 9-12). It was further realized that the formation of product **3a** was inhibited, if the reaction was carried out in absence of catalyst (in SI) and aerobic conditions (Entry 13). Finally, 10 mol% of 3-nitropyridine-N-oxide was introduced as catalyst for the reaction between **1a** and **2a** under identical conditions, which resulted the formation of product **3a** in 85% yield (Entry 14). The result explains the involvement of 3-nitropyridine-N-oxide as the key catalytic species which is in accordance with the proposed mechanism depicted in Scheme 5.

After having a detailed screening exercise for the ideal reaction conditions (Table 1, Table 2 and in SI), it was concluded that the highest yield of the product **3a** was obtained when the reaction between 1.0 mmol **1a** and 1.0 mmol **2a** was conducted in the presence of 10 mol% 3-nitropyridine as catalyst and 1 equiv. of NaO^{t}Bu as additive using DMSO as solvent under aerobic conditions at 110 °C for 16 hours (Table 2, Entry 6). Hence, these reaction parameters were considered as optimal conditions to execute the scope of the developed method.



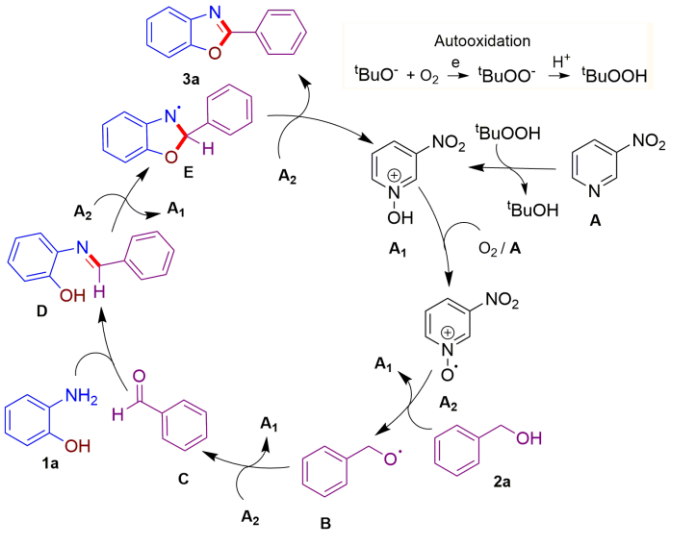
Scheme 3. Synthesis of 2-substituted naphthoxazoles under the optimized conditions.

Using the optimized conditions, a variety of *o*-aminophenols **1a-h** and benzyl alcohols **2a-e** or cinnamyl alcohol **2f** were tested for the transformation to afford the desired benzoxazole derivatives **3a-v** (Scheme 2). It has been realized that the electron-donating groups such as methyl and methoxy, and the electron-withdrawing substituents such as halogen and nitro were well tolerated on the aromatic moieties of both the substrates. Substrate scope revealed that the yield of the products **3a-v** seems to be general (ranging from 51-96%) with both electron-donating and electron-withdrawing groups. The reactivity of cinnamyl alcohol **2f** derivatives was also tested under the developed conditions to afford the corresponding products **3j**, **3l** and **3t** in good yields ranging from 66-90%. On the other hand, it was also realized that the developed method is not only restricted to the synthesis of benzoxazole derivatives, rather the described approach can be further extended for the preparation of naphthoxazoles, **5a-f** using 1-amino-2-naphthol **4a** in high yields (Scheme 3). In addition, the scope of the reaction was further extended for the synthesis of benzothiazoles **8a-f** and benzimidazoles **9a-c** in high yields using *o*-aminothiophenol **6a** or *o*-phenylenediamine **7a as** starting materials (Scheme 4).



Scheme 4. Synthesis of 2-substituted benzothiazoles and benzimidazoles.

On the basis of our experimental observations and literature evidence,[51] a plausible mechanism has been drawn in Scheme 5. Based on the literature report,[52] it is expected that the catalytic amounts of ^{t}BuOOH might be generated using *tert*-butoxide base by auto-oxidation. Next, the catalytic amounts of 3-nitropyridine-N-hydroxide **A1** can be formed *in-situ* by the reaction between 3-nitropyridine **A** and ^{t}BuOOH which can be further converted to **A2** in presence of aerial oxygen and 3-nitropyridine **A**. The intermediate **B** is formed via hydrogen abstraction from **2a** by **A2** which can be generated by reoxidation of intermediate **A1**. Finally, the interaction between intermediate **B** and **A2** leading to the formation of the intermediate **C** and **A1**. It is expected that the intermediate **D**, can be formed by the condensation reaction between **1a** and **C**. The intermediate **E** is formed via hydrogen abstraction by **A2** which can be generated by reoxidation of intermediate **A1**.



Control experiment with radical scavenger

10 mol% 3-nitropyridine
1 equiv. NaO^{t}Bu
DMSO, 110 °C, 16 h

1a + **2a** → **3a**

radical scavenger

Amount of BHT in equiv.	Isolated yield of **3a** (%)
0.3	32
1.1	0

Scheme 5. Plausible mechanism for the 3-nitropyridine catalyzed synthesis of azoles under aerobic conditions.

Finally, the interaction between intermediate **E** and **A2** leading to the formation of the product **3a** and **A1**. To check the proposed radical pathways for the formation of the expected products **3a**, the control reactions were carried out in presence of butylated hydroxytoluene (BHT) as radical scavenger. The experiments shows that using catalytic amounts of BHT the yield (32%) of the product **3a** was diminished considerably; whereas the formation of the product **3a** was completely inhibited when the reaction between **1a** and **2a** was performed in presence of 1.1 equiv. of BHT as radical scavenger (Scheme 5).

In summary, we have demonstrated the metal-free 3-nitropyridine catalyzed facile synthesis of 2-functionalized benzoxazoles, naphthoxazoles, benzothiazoles and benzimidazoles using simple and easy available starting materials. The described method excludes harsh oxidants and expensive metals like Pd, Rh, Ru, and Au. The approach has been extended for the synthesis of diverse range of products decorated with electron-donating and electron-withdrawing groups in excellent yields up to 96%.

Acknowledgments

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Supplementary Material

A detailed supporting information is available which includes the purity and source of the reagents, experimental procedures, additional optimization table, ^{1}H NMR and ^{13}C NMR of the final products. Supplementary material for this article can be found in online version, at doi ……..

Experimental Section

General Method: All starting materials were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media) and were used without further purification unless otherwise indicated. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. The reactions were performed in pressure tube purchased from Sigma-Aldrich glassware. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on TLC plates purchase from Merck. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Products were purified by flash column chromatography on silica gel, 100 -

200 mesh. ^{1}H (^{13}C) NMR spectra were recorded at 600 (150) and 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26 /77.28 ($CDCl_3$) and $\delta_{H/C}$ 2.51 /39.50 (DMSO-d_6) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

General experimental procedure for the synthesis of products benzoxazoles (3a-v), naphthoxazoles (5a-f), benzothiazoles (8a-f) and benzimidazoles (9a-c) using 3-nitropyridine as organocatalyst: A 25 mL RB was charged with a mixture of *o*-aminophenols **1a-h** (1.0 mmol) or 1-amino-2-naphthol **4a** (1.0 mmol) or *o*-aminothiophenol **6a** (1.0 mmol) or *o*-phenylenediamine **7a** (1.0 mmol) and benzyl alcohols **2a-e**, **g-j** or cinnamyl alcohol **2f** (1.0 mmol) along with 3-nitropyridine (0.1 mmol, 12.4 mg), NaO^{t}Bu (1.0 mmol, 96 mg) and DMSO (2 mL). The RB was loosely fitted with septum and then heated at 110 °C for 16 h. After completion of the reaction, the mixture was diluted with hot ethyl acetate (20 mL) and water (40 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and dried over anhysdrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography over silica gel using hexane / ethyl acetate = 9:1 (*v*/v) as an eluent to obtain the desired products benzoxazoles **3a-v**, naphthoxazoles **5a-f**, benzothiazoles **8a-f** and benzimidazoles **9a-c** in high yields.

White solid, $\mathbf{R_f}$ = 0.70 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 102 - 105 °C (Lit[45] 103 - 104 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.36 - 7.41 (m, 2H; 4-H,7-H), 7.54 - 7.58 (m, 3H; 12-H,13-H, 14-H), 7.62 (dd, ^{3}J = 7.0 Hz, 1H; 5-H), 7.81 (dd, ^{3}J = 7.0 Hz, 1H; 6-H), 8.29 (d, ^{3}J = 8.0 Hz, 2H; 11-H, 15-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 110, 120.1, 124, 125, 127, 127.6, 129, 131, 142, 150, 163 ppm ; **HRMS** (EI, M^+) calculated for $C_{13}H_9NO$ (195.06841); found (195.06820).

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Highlights

(i) No sensitive and hazardous reagents were used.

(ii) Reaction excludes the involvement of precious metals, additives, ligands and radical initiators.

(iii) Reaction proceeds without formation of any toxic side products.

(iv) Developed method utilizes 3-nitropyridine as organocatalyst under aerobic conditions.

(v) Potential application for the synthesis of a broad range of compounds in excellent yields.

Graphical Abstract

Organocatalytic Oxidative Synthesis of C2-Functionalized Benzoxazoles, Naphthoxazoles, Benzothiazoles and Benzimidazoles

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Dhananjaya Kaldhi, Nagaraju Vodnala, Raghuram Gujjarappa, Subhashree Nayak, V. Ravichandiran, Sreya Gupta, Chinmoy K. Hazra, and Chandi C. Malakar