



An efficient and green protocol for the synthesis of 1-hydroxy-2-arylimidazole-3-oxide derivatives under solvent-free condition using inexpensive copper borate (CuB_4O_7) catalyst

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Abstract

A highly efficient, simple, and environmental friendly protocol for the synthesis of 1-hydroxy-2-arylimidazole-3-oxide derivatives was devised using inexpensive and unconventional copper borate (CuB_4O_7) catalyst under solvent-free condition. The documented method features a wide range of chemical substrate scope. All the products formed were characterized by different analytical and spectroscopic techniques.

Graphical abstract



Features:

1. Solvent free protocol
2. First report of copper borate as catalyst
3. Wide range of substrate scope
4. Excellent yield of the product
5. Easy work up of the product
6. High recyclability of the catalyst

Keywords Imidazole · Copper borate · FT-IR · NMR · Multicomponent reaction

Introduction

During the past, drugs containing heterocyclic scaffold have occupied a unique position because of their high therapeutic values. A number of drugs containing the heterocyclic core are in clinical use to treat many infectious diseases [1]. Among a large number and diverse heterocyclic compounds, imidazole, a five-membered nitrogen-containing heterocyclic compound, has gained a lot of interest in the field of drug discovery and has occupied a special position in the field of heterocyclic chemistry [2]. The polar nature of imidazole scaffold could be largely exploited to improve

the pharmacokinetic property of drug molecule and help in improving the aqueous solubility of many drugs which are poorly soluble in water [3]. A large variety of compounds containing the imidazole scaffold show promising therapeutic activities such as antiviral [4], antitumor [5], antiinflammatory [6], antidiabetic [7], anticonvulsant [8], antiasthmatic [9] and antiamebic [10] properties. Etonitazene (analgesic), enviroxime (antiviral), pantoprazole (antiulcer) [11], metronidazole (antibacterial) [12], and carbimazole (antithyroid) [13] are commercially available drugs which contain the imidazole scaffold (Fig. 1).

Interestingly, 1-hydroxyimidazole-3-oxide is regarded as a versatile heterocyclic compound, as these compounds are mostly involved in the synthesis of room temperature ionic liquids [14]. Particularly, the incorporation of the N–O moiety in imidazolium-based ionic liquid may give rise to a greener solvent, which is degradable by design and may fulfill the primary aspect of green chemistry principles [15].

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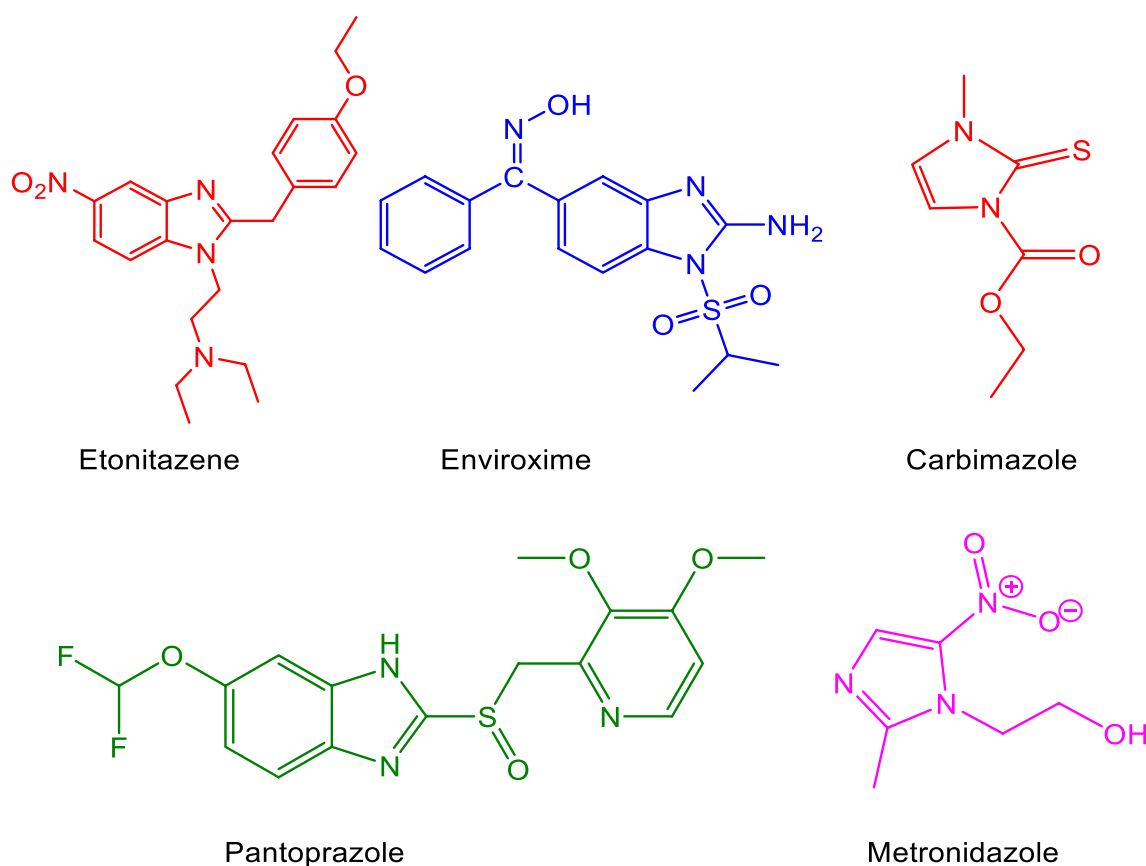


Fig. 1 Example of drugs containing the imidazole scaffold

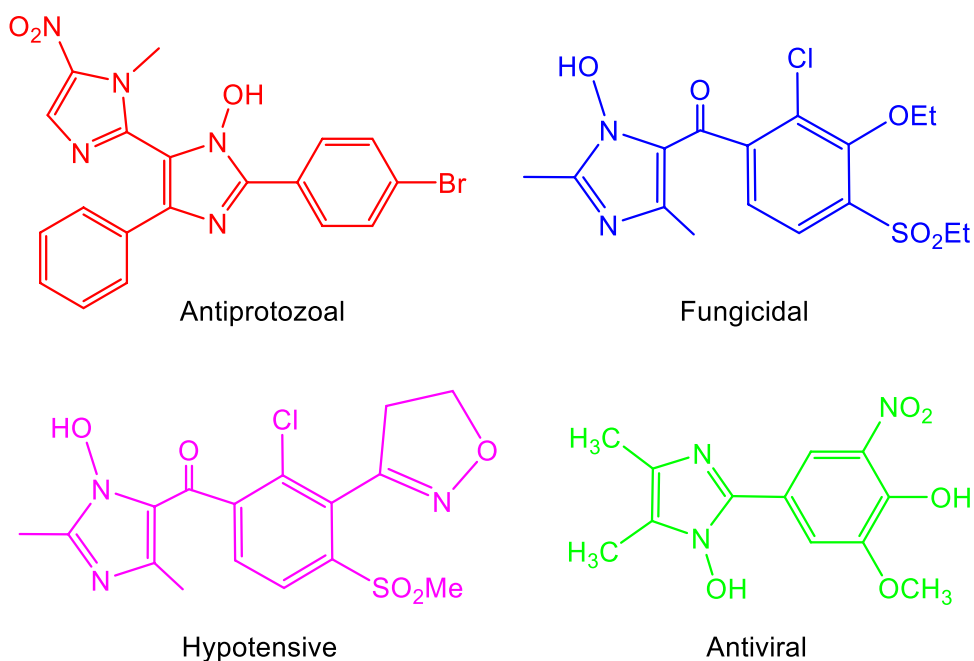
Moreover, the imidazolium salt, namely, 1-alkoxy-3-alkylimidazolium salts, were found to be liquid at room temperature, the synthesis of which requires a two-step alkylation of the precursor 1-hydroxyimidazole [16].

The precursor 1-hydroxyimidazole-3-oxide could readily be obtained by cyclization of glyoxime and formaldehyde [17]. The employment of alkyl or aryl aldehydes in the synthesis of 1-hydroxyimidazole results in the formation of the corresponding 1-hydroxy-2-alkylimidazole-3-oxide and 1-hydroxy-2-arylimidazole-3-oxide derivatives, respectively. In general, heterocyclic compounds commonly containing a dipolar R_3-N-O linkage, in which the nitrogen is either sp^3 or sp^2 hybridized, are known as heterocyclic *N*-oxides [18, 19]. Interestingly, incorporation of a negative charge on the oxygen of heterocyclic *N*-oxides changes most of the physical properties including the reactivity of the compounds, and the most common heterocyclic *N*-oxide is pyridine-*N*-oxide which has excellent donor properties as compared to normal pyridine [20, 21]. Imidazole-*N*-oxides fall under the category of *N*-substituted imidazole which has a wide variety of applications. These compounds have gained popularity due to their anti-protozoal [22], fungicidal, herbicidal, pesticidal

[23], hypotensive [24], antitumor [25], and antiviral [26] properties (Fig. 2).

Apart from their pharmaceutical applications, imidazole-*N*-oxides are also used for the generation of *N*-containing heterocyclic carbenes (NHCs) which act as intermediates in various organic reactions [27]. A current survey revealed that only few works on the synthesis of 1-hydroxy-2-arylimidazole-3-oxide have been documented in the literature [28]. Moreover, the present-day organic synthesis demands a designing of an operationally simple, useful, and practical strategy, which is cost-effective and has less detrimental impact on the environment. A rational design in multicomponent reactions (MCRs) plays a chief role in the current scenario because of the convergent nature, higher atom economy, and easy experimental procedures in the production of target compounds by the introduction of diverse elements in a single operation, with minimization of waste, labor, time, and cost [29–33]. A lot of effort has been incorporated to extend the scope of the well-known classical multicomponent reactions to newer systems. Thus, it was thought worthwhile to undertake the research work in the synthesis of 1-hydroxy-2-arylimidazole-3-oxide derivatives

Fig. 2 Example of 1-hydroxyimidazole compounds having biological activities



under green chemical condition by employing inexpensive and unconventional copper borate as a catalyst.

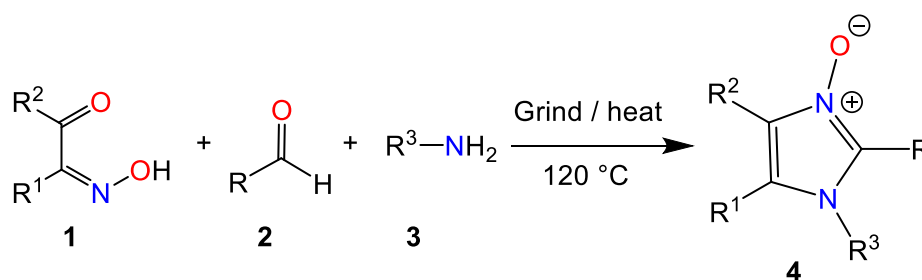
Results and discussion

Considering the diverse applications of imidazole-3-oxides and 1-hydroxyimidazole-3-oxide, various methodologies have been developed in the past for the synthesis of these compounds. The most common and the conventional method for the synthesis of imidazole-3-oxides **4** is from mono-oximes (α -hydroxyiminoketones) **1** and aldehydes **2** in the presence of amines **3** [34, 35] (Scheme 1). Substitution of the amine precursor with NH₄OAc for the above reaction results in the formation of the 1-hydroxyimidazole derivatives **4** [36, 37] (Scheme 2). However, when hydroxylamine hydrochloride (NH₂OH·HCl) is used instead of amine and NH₄OAc, the corresponding 1-hydroxy-2-alkylimidazole-3-oxide or

1-hydroxy-2-arylimidazole-3-oxide is formed depending on the aldehyde precursor used [38] (Scheme 3).

Although the above-mentioned procedures are widely used for the synthesis of imidazole-*N*-oxides and 1-hydroxyimidazole-3-oxides, there are very few reports on the solvent-free and green procedures for the synthesis of the above-mentioned compounds [34]. These factors prompted us to devise a synthetic method for the synthesis of 1-hydroxy-2-arylimidazole-3-oxide derivatives under solvent-free conditions using copper borate as a catalyst. Thus, in this article, we represent the catalytic efficacy of inexpensive copper borate (CuB₄O₇) as a catalyst for the solvent-free synthesis of 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxide derivatives. Initially, for the synthesis of 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxide **4**, we selected diacetyl monoxime **1**, benzaldehyde (**2**), and hydroxylamine hydrochloride (NH₂OH·HCl, **3**) as model compounds under different reaction conditions at 100 °C

Scheme 1



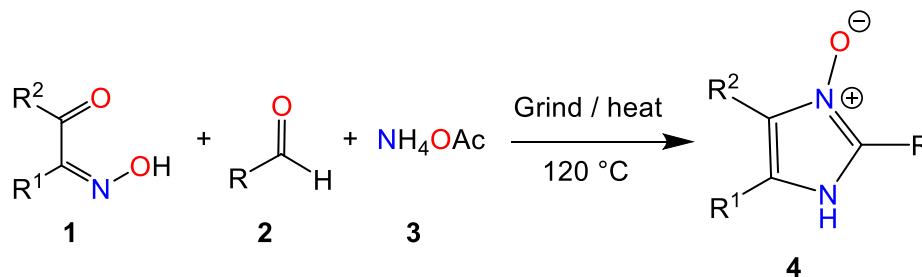
for 2 h using varied amounts of catalyst (0.5–3.5 mol%) (Scheme 4).

Again for the optimization of the reaction condition, different solvent systems were chosen taking five polar protic and polar aprotic solvents to screen the efficacy of the employed catalyst for the desired reaction (Table 1). Interestingly it was observed that the above reaction proceeds well in more polar protic and aprotic solvent such as alcohol and DMF and DMSO, respectively (Table 1, entries 1, 2, 3, and 4), but under this condition the reaction needs more time for completion. Therefore, the focus was made toward the green protocol by utilizing solvent-free condition for the synthesis of 1-hydroxy-2-arylimidazole-3-oxide. Moreover, it was observed that under solvent-free condition, the reaction proceeds well and requires less time for completion without

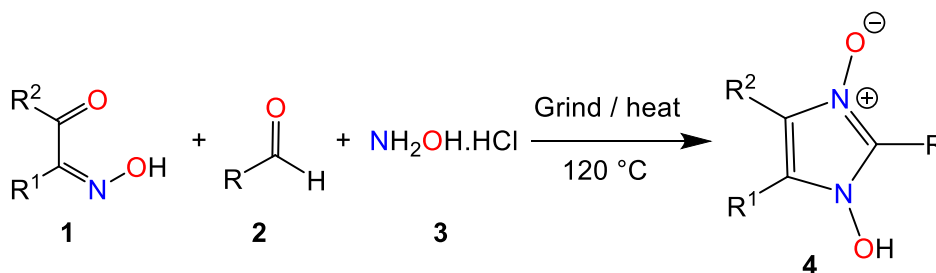
forming the by-product and therefore making the workup procedure more facile and efficient (Table 1, entry 6).

The above reaction was carried out with model components using different mol% of the catalyst to optimize the catalyst loading for the desired product and it was observed that the reaction proceeds well when the amount of catalyst loading is 2.5 mol% at the optimized reaction temperature of 100 °C (Table 2). Then the reaction time was optimized for the model reaction and it was found that the reaction is completed within 10 min under solvent-free condition. Therefore, it may be concluded that the reaction is completed when the amount of catalyst loading is 2.5 mol% at 100 °C and at 10 min of reaction time (Table 2, entry 5). It was also observed that only a negligible amount of product was formed in the absence of catalyst (Table 2, entry 1). It was observed that when the amount of catalyst loading is

Scheme 2



Scheme 3



Scheme 4

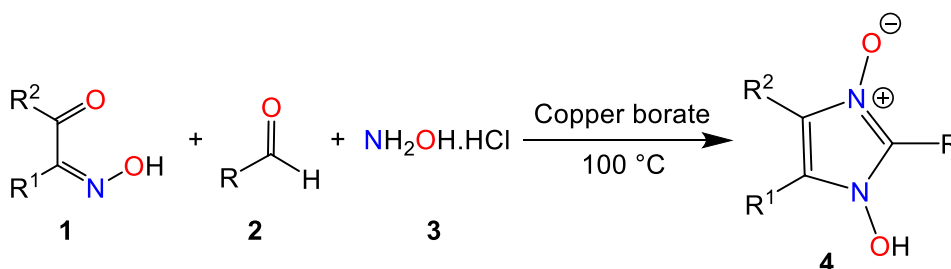


Table 1 Screening of the solvent for the model reaction

Entry	Solvent ^a	Time/h	Yield ^b /%
1	Ethanol	2	90
2	Methanol	2	86
3	DMF	2	88
4	DMSO	2	79
5	Water	2	55
6	Neat	10 min	97

^aThe reaction was carried out with diacetyl monoxime (1 mmol), benzaldehyde (1 mmol), and hydroxylamine hydrochloride (2.5 mmol) with the catalyst using different solvents at 100 °C

^bIsolated yields

Table 2 Screening of the amount of catalyst loading for the model reaction

Entry	Catalyst/mol% ^a	Temperature/°C	Time/min	Yield ^b /%
1	0	100	10	12
2	0.5	100	10	59
3	1.0	100	10	62
4	2.0	100	10	85
5	2.5	100	10	97
6	3.0	100	10	95
7	3.5	100	10	94

Bold represents signifies the optimum reaction condition

^aThe reaction was carried out with diacetyl monoxime (1 mmol), benzaldehyde (1 mmol), and hydroxylamine hydrochloride (2.5 mmol) with the catalyst using different solvents at 100 °C

^bIsolated yields

more or less than 2.5 mol%, the isolated yield of the product was found to be decreased by a negligible amount.

After recognizing the optimum reaction conditions, this protocol was utilized to extend the scope by using other aromatic/heteroaromatic aldehydes to synthesize 1-hydroxy-2-aryl/heteroaryl-4,5-dimethylimidazole-3-oxide derivatives **4**, and in almost all the cases the reaction proceeded in a short time with excellent yield of the products. With this optimized condition, the reaction protocol was extended for a number of aromatic/heteroaromatic aldehydes having electron-withdrawing and electron-releasing groups and it was observed that this catalytic protocol works well with both types of aldehyde precursors. However, this study shows that aldehydes having electron-withdrawing group successfully afforded the desired product more efficiently in excellent yield than aldehydes having the electron-releasing group (Fig. 3).

Furthermore, the recyclability of the catalyst for the given reaction protocol was adjudged and it was observed that the catalyst was easily recoverable with simple filtration from

the reaction mixture. Thus, the catalyst recovered after the first run of the reaction was purified by simply washing with methanol and drying at 100 °C in an oven. The recovered catalyst was again used for further reaction, and interestingly it was observed that the catalyst did not lose its efficiency up to the fifth run of the reaction (Table 3). However, after the fifth run of the reaction, the morphology of the catalytic surface has changed significantly which resulted in the decrease in yield of the product. Thus, we can infer that the catalyst could be used up to the fifth run for the studied reaction protocol (Figs. 4, 5).

A plausible mechanism for the synthesis of 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxide **4** by the condensation of diacetyl monoxime, substituted benzaldehyde, and hydroxylamine hydrochloride is depicted in Fig. 6. As per the literature, it was presumed that the aromatic aldehyde in the presence of hydroxylamine hydrochloride forms the corresponding aldoxime **5** in the presence of the catalyst, which helps in polarizing the oxygen of carbonyl carbon for the nucleophilic attack by hydroxyl amine [39]. A subsequent nucleophilic addition of nitrogen atom of aldoxime **5** to the carbon atom of carbonyl group of diacetyl monoxime (**1**) followed by cyclization gives the intermediate **6**. The intermediate **6** undergoes dehydration, followed by deprotonation to produce 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxide **4**.

Conclusion

In this article, we have reported an efficient, simple, and green protocol for the synthesis of 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxides **4a–4p** using an unconventional copper borate catalyst under solvent-free condition. The reaction provides a method for the synthesis of a variety of 1-hydroxy-2-aryl/heteroaryl-4,5-dimethylimidazole-3-oxides with good to excellent yields, and it has been observed that the catalyst is highly recyclable up to the fifth run of the reaction.

Experimental

All starting materials of high purity for the desired synthesis were purchased commercially and used as received. The FT-IR spectra of the prepared compounds were recorded in Bruker Alpha III spectrophotometer operating in the wave number region 4000–400 cm⁻¹ in dry KBr. The melting points of the synthesized compounds were determined by the open capillary method. NMR spectra of the synthesized 1-hydroxy-2-aryl/heteroarylimidazole-3-oxide derivatives were recorded at room temperature on an FT-NMR (Bruker Advance-II 400 MHz) spectrometer using DMSO-*d*₆ as solvents and the chemical shifts are quoted in ppm downfield

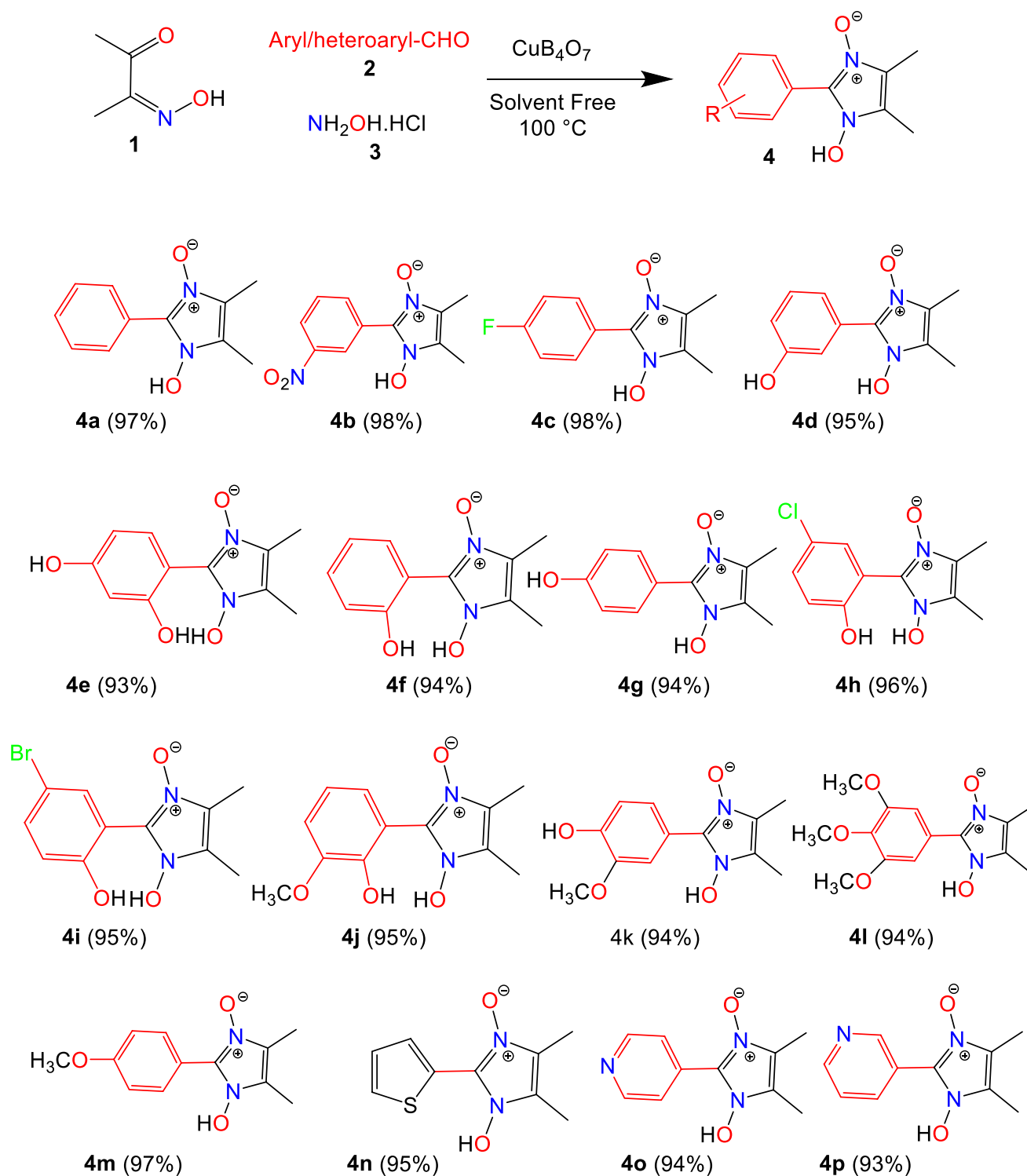


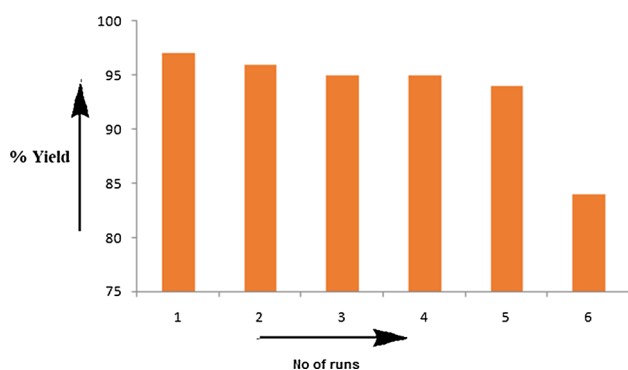
Fig. 3 Substrate scope of 1-hydroxy-2-aryl-4,5-dimethylimidazole-3-oxides **4a–4p**

Table 3 Study on the recyclability of the catalyst

Entry ^a	No. of runs	Yield ^b /%
1	1	97
2	2	96
3	3	95
4	4	95
5	5	94
6	6	84

^aThe reaction was carried out with diacetyl monoxime (1 mmol), benzaldehyde (1 mmol), and hydroxylamine hydrochloride (2.5 mmol) in the presence of copper borate catalyst using different solvents at 100 °C

^bIsolated yield

**Fig. 4** Recyclability of the catalyst

of internal standard tetramethyl silane (TMS). The surface morphology of the catalyst was studied using field emission scanning electron microscopy (FESEM, INSPECT F50, FEI, The Netherlands).

General procedure for the synthesis of 1-hydroxy-2-aryl/heteroaryl-4,5-dimethylimidazole-3-oxides 4a–4p

In a typical green procedure, a mixture of diacetyl monoxime (1 mmol), substituted benzaldehyde/heteroaryl aldehyde (1 mmol), hydroxylamine hydrochloride (2.5 mmol), and copper borate (2.5 mmol) were thoroughly ground and

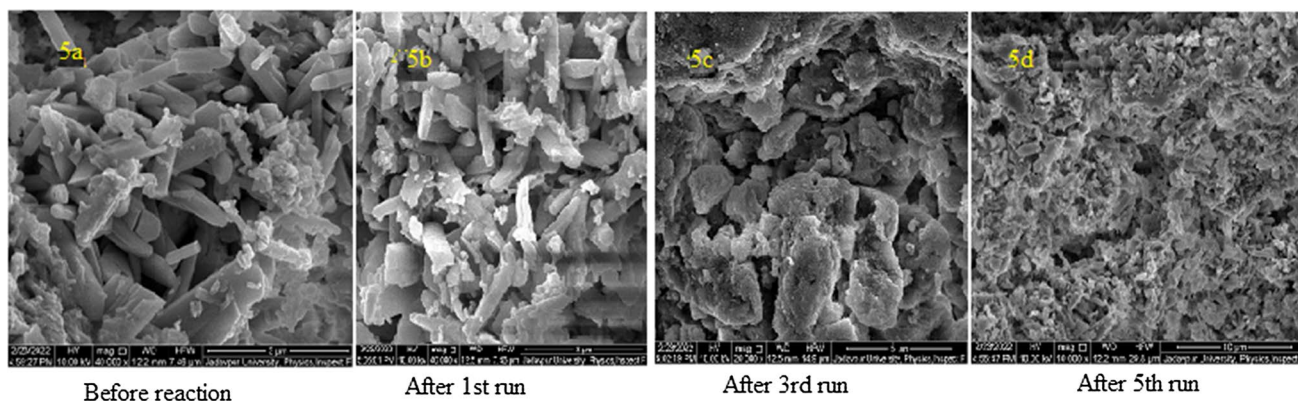
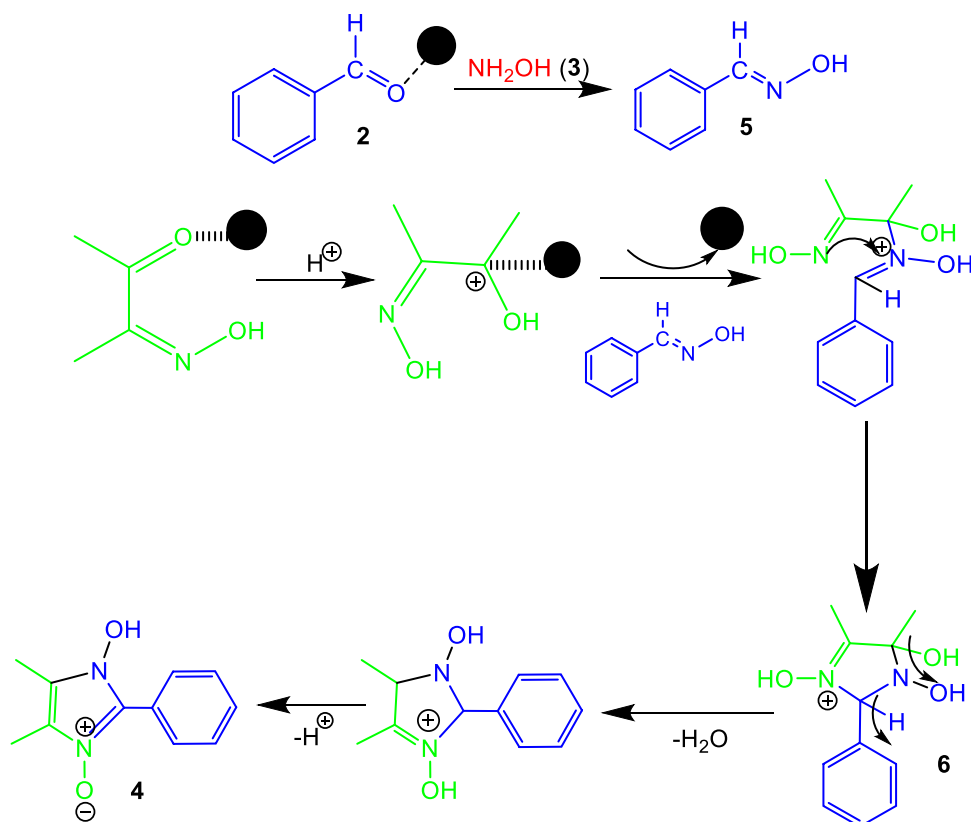
**Fig. 5** **a** SEM image of the catalyst before the reaction. **b** SEM image of the catalyst after the first run. **c** SEM image of the catalyst after the third run. **d** SEM image of the catalyst after the fifth run

Fig. 6 Plausible mechanism for the formation of 1-hydroxy-2-aryl/heteroaryl-4,5-dimethylimidazole-3-oxides **4**



mixed in a mortar and pestle to make a homogeneous mixture. The mixture was then transferred to a test tube. The mixture was heated at 100 °C for 10 min. The progress of the reaction was monitored by TLC using hexane/ethyl acetate (80:20) solvent. After completion of the reaction, the reaction mixture was dissolved in methanol and filtered. The filtrate was evaporated under vacuum and subsequently dried to afford the desired product. All the synthesized products, **4a–4p**, were recrystallized from ethanol, characterized by their analytical and spectroscopic data (FT-IR and NMR) and compared with the literature values.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00706-023-03068-1>.

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Data availability All the analytical and spectroscopic data for the synthesized compounds have been embedded in the supplementary information file.

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