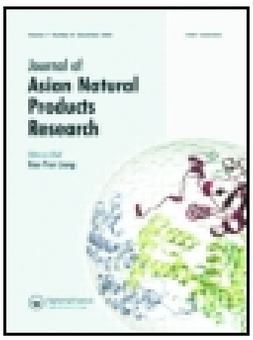

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A sustainable approach towards the three-component synthesis of unsubstituted 1*H*-imidazoles in the water at ambient conditions

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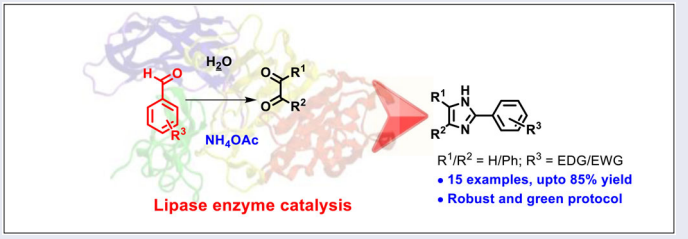
ABSTRACT

A green protocol for the synthesis of unsubstituted imidazoles has been demonstrated herein. The reaction is realized using commercially available lipase enzyme, porcine pancreas lipase (PPL) in water. The reaction conditions are selective and mild which helped to tolerate a wide variety of functional groups to give the desired products in good chemical yields.



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Imidazole; aldehyde; ammonium acetate; lipase

1. Introduction

Enzyme catalysis is advancing very rapidly where directed evolution [1], enzyme immobilization [2], cascade, and asymmetric reactions have attracted tremendous attention [3]. In this regard, the 2018 Nobel prize besotted to enzyme catalysis should not be a surprize considering the growth and potential of this field [4]. The advanced study or mutation of genes there by directed evolution of enzyme by Arnold group from Caltech has taken the application of the enzyme in organic synthesis to the next level, and there is now no limit on how the enzyme can manipulate organic transformations those were hard to achieve through traditional ways.

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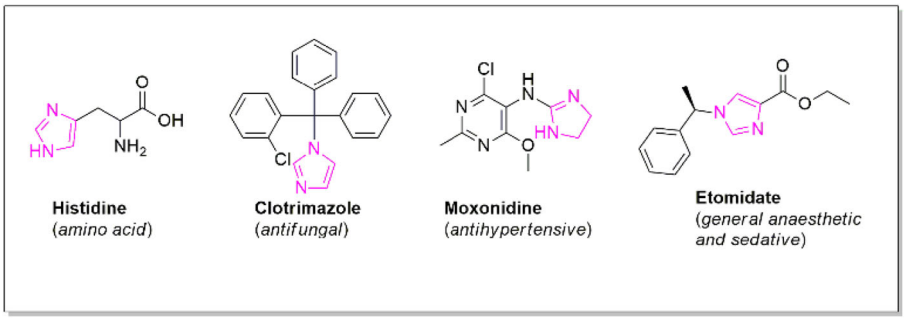


Figure 1. Important drugs bearing mono-or disubstituted imidazole.

While there is a lot to be done in engineering enzymes [5], the naturally occurring enzymes are cheap and very easy to access due to their commercial availability to be directly used in manufacturing organic compounds. In other words, if the chemistry is done using commercially available ligands, then it can be explored quickly by communities who have little or no access to engineering enzymes. For example, lipase which in the human body helps to break fats to fatty acid and glycerol is easily available and hence, also widely studied in a series of organic transformations [6–8]. Also, enzyme catalysis mostly follows twelve principles of green chemistry [9], which shall not be overlooked by looking at the current scenario of pollution created through wastes from chemical factories. Keeping these points in mind and our interest in developing new technologies for synthesis of medicinally important heterocycles [10], to demonstrate that easily available lipase enzyme can be used for three-component condensation, leading to the formation of imidazoles which are considered to be highly important blocks of medicinal products [11,12]. Some mono- and disubstituted imidazole containing drugs examples are mentioned in Figure 1. Nevertheless, such moieties could be prepared in good chemical yields using organic or inorganic reagents including metal catalysts [13,14]. These protocols are although efficient; never clean enough to get the desired product in purest form. Pertaining to regulation from pharmaceutical bodies, only no or few ppm of toxic metal impurities were accepted in newly developed drugs [15].

2. Results and discussion

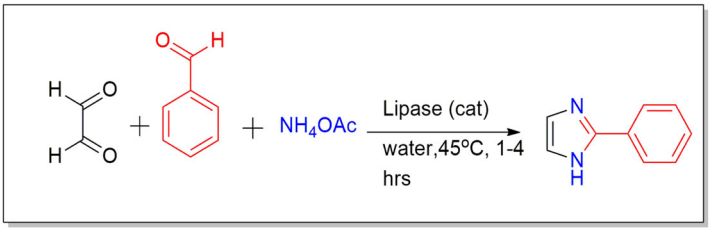
Considering now nature does chemistry using enzymes, attempts were made to perform this condensation of the reaction in water as a reaction solvent. As expected, reaction took place in water to give 80% yield of the desired product. Across examination of howg organic solvents work for this reaction, the solvents which are generally preferred for enzyme catalysis but not greener were screened. As presented in Table 1, dimethylsulfoxide (DMSO), ethanol, methanol, acetic acid, and dimethyl formamide (DMF) were tested. Out of these, ethanol gave comparable results to that of water. Other unusual solvents for such chemistry lead to decreased chemical yield. Also reducing the catalyst loading to half resulted in lower yield.

The best conditions were then applied on different substrates to see the generality of the reaction (Scheme 1). The variation in aldehydes shows that both electron-donating and electron withdrawing groups were tolerated by the reaction conditions to

Table 1. Solvent optimization study for the synthesis of imidazoles.[a]

Entry	Solvent	*t* (h)	Yields (%)[b]
1	Water	1	70 (55)[c]
2	Ethanol	1	40
3	Methanol	2	60
4	DMSO	4	50
5	DMF	4	55
6	Acetic acid	4	70
7	THF	4	50
8	Chloroform	4	40
9	CH_2Cl_2	4	50
10	Acetonitrile	4	50

[a]Reaction conditions: Glyoxal (1mmol), Benzaldenyde (1mmol), Ammonium acetate (2mmol) and [b]Isolated yields. [c]Reaction was carried out using (50mg) of lipase catalyst in the water at 45 °C for 1 hr are shown in Scheme 1.



Scheme 1. General procedures for the synthesis of unsubstituted imidazoles.

give moderate to good chemical yields (entries 3a & 3 b vs 3e & 3f in Figure 2. Halo substitution on benzaldehyde has no problem in the reactivity (3c). Polar and strong coordinating functional groups such as NH_2 (entry 3d), -COOH (entry 3f) were also found to give good chemical yields. Hetetro aryl aldehydes such as pyridine thiophene gave a moderate yield of the desired products (entries 3 g & 3 h). This protocol was then extended to the synthesis of tri-substituted imidazoles. From entries 3i-3m, it is clear that reaction could be performed on all types of aldehydes. However, this reaction was unable to give the desired products when either 1-Phenylpropane-1, 2-dione (3n) or aliphatic aldehyde were used as one of the reaction components, which is in complete harmony with enzyme catalysis where substrate specifications are highly important.

In a similar way, when glyoxal was treated with ammonium acetate and different substituted benzaldehydes, 2-aryl substituted imidazole could be easily prepared (Figure 2). Again, various functional groups are tolerated here.

In summary, it has been shown that monosubstituted imidazoles which are an integral part of pharmaceuticals could be synthesized using commercially available enzymes in water. The reaction is much greener compared to the ones reported in the literature. This protocol is also applied for the synthesis of trisubstituted imidazoles. Further, the reaction could be applied to a wide variety of substrates.

3. Experimental

3.1. General experimental procedures

Melting points of all the compounds were recorded by the Analab Thermo Cal melting point apparatus in the open capillary tube and are uncorrected from ^{1}H NMR

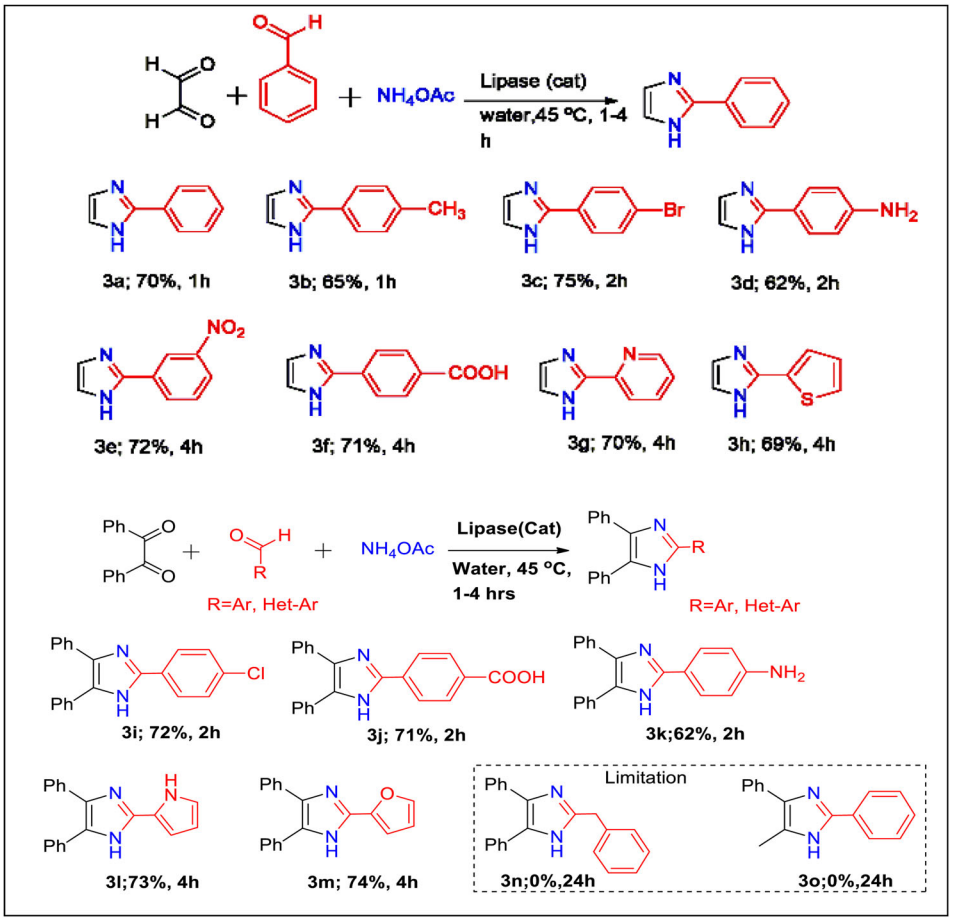


Figure 2. Substrate scope for the synthesis of 2-Arylimidazole.

spectra were recorded on MR400 Agilent Technology NMR spectrometer using tetramethylsilane (TMS) as an internal standard the spectral data were obtained from the ICT, Mumbai, India and DMSO-D_6/$CDCl_3$ as a solvent. Chemicals and solvents used were of LR grade and purchased from SD fine, Aldrich, Avra Synthesis and Spectrochem, Mumabi, India Ltd, used without purification. The purity determination of the starting materials and reaction monitoring was accomplished by thin-layer chromatography (TLC) on Merck silica gel G F_{254} plates were purchased from Viresh Chemicals Mumbai, India Ltd.

3.2. General procedures for the synthesis of unsubstituted imidazoles

A mixture of glyoxal (0.058 g), benzaldehyde (0.106 g), ammonium acetate (0.154 g), and lipase (0.05 g) were taken in a 50-ml, two-necked, round-bottomed flask. The reaction mixture was stirred for 1-4 h at 45 °C. in 10 ml water. After completion of the reaction as indicated by thin-layer chromatography (TLC; ethyl acetate/n-hexane, 2:1), the reaction mixture was filtered and washed with water (3 × 10 ml), and the solid residue was crystallized from ethyl acetate to give pure product **3a** as white

solid. All other products were prepared following this procedure and were identified by their melting point, ^{1}H NMR comparing to the literature.

In similar way, tri-substituted imidazoles are synthesized from benzil (0.004 g), benzaldehydes (0.009 g), ammonium acetate (0.026 g), lipase (0.05 g) in 10 ml water, were taken in a 50 ml two-necked round bottomed flask. The reaction mixture was stirred for 4 hrs at 50 °C.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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