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One-pot Synthesis of 2,4,5-trisubstituted Imidazoles Catalyzed by Lipase

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Abstract A simple and efficient protocol of synthesizing 2,4,5-trisubstituted imidazoles has been developed using lipase as a novel catalyst under mild conditions. A series of imidazole derivatives were synthesized with good yields. The probable enzymatic mechanism was proposed. This method expands the catalytic scope of lipase and provides a novel method to prepare imidazole derivatives.

Keywords Cyclization · Heterocycles · Enzymes · Catalysis · Imidazoles

1 Introduction

Imidazole and its derivatives play a significant role in organic synthesis and have found many applications as biological and pharmacological agents [1–4]. Imidazole moieties have been observed as active scaffolds in numerous existing drugs [4, 5], kinase inhibitors [6–8], modular of glucagon receptors [9, 10], and even in ionic liquids [11, 12]. Due to its chemical significance, the synthesis of imidazole and its derivative has captured much attention. A number of methods to synthesize 2,4,5-trisubstituted imidazoles have been developed by cyclocondensation of benzil, aldehyde and ammonium acetate, under various conditions such as refluxing in acetic acid [13], silica sulfuric acid [14], microwaves [15], ionic liquids [16], $InCl_3$ [17] and tetrabutylammonium bromide [18]. These processes, however, suffered from harsh conditions including high temperature, strongly acidic conditions and expensive reagents and catalysts. Hence, developing a facile and mild method is still in demand for the preparation of trisubstituted imidazoles.

In recent years, enzymes have been increasingly used in organic synthesis due to the efficiency and mild-reaction conditions involved [19]; for instances, racemase can catalyze PLP-dependent Aldol reactions [20]; hydrolase can catalyze the formation of C–C [21], C–N [22], C–S [23] through Henry reaction, Michael addition, Markovnikov addition and Aldol reactions. Lipase belongs to the hydrolases family. This family of enzymes includes thioesterases, carboxylic acid esterases, and halo peroxidases [24, 25]. Compared to esterases, lipase is becoming more attractive, and a number of research results have been reported that lipase can efficiently catalyze some reactions by accelerating the process of dehydration [26]. For our continuous interest in the enzymatic synthesis and efforts on exploring new heterocycle synthetic approaches [27], we want to explore the catalytic scope of lipase in heterocyclic synthesis and to establish a useful protocol to synthesize the 2,4,5-trisubstituted imidazoles.

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Scheme 1 The model reaction of 2,4,5-trisubstituted imidazoles

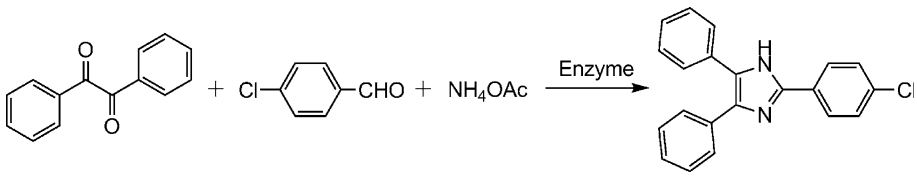


Table 1 Optimization of enzyme[a]

Entry	Enzyme	Yield (%)[b]
1	Lipase AT30	71
2	Trypsin from porcine pancreas	56
3	Diastase	60
4	α-Amylase from *Aspergillus oryzae*	65
5	α-Amylase from hog pancreas	66
6	Albumin from bovine	45

[a] Reaction conditions: 1 mmol benzil, l mmol aldehyde, and l mmol ammonium acetate, 2 mL solvent, 15 mg enzyme, 45 °C, shaken at 160 rpm for 9 h

[b] GC yields are based on tridecane as an internal standard

Table 2 Optimization of solvent[a]

Entry	Solvent	Yield (%)[b]
1	C_2H_5OH	75
2	CH_3OH	58
3	$CH_3COOC_2H_5$	50
4	*n*-Hexane	32
5	H_2O	25
6	CH_3CN	20
7	Isopropanol	15

[a] Reaction conditions: 1 mmol benzil, l mmol aldehyde, and l mmol ammonium acetate, 2 mL solvent, 15 mg enzyme, 45 °C, shaken at 160 rpm for 9 h

[b] GC yields are based on tridecane as an internal standard

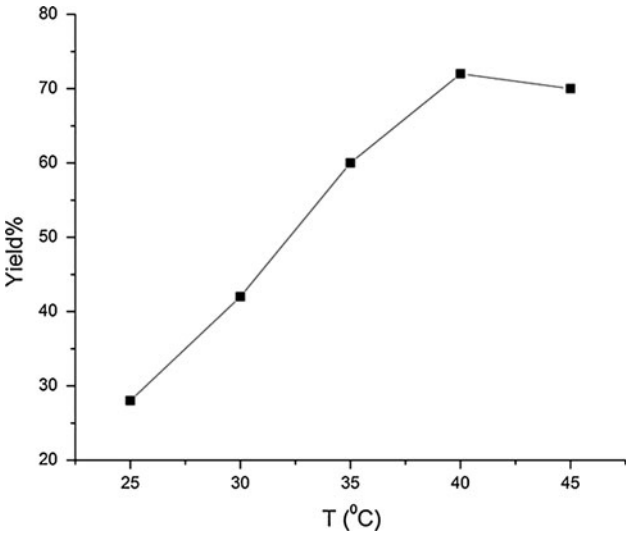


Fig. 1 The influence of temperature

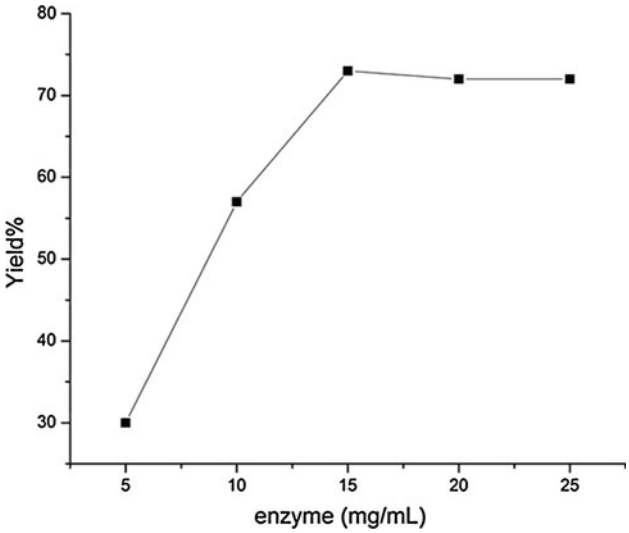


Fig. 2 The influence of the amount of enzyme

2 Experimental

Commercial reagents were used without further purification. Reactions were performed in an end-over-end rotator. TLC: Merck precoated TLC (silica gel 60 GF 254) plates. The melting points were determined using a XT-4 melting-point apparatus and were uncorrected. IR spectra were recorded on a Bruker Equinox-55 spectrophotometer using KBr discs in the 4,000–400 cm^{-1} region. ^1H NMR spectra: Bruker Advance 400 spectrometer in DMSO and $CDCl_3$ using TMS as internal standard. GC/MS: Agilent 5975C. All enzymes were purchased from Acros, Alfa, Aldrich and TCI, and used directly.

General procedure for the synthesis of 2,4,5-trisubstituted imidazoles: The mixture of l.0 mmol benzil, l.0 mmol aldehyde, 3 mmol NH_4OAC, 2 mL C_2H_5OH and 30 mg lipase AT30, was introduced to a test tube (10 mL), then the mixture was subjected to a shaker under 160 rpm end-over-end rotation at 45 °C for 9 h. The reaction was monitored by TLC. The residue was filtered off and the solvent was vaporized and purified by the silica gel chromatography with an eluent consisting of petroleum/ethyl acetate (5:1, v/v).

Scheme 2 The synthesis of different 2,4,5-trisubstituted imidazoles catalyzed by lipase

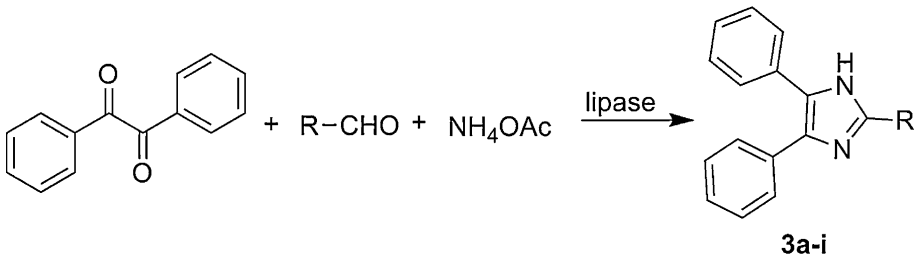


Table 3 Lipase catalyzed synthesis of 2,4,5-trisubstituted imidazoles **3a–3i**[a]

Entry	R	Product	Yield[b]
1	4-Cl-C_6H_4	**3a**	75
2	2-Cl-C_6H_4	**3b**	73
3	3-CH_3-C_6H_4	**3c**	87
4	2-OCH_3-C_6H_4	**3d**	72
5	4-OCH_3-C_6H_4	**3e**	65
6	3-NO_2-C_6H_4	**3f**	74
7	4-CN-C_6H_4	**3g**	67
8	2-Pyridyl	**3h**	78
9	2-Thiophenyl	**3i**	71

[a] Reaction conditions: 1 mmol benzil, l mmol aldehyde, and l mmol ammonium acetate, 2 mL C_2H_5OH, 15 mg enzyme, 45 °C, shaken at 160 rpm for 9 h

[b] GC yields are based on tridecane as an internal standard

3 Results and Discussions

To identify the most efficient enzyme, we started to test the efficacy of different enzymes in the model reaction under the same conditions (Scheme 1; Table 1). Benzil (1 mmol), *p*-chlorobenzaldehyde (1 mmol), ammonium acetate (3 mmol) and 30 mg various enzymes were added to the tube under 45 °C in ethanol (2 mL). The results showed that the highest conversion yield was achieved by using lipase from porcine pancreas lipase AT30 as catalyst (Table 1, Entry 1); the other tested enzymes exhibited lower activities. It maybe attributes to the dehydration function of lipase and makes the reaction smoothly.

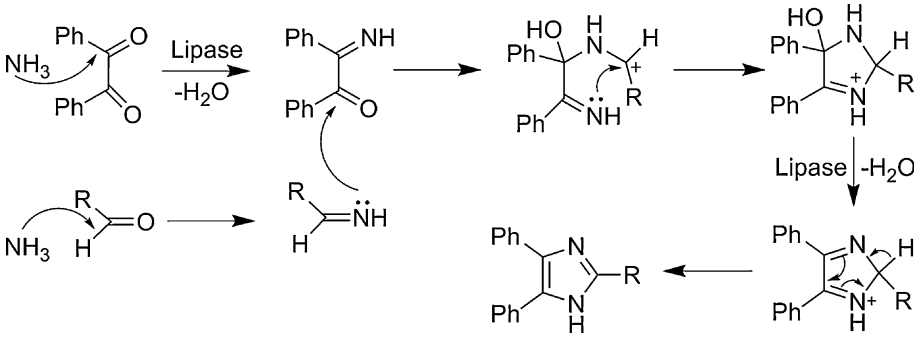
Among tested solvents of ethanol, methanol, water, acetonitrile, ethyl acetate, and isopropanol, ethanol was the solvent that afforded the highest yield (75 %, Table 2, Entry 1). Therefore, ethanol was selected as the optimized solvent for the following reactions.

We next performed experiments to explore the specific catalytic effect of lipase AT30 (Figs. 1, 2). Figure 1 showed that the percent yield increased as the system was heated up from 25 to 40 °C. When the temperature exceeded 40 °C, the yield decreased slightly. Generally speaking, enzymes play its catalytic role in suitable temperature. This result shows that 40 °C is the best temperature for lipase AT30 to catalyze this reaction, and the higher temperature makes the enzyme inactive. Figure 2 revealed the relationship between the percent yields and the amount of enzymes used; the amount of 15 mg enzymes was found to be the optimal.

Taking into account these optimized conditions, we employed this reaction with various aromatic and heterocyclic aldehydes in order to extend the substrate, the experiment results (Scheme 2; Table 3) demonstrated that all aromatic aldehydes containing different functional groups (electron donating and withdrawing) worked well. This implied that the reaction outcome were independent of the electronic effects of substituents. This is an advantage of using lipase because most organic reactions would be affected by electronic effect. So this enzymatic synthesis method has a broad adaptability with different substrates.

For our continuous study in enzymatic reactions [28], we found that lipase can effectively promote dehydration during the process of organic synthesis. Thus we proposed a plausible reaction mechanism (Scheme 3). Based on the

Scheme 3 The plausible reaction mechanism of this reaction



literature [28] and the experimental results, the enzyme plays an important role to promote the cyclization process of forming imidazole derivatives in last two steps. So it seemed the existence of lipase accelerated the dehydration and gave trisubstituted imidazoles **3a**–**3i** with good yields

4 Conclusions

In conclusion, we herein developed a novel and efficient, one-pot, three-component reaction for the synthesis of 2,4,5-trisubstituted imidazoles via the condensation of an aromatic aldehyde, benzil and ammonium acetate catalyzed by lipase AT30 in ethanol with good yields. This reaction can be carried out under mild conditions and covers a great range of substrates with good yields. This novel protocol provides an efficient and mild synthetic route for synthesizing trisubstituted imidazole derivatives, and further expands the catalytic scope of lipase in organic chemistry.

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