



# An efficient method for the synthesis of 2,4,5-trisubstituted imidazoles using lactic acid as promoter

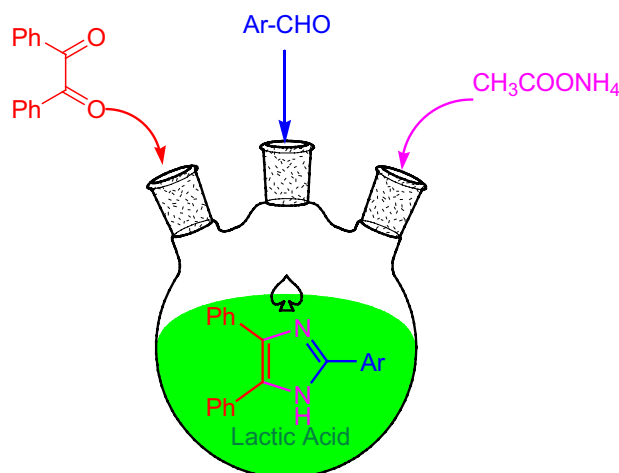
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## Abstract

Synthesis of 2,4,5-trisubstituted imidazole compounds from an aromatic aldehyde, benzil and ammonium acetate is demonstrated using biodegradable lactic acid at 160 °C. This method is a simple, environmentally benign, and works for aromatic aldehyde containing electron donating and electron withdrawing groups.

## Graphic abstract



**Keywords** Lactic acid · Promotor · Green solvent · 2,4,5-Trisubstituted imidazoles

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SN Applied Sciences (2019) 1:1045

| <https://doi.org/10.1007/s42452-019-0935-0>

Received: 7 May 2019 / Accepted: 16 July 2019

Published online: 17 August 2019

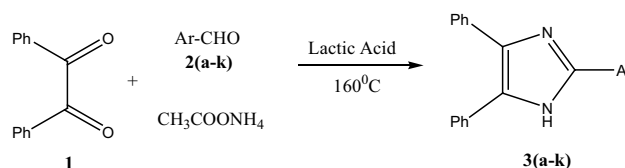
## 1 Introduction

Imidazole is an important core organic molecule. It is found in many naturally occurring compounds like vitamin B<sub>12</sub>, histidine [1], histamine, pilocarpine alkaloids, nucleic acid bases, and biotin [2–5]. Imidazole is also found to be an active part of antifungal compounds like clotrimazole, ketoconazole, miconazole, isoconazole, econazole [6]. Along with this, it is also showing good activity as herbicide [7], plant growth regulator [8], anti-epileptic [9], anticonvulsant [10], anti-inflammatory, analgesic [11], anti-cancer, etc. [12, 13]. Also, imidazoles are found as the main core molecule in drugs like Omeprazole, Pimobendan, Losarton, Olmesartan, Eprosartan, and Trifenagrel [14].

In organic synthesis, the product yield and reaction time are extremely important. The increase in reaction steps results in a decrease in final product yield and increase in total reaction time. Multicomponent reactions help to solve this problem. By novel developing multicomponent reaction strategies, synthesis of the desired product in the one-pot method is possible thereby increases the product yield and reducing reaction time required for the reaction. Thus, it can be considered as a greener way in organic synthesis and have attracted significant attention from many researchers in recent years [15].

Various methods are reported in the literature for the one-pot synthesis of imidazole derivatives from benzil, aromatic aldehyde, and ammonium acetate. Heterogeneous catalyst such as Lewis acids (NiCl<sub>2</sub>·6H<sub>2</sub>O [16], Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub> [17], ZrCl<sub>4</sub> [18], CrCl<sub>3</sub>·6H<sub>2</sub>O [19], Pb(OAc)<sub>2</sub> [20], etc.), nano particles (MgAl<sub>2</sub>O<sub>4</sub> [21], nanorod vanadate sulfuric acid [22], magnetic Fe<sub>3</sub>O<sub>4</sub> [23], etc.) are reported for imidazole synthesis. CrCl<sub>3</sub>·6H<sub>2</sub>O and Pb(OAc)<sub>2</sub> are toxic in nature. Ionic liquids (ILs) [24–28] are also reported for the efficient synthesis of substituted imidazoles. However, ILs are expensive and recyclability of ILs are difficult [29]. Organic solvents like glycerol [30], Pr<sub>2</sub>NEt [31], PEG [32], acetic acid [33, 34], Glyoxylic acid [35], natural acids [36] are reported for the synthesis of imidazoles.

The available reported method for the synthesis of substituted imidazoles suffers from drawbacks such as the catalysts used for synthesis are either toxic or expensive and requires harsh reaction condition. To overcome these problems, we employed inexpensive, biodegradable, environmentally friendly green solvent lactic acid [37, 38] for the synthesis of 2,4,5-triaryl-1H-imidazoles. The synthesis method does not require any sophisticated assembly, and lactic acid used in this reaction acts as promoter and also solvent. Lactic acid is obtained from fermentation of carbohydrates, it is easy to handle and readily available. Lactic acid is reported as organocatalyst in several organic reactions [39–48]. In the present method we are reporting



**Fig. 1** General reaction scheme for the synthesis of 2,4,5-trisubstituted imidazole

**Table 1** Effect of solvent for the synthesis of 2,4,5-triphenyl-1H-imidazole

Entry	Lactic acid (mL)	Solvent (10 mL)	Time (min)	Temp. (°C)	Yield (%)
1	0.1	Water	180	50	37
2	0.1	Acetonitrile	180	50	30
3	0.1	Methanol	180	50	42
4	0.1	DMF	180	50	45
5	0.1	DCM	180	50	20
6	0.1	Dioxane	180	50	32
7	0.1	Ethanol	180	50	55
8	0.1	Ethanol	180	70	72
9	0.2	Ethanol	240	Reflux	72
10	0.4	Ethanol	240	Reflux	75

Benzaldehyde 1 mmol, ammonium acetate 3 mmol, benzil 1 mmol

lactic acid for the synthesis of 2,4,5-trisubstituted imidazole compounds from an aromatic aldehyde, benzil, and ammonium acetate under milder reaction conditions (160 °C) (Fig. 1).

## 2 Result and discussion

Initially, benzaldehyde was selected as a prototype for the reaction with benzil and ammonium acetate to study the catalytic activity of lactic acid. The reaction conditions were optimized to efficiently synthesize the 2,4,5-triphenyl-1H-imidazole in solvent-free condition with the catalytic amount of lactic acid, but the results were not satisfactory even at higher temperatures. Hence, we added lactic acid in various solvents and reactions were performed with different temperature (Table 1). Through the experimentation, we achieved 55% of product yield in ethanol-lactic acid system. The better results are witnessed at 70 °C (3 h) with 1:1:3 equivalent proportions of benzil, an aromatic aldehyde, and ammonium acetate, respectively.

The result shows that with an increase in the quantity of lactic acid in ethanol is not exhibiting improvement in the product yield (Table 1). Further, we conducted reactions

**Table 2** Optimization of reaction parameters for the synthesis of 2,4,5-triphenyl-1H-imidazole using lactic acid

Entry	Lactic acid (mL)	NH <sub>4</sub> OAc (mmol)	Temp. (°C)	Yield (%)
1	0.5	2	100	62
2	1.0	2	130	70
3	1.0	2.5	130	74
4	1.0	3.0	130	75
5	1.0	2.5	160	90
6	1.0	3.0	160	89
7	1.0	2.5	170	92

Benzaldehyde 1 mmol, benzil 1 mmol, 180 min

**Table 3** Comparison of natural acids for the synthesis of 2,4,5-trisubstituted imidazoles

Entry	Acid	Temp. (°C)	Time (min)	Yield (%) <sup>a</sup>
1	Citric	160	20	76 [36]
2	Fumaric	290	20	65 [36]
3	Malic	140	20	78 [36]
4	Malonic	140	20	80 [36]
5	Oxalic	110	20	77 [36]
6	Succinic	190	20	68 [36]
7	Tartaric	180	20	75 [36]
8	Lactic	160	180	92

<sup>a</sup>4-Cl- Benzaldehyde

only in the lactic acid, and the result shows an increment in the product yield in 1 mL lactic acid.

The proportions of lactic acid and ammonium acetate were varied at different temperature (Table 2). This showed the best product yield with 1 mL of lactic acid, 2.5 mmol of ammonium acetate at 160 °C (Table 2, entry 5). The obtained results were compared with other natural acids (Table 3) [36] for the synthesis of imidazoles and it shows that our method is efficient for better product yields using lactic acid.

As shown in Table 4, this catalytic system works well for both aromatic aldehydes containing electron donating and electron withdrawing groups. For 4-nitro benzaldehyde (entry f) 83% yield was obtained in 180 min while for 4-(dimethylamino)benzaldehyde 91% yield was obtained in 150 min (entry h). It means there is no specific effect of electron density on the product yield. However, the desired reaction time can be changed depending on

the type of aldehyde used for the reaction. The probable mechanism of reaction is depicted in Fig. 2.

### 3 Experimental

All the melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu IR Affinity 1 spectrophotometer in KBr disc. <sup>1</sup>H NMR were recorded on a BRUKER AVANCE II 400 MHz spectrometer in DMSO d<sub>6</sub>, chemical shifts are in ppm relative to TMS. Mass spectra were taken on a Macro mass spectrometer by electron spray method (Es). The structures of various synthesized compounds were assigned on the basis of spectral studies and it has been reported in experimental protocols. The progress of reaction was monitored on Alumina coated TLC plates in ethyl acetate and n- hexane system.

**General experimental procedure:** In 10 mL round bottom flask aromatic aldehyde (1 mmol), benzil (1 mmol) and ammonium acetate (2.5 mmol) were added. To this reaction mixture, 1 mL of lactic acid was added and then reaction mixture was heated at 160 °C for an appropriate time (Table 4). The progress of reaction was monitored with the help of TLC (hexane: ethyl acetate 8:2 v/v). After completion of reaction, the mixture was poured over crushed ice (100 g and neutralized by saturated solution of sodium carbonate. The solid obtained was filtered and purified by column chromatography using hexane–ethyl acetate as eluent (9:1 v/v).

#### Characterization:

**1-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenyl)piperidine (3j):**

IR (KBr, cm<sup>-1</sup>): 3080, 2880, 1600–1500

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 1.56–1.62 (m, 6H, 3CH<sub>2</sub>), 3.21–3.23 (t, 4H, 2CH<sub>2</sub>), 6.99 (d, J = 8 Hz, 2H, Ar-H), 7.21–7.55 (m, 10H, Ar-H), 7.94 (d, J = 8 Hz, 2H, Ar-H), 12.29 (s, 1H, NH)

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): 23.90, 25.10, 48.87, 114.98, 120.24, 126.25, 127.05, 127.38, 128.08, 128.24, 128.52, 129.49, 129.55, 131.31, 135.52, 136.59, 146.19, 151.23

ESI-MS (m/z): 379.49 (M + 1)

**4,5-diphenyl-2-(4-(pyrrolidin-1-yl)phenyl)-1H-imidazole (3k):**

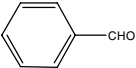
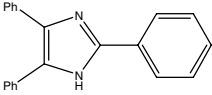
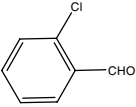
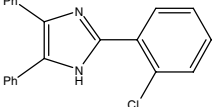
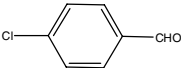
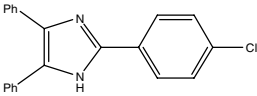
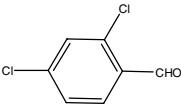
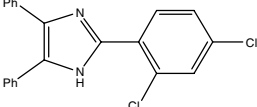
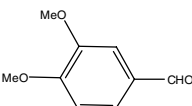
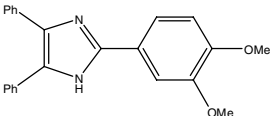
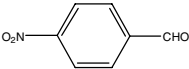
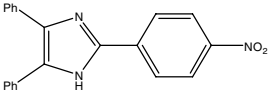

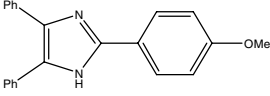
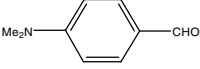
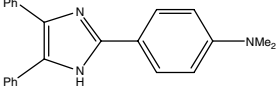
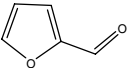
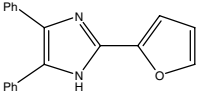
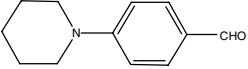
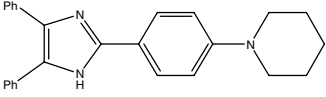
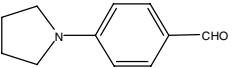
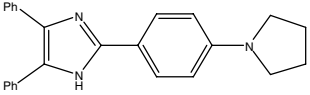
IR (KBr, cm<sup>-1</sup>): 3100, 2930, 1600–1500

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 1.96 (t, 4H, 2CH<sub>2</sub>), 3.28 (t, 4H, 2CH<sub>2</sub>), 6.61 (d, J = 8 Hz, 2H, Ar-H), 7.20–7.56 (m, 10H, Ar-H), 7.91 (d, J = 8 Hz, 2H, Ar-H), 12.29 (s, 1H, NH)

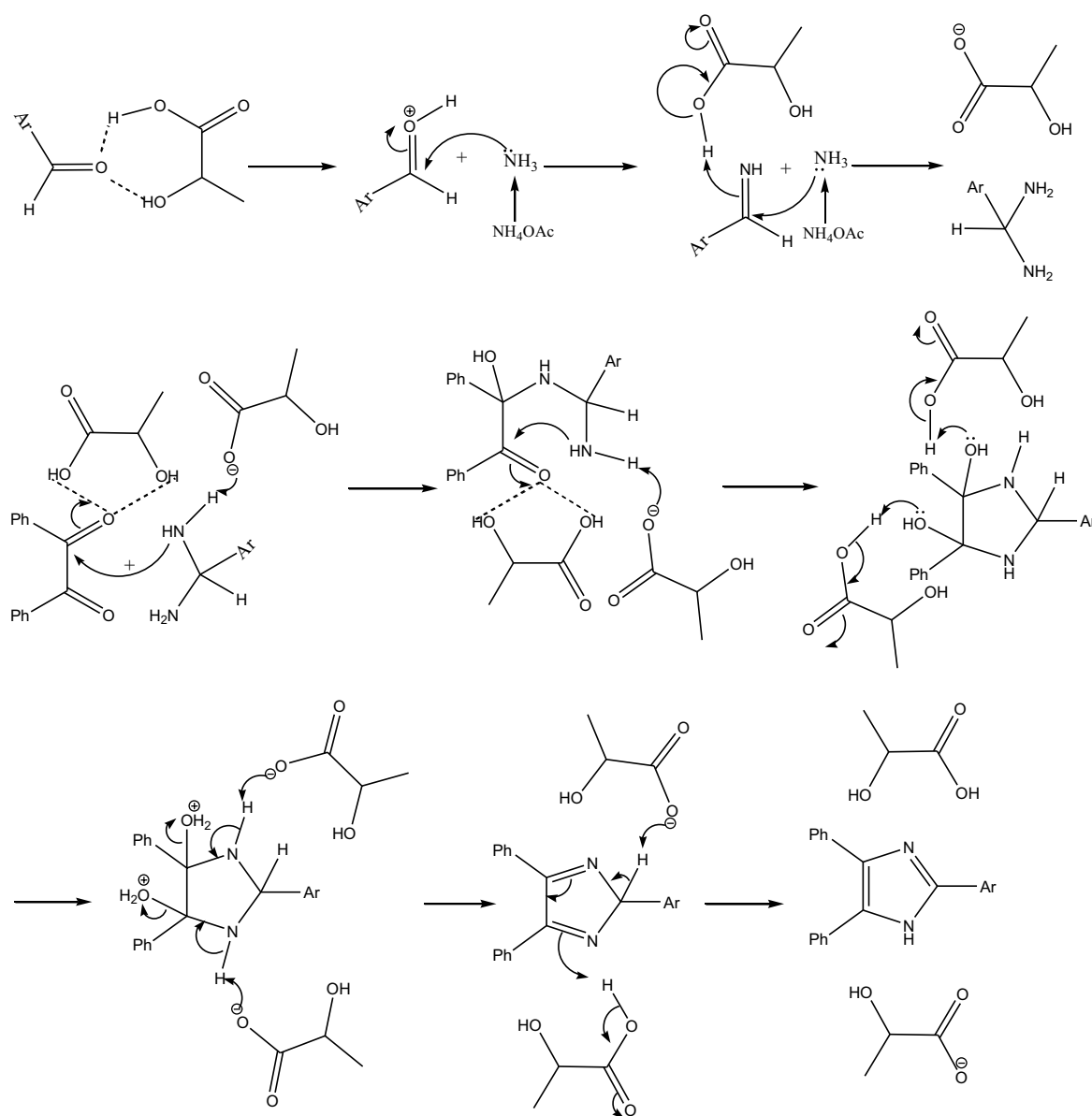
<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>): 24.95, 47.21, 11.37, 117.52, 126.20, 126.41, 126.89, 127.03, 127.30, 128.06, 128.21, 128.52, 131.46, 135.60, 136.45, 146.71, 147.59

ESI-MS (m/z): 365.4 (M + 1)

**Table 4** Synthesis of 2,4,5-trisubstituted imidazoles 3(a–k) using lactic acid<sup>a</sup>

Entry	Aldehyde 2(a–k)	Product 3(a–k)	Time (min)	Yield (%)	Melting points (°C)	
					Obs.	References
a.			180	90	275–276	278 [47]
b.			180	94	190–192	194–196 [47]
c.			180	92	262–263	263–264 [47]
d.			180	85	172–174	174–176 [47]
e.			150	89	220–221	217–219 [48]
f.			180	83	225	225–227 [47]
g.			170	90	230	230–232 [47]
h.			150	91	257–259	260–261 [49]
i.			150	84	240	237–238 [50]
j.			150	92	215–216	—
k.			150	90	220–221	—

<sup>a</sup>Aromatic aldehyde 1 mmol, ammonium acetate 2.5 mmol, benzil 1 mmol, lactic acid 1 mmol, temperature 160 °C



**Fig. 2** Plausible mechanism for the synthesis of 2,4,5-trisubstituted imidazoles using lactic acid

## 4 Conclusion

Herein we are reporting the efficient method using inexpensive, biodegradable and environmental benign green solvent for the synthesis of 2,4,5-trisubstituted imidazole. This method provides a better performance and higher product yield for aromatic aldehydes containing electron donating and electron withdrawing groups.

**Acknowledgements** Authors are thankful to the Principal, V. P. Mahavidyalaya, Vaijapur and the Principal, Deogiri College for providing laboratory facilities. Authors are also thankful to The Director, SAIF, Panjab University for providing spectral analysis.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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