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One-pot synthesis of tri- and tetra substituted imidazoles using nano-LaMnO$_3$ perovskite-type oxide as heterogeneous catalyst in solvent-free condition

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ABSTRACT

A convenient synthetic method for the synthesis of *2,4,5*-trisubstituted and *1,2,4,5*-tetra substituted imidazole derivatives, has been developed via one-pot condensation reaction when aldehydes, ammonium acetate/amines, and 1,2-diketone are reacted using 0.8 mol% of NP-LaMnO$_3$ at 80 °C under solvent free conditions. Catalyst could be recovered and reused in five reaction cycles without any loss of its activities, giving a total turnover number (TON) = 594 and turn over frequency (TOF) = 71 h^{-1}. High yield, little catalyst loading, elimination of solvent, simple workup, recovery and reusability of the catalyst are some of the impressive features of the present method.

Keywords: Perovskite-type oxide; Imidazole; Solvent-free condition; One-pot synthesis.

1. Introduction

Nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic and biomedical research [1,2]. Imidazoles in particular are common scaffolds in remarkable biomolecules [3], including biotin, histamine, histidine and pilocarpine alkaloids (Fig 1). The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novels chemotherapeutic agents [4]. Imidazole derivatives have emerged as versatile drug templates in medicinal chemistry spanning applications to anti-microbial [5], anti-tumor [6], anti-cancer agents [7] and so on. A condensation to approach such fused imidazoles first time was developed by Debus [8] in 1858 and followed by Radzisewski [9] in 1882. Since the first reports were published, various methods have been performed to improve this synthetic methodology. Recently, several multi-component reactions (MCRs) have been reported for the synthesis of 2,4,5-trisubstituted imidazoles by three-component condensation of a 1,2-diketone with aldehydes and ammonium acetate in the presence of InCl$_3$.3H$_2$O [10], Lipas [11] and MgAl$_2$O$_4$ [12], on the other hand, the syntheses of 1,2,4,5-tetrasubstituted imidazoles are carried out by four-component condensation of a 1,2-diketone, with aldehydes, primary amines and ammonium acetate using I$_2$ [13], DABCO [14] and PEG-200 [15], InCl$_3$.3H$_2$O [16], ZrCl$_4$ [17], HClO$_4$–SiO$_2$ [18], BF$_3$.SiO$_2$ [19], and silica-bonded propylpiperazine N,N-sulfamic acid (SBPPSA) [20]. However, some of these methods have certain disadvantages such as harsh conditions, low yields and side reactions. To avoid such problems, it is important to develop rewarding catalytic system that meets the concept of green chemistry.

Crystalline ceramics mainly perovskite-type oxides (PTOs) are probably the best studied family of oxides [21]. PTOs are generally expressed as ABO$_3$, where the metal cations at A and B sites can be partially substituted by other metal cations. The interest in compounds belonging to this family of crystal structures arise in the large and ever surprising variety of properties exhibited and the flexibility to accommodate almost all of the elements in the periodic system. Because of their thermal stability and a variety

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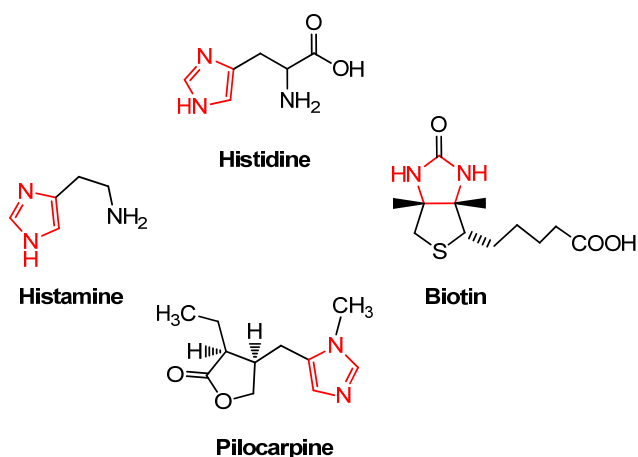Tel.: +98 61 3445 7612; Fax: +98 61 3443 5288

Fig. 1. The structure of Histamine, Histidine, Biotin and Pilocarpine.

of physical and chemical properties, which can be controlled by choosing constituent elements, they are widely used as catalysts and their ferroelectric and piezoelectric properties as well as their usage as gas sensors were investigated [22-24]. To the best of our knowledge, no study up to our previous work [25] has investigated catalytic activity of PTOs for the synthesis of organic compounds through the MCRs.

In continuing our interest in MCRs [26-29] and since very little attention has been paid to investigation catalytic activity of PTOs [25], we decided to developed an efficient method for the one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles using NP-LaMnO3 without the requirement for any solvent, salt, or additive (Scheme 1).

2. Experimental

2.1. General

All chemicals and reagents were obtained from Sigma–Aldrich or Merck and were used without further purification. NP-LaMnO$_3$ was prepared according to the reported method [25]. The melting points of products were determined with an Electrothermal 9200 melting point apparatus. The FT-IR spectra were recorded on a Perkin-Elmer BX-II IR spectrometer. The ^{1}HNMR and ^{13}CNMR spectra were provided on Bruker DRX-400 and DRX-300 Avance instruments in CDCl$_3$.

2.2. Typical procedure for the synthesis imidazoles

2.2.1. Typical procedure for the synthesis of 2,4,5-trisubstituted imidazoles

A mixture of 1,2-diketone (1 mmol), ammonium acetate (2 mmol), aldehyde (1 mmol), and NP-LaMnO$_3$ (0.002 g) was stirred at 80 °C for an appropriate time as indicated by TLC. After cooling, the mixture was filtered and washed with chloroform to separate catalyst. The filtrate was concentrated on a rotary evaporator under reduced pressure. To obtain pure products the solid residue was recrystallized from ethanol–water 9:1 (v/v).

#### 2.2.2. Typical procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles

A mixture of 1,2-diketone (1 mmol), ammonium acetate (1 mmol), amine (1 mmol), aldehyde (1 mmol), and NP-LaMnO$_3$ (0.002 g) was stirred at 80 °C for an appropriate time as indicated by TLC. After cooling, the mixture was filtered and washed with chloroform to separate catalyst. The filtrate was concentrated on a rotary evaporator under reduced pressure. To obtain pure products the solid residue was recrystallized from ethanol–water 9:1 (v/v).

The authenticity of the known products was established by comparing their melting points with the counterparts in the literatures.

Selected spectral data

*2-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazole (**4e**):*

Yellow powder. m.p.= 263-265°C. IR (KBr): $\bar{v}$ = 3226, 1503, 1486, 1418, 1073,734 cm^{-1}. ^{1}HNMR (400 MHz, CDCl$_3$): δ= 7.22-7.72 (m, 12H, Ar-H), 7.95-8.02 (m, 2H, Ar-H), 13.80 (s, 1H, NH) ppm. ^{13}CNMR (75 MHz, CDCl$_3$): δ= 124.3, 127.3, 128.1, 128.6, 129.1, 129.9, 130.9, 133.0, 134.9, 144.5 ppm.
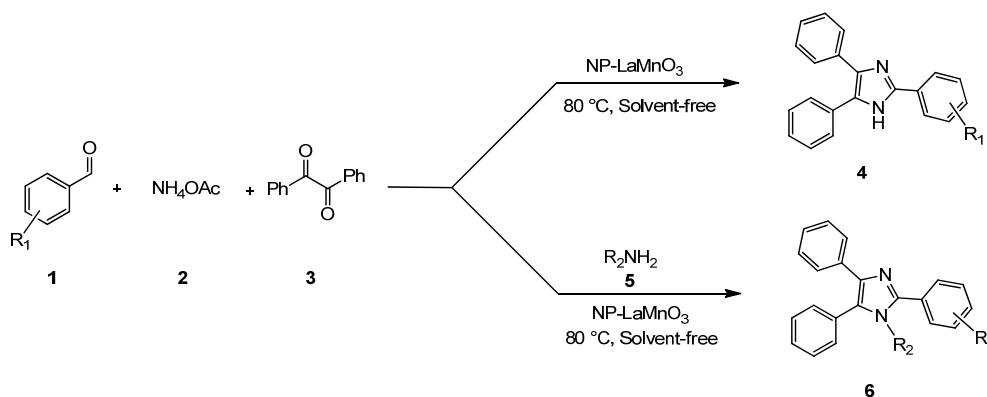
Scheme 1. Synthesis of tri- and tetrasubstituted imidazoles.

2-Fluorenyl-4,5-diphenyl-1H-imidazole (4h):

Yellow powder. m.p.= 283-285°C. IR (KBr): $\bar{v}$ = 3065, 2949, 2867, 1601, 1566, 1500, 1468 cm^{-1}. ^{1}HNMR (300 MHz, DMSO-d$_6$): δ= 3.38 (s, 2H), 7.23-7.61 (m, 13H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.35 (s, 1H), 12.72 (s, 1H) ppm. ^{13}CNMR (75 MHz, DMSO-d$_6$): δ= 36.4, 120.1, 120.2, 121.9, 124.1, 125.2, 126.9, 127.0, 127.1, 127.7, 128.2, 128.4, 128.6, 128.9, 140.7, 141.1, 143.41, 143.5, 145.9 ppm.

4,5-Diphenyl-1-propyl-2-p-tolyl-1H-imidazole (6f):

Yellow powder. m.p.= 99-101°C; IR (KBr): $\bar{v}$ = 3435, 1596, 1496, 1479, 763, 695 cm^{-1}. ^{1}HNMR (300 MHz, CDCl$_3$): δ= 0.6 (t, *J* = 7.50 Hz, 3H), 1.38 (sext, *J* = 7.50 Hz, 2H), 3.87 (t, *J* = 7.50 Hz, 2H), 2.43 (s, 3H), 7.16 -7.63 (m, 14 H) ppm. ^{13}CNMR (75 MHz, CDCl$_3$): δ = 10.9, 21.4, 23.9, 46.4, 126.2, 126.9, 128.0, 128.6, 128.7, 129.1, 129.3, 129.6, 129.9, 131.0, 131.7, 134.7, 137.6, 138.7, 148.8 ppm.

3. Results and Discussion

In order to investigate the catalytic activity and application of NP-LaMnO$_3$, its efficiency in a model reaction between benzyl, ammonium acetate and *para*-chlorobenzaldehyde was examined. It is noticed that the reaction proceeded smoothly with 0.002 g NP-LaMnO$_3$. Thus, after 100 min at 80°C, the desired product was obtained in 97% yield under solvent-free condition. Due to the fact that the solvent may play important roles in this process, various solvent systems were screened (Table 1). It was observed that solvent-free condition gave the best result in terms of reaction time and yield. The presence of solvent is unfavorable for this reaction, as can be seen there is a reduction in the yield, that's may be due to the reducing in the adsorption of the reactant molecules on the surface of the catalyst. However polar solvent systems have shown higher yields comparing to non-polar solvents.

Initially, in search of best catalytic system, various catalyst studies were executed in solvent-free condition (Table 2). In order to establish the effectiveness of the NP-LaMnO$_3$, a test reaction was performed without catalyst at room temperature. It was found that only a trace amount of final product was obtained in the absence of catalyst even after 180 min (entry 1). Although when temperature was increased up to 100 °C for this catalyst-free reaction, there was no appreciable improvement in yield (entry 2). A model reaction was carried out using 0.8 mol% (0.002 g) of NP-LaMnO$_3$ at room temperature under solvent free reaction, as shown in entry 10 yield was only 47%. Next, the effect of temperature on rate of reaction was studied at different temperatures. When the reaction was carried out at 80°C, the maximum yield was obtained in a short reaction period. However, increasing the temperature more than 80°C has no change on the yield or reaction time. Meanwhile, the effect of amount of catalyst on the yield and rate was also investigated. It was found that the use of 0.8 mol% catalyst is sufficient to promote the reaction (entry 13). The fewer amounts gave lower yields, and when more amounts of catalyst was used, no changes in yield of the product and time of the reaction were observed. A series of comparative experiments were performed to compare the effectiveness of NP-LaMnO$_3$ versus other catalyst. In some cases, data for other catalysts were taken from the literature (entry 7-9). NP-LaMnO$_3$ was assessed to be the most efficient of all tested catalysts [30-33] (entry 3-6), in terms of reaction time, yield and catalyst loading.

To investigate the generality and versatility of this method, the reaction was extended to various diverse aldehydes and amine sources; the results are summarized in Table 3.

Table 1. Initial solvent effect studies for synthesis of trisubstituted imidazoles using 0.8 mol% catalyst.[a]

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	CHCl$_3$	Reflux	180	49
2	CH$_3$CN	Reflux	180	73
3	EtOH	Reflux	180	74
4	MeOH	Reflux	180	77
5	Acetone	Reflux	180	79
6	Toluene	Reflux	180	<30
7	*n*-Hexane	Reflux	180	<30
8	DMSO	Reflux	180	76
9	**Solvent-free**	**80**	**100**	**97**

[a]Reaction conditions: Benzil:4-Chlorobenzaldehyde: NH$_4$OAc (1 mmol:1 mmol:2 mmol), nano-LaMnO$_3$: 0.8 mol% in 2 mL solvent, stirring.

Table 2. Condensation reaction of benzil, *p*-Chlorobenzaldehyde and NH$_4$OAc in the presence of different loading of the catalyst under solvent-free conditions.[a]

Entry	Catalyst	Catalyst loading (g)	Temp. ($^\circ$C)	Time (min)	Yield (%)[b]	Ref.
1	-	-	r.t.	180	Trace	This work
2	-	-	100	120	<30	This work
3	Na$_2$CO$_3$/SiO$_2$	0.02	100	120	80	This work
4	P$_2$O$_5$/Al$_2$O$_3$	0.02	100	120	90	This work
5	KF.Al$_2$O$_3$	0.02	100	120	81	This work
6	NH$_4$OAc.Al$_2$O$_3$	0.05	100	120	83	This work
7	InCl$_3$·3H$_2$O	10[c]	r.t.[d]	564	71	[10]
8	Lipase	0.03	45[d]	540	75	[11]
9	MgAl$_2$O$_4$	0.05	120	30	92	[12]
10	NP-LaMnO$_3$	0.002	r.t.	120	47	This work
11	NP-LaMnO$_3$	0.002	50	100	66	This work
12	NP-LaMnO$_3$	0.002	65	100	78	This work
13	**NP-LaMnO$_3$**	**0.002**	**80**	**100**	**97**	**This work**
14	NP-LaMnO$_3$	0.001	80	100	92	This work
15	NP-LaMnO$_3$	0.004	80	100	97	This work
16	NP-LaMnO$_3$	0.01	80	100	97	This work
17	NP-LaMnO$_3$	0.02	80	100	97	This work

[a]Reaction conditions: Benzil:*p*-Chlorobenzaldehyde:NH$_4$OAc (1 mmol:1 mmol:2 mmol).
[b]Isolated yield.
[c]mol%.
[d]In presence of solvent.

It was clear that the product yield was influenced by both electronic and steric effects of the substituted groups. The aromatic aldehydes with electron-donating groups afforded lower yield of the corresponding products. Furthermore, the effect of steric hindrance on the aromatic aldehydes was noticeable. The *ortho*-substituted aromatic aldehydes gave lower yields comparing to their *para*-substituted (entries 4-7, Table 3). Moreover, aromatic amines gave lower yields of substituted imidazoles comparing to aliphatic amines.

Ease of recycling of the catalyst is one of the most advantages of our method. When the reaction was completed, the catalyst was separated by filtration. Then the catalyst was washed with chloroform (3 × 5 mL) and subsequently dried at 80 $^\circ$C to the reused. It should be mentioned that NP-LaMnO$_3$ could be reused in subsequent reactions without any significant decrease in catalytic activity even after five runs. Turn over number (TON) and turn over frequency (TOF) of **4e** after the fifth run were calculated, TON= 594 and TOF= 71 h^{-1}.

From mechanistic point of view, the catalytic efficiency of NP-LaMnO$_3$ in this reaction attributed to its Lewis acidity and high surface area. The formation mechanism of tri- and tetra-substituted imidazoles is similar, therefore to avoiding repetitive information it was decided to show only the formation of tri-substituted imidazoles.

The plausible pathway for the formation of tri-substituted imidazoles using NP-LaMnO3 can be demonstrated as follows (Scheme 2): It is assumed that, after coordination of aldehyde 1 to the Lewis acidic site present at the catalyst surface, ammonium acetate 2 subsequently attacks the activated carbonyl of aldehyde (I) to affording (II). Then, the elimination of water leads to iminium salt (III) which undergoes nucleophilic addition with the ammonium acetate 2 affording diamine intermediate (IV). The protonation of benzyl 3 by the NH-acidic of (IV) followed by attack of the resulting nucleophile (V) on the activated carbonyl of benzyl and dehydration to form the imino intermediate (VI).

Table 3. Synthesis of tri- and tetrasubstituted imidazoles in the presence of nano-LaMnO$_3$.[a]

Entry	R$_1$	R$_2$	Product	Yield (%)[b]	m.p. ($^{\circ}$C) Found	m.p. ($^{\circ}$C) Reported	Ref.
1	Ph	-	**4a**	88	268-270	274-275	[33]
2	*p*-Me-Ph	-	**4b**	90	233-234	232-235	[34]
3	*p*-OH-Ph	-	**4c**	85	262-264	266	[33]
4	*o*-Cl-Ph	-	**4d**	94	193-195	197-199	[33]
5	*p*-Cl-Ph	-	**4e**	97	263-265	262-264	[33]
6	*o*-Br-Ph	-	**4f**	90	201-202	201-202	[33]
7	*p*-Br-Ph	-	**4g**	96	260-262	261-263	[35]
8	2-Fluorenyle	-	**4h**	95	283-285	283-286	[36]
9	2-Thienyl	-	**4i**	89	259-261	260-261	[37]
10	2-Furyl	-	**4j**	87	200-202	200-201	[37]
11	Ph	PhCH$_2$	**6a**	88	161-163	163-165	[38]
12	*p*-Me-Ph	PhCH$_2$	**6b**	94	164-165	165-166	[39]
13	*p*-OH-Ph	PhCH$_2$	**6c**	83	136-138	134-135)	[40]
14	*p*-OMe-Ph	PhCH$_2$	**6d**	80	153-154	148-151	[39]
15	*p*-Cl-Ph	PhCH$_2$	**6e**	96	155-157	162-165	[40]
16	*p*-Me-Ph	CH$_3$CH$_2$CH$_2$	**6f**	93	214-215		
17	Ph	Ph	**6g**	86	216-218	216-218	[40]
18	*p*-Me-Ph	Ph	**6h**	87	188-190	186-188	[41]
19	*p*-Cl-Ph	Ph	**6i**	92	151-153	149-151	[13]

[a]Reaction conditions: Benzil:benzaldehyde:Amin source (1 mmol:1 mmol:2 mmol) nano-LaMnO$_3$: 0.8 mol%, stirring at 80 $^{\circ}$C, 100 min.
[b]Isolated yield.

This intermediate dehydrates under the reaction conditions to afford the 2,4,5-arylimidazoles (VII), the intermediate catalyst specie (VII) regenerates the solid catalyst via elimination of the final product 4.

4. Conclusions

In summary, we have developed one-pot synthesis for the preparation of 2-substituted aryl (indolyl) kojic acid derivatives through three-component reactions of kojic acid with indoles and aryl aldehydes in the presence of a catalytic amount of nano silica sulfuric acid in EtOH. By incorporating two biologically potential moieties in a single molecule the biological activity of these compounds may be enhanced. Also we employed nano silica sulfuric acid as an easily available and less costly, less toxic, and operable under environmentally friendly conditions catalyst in this reaction and obtained desired products with high yields. Therefore, this method is green, simple, efficient and convenient

for formation of a wide range of 2-substituted aryl (indolyl) kojic acid derivatives.

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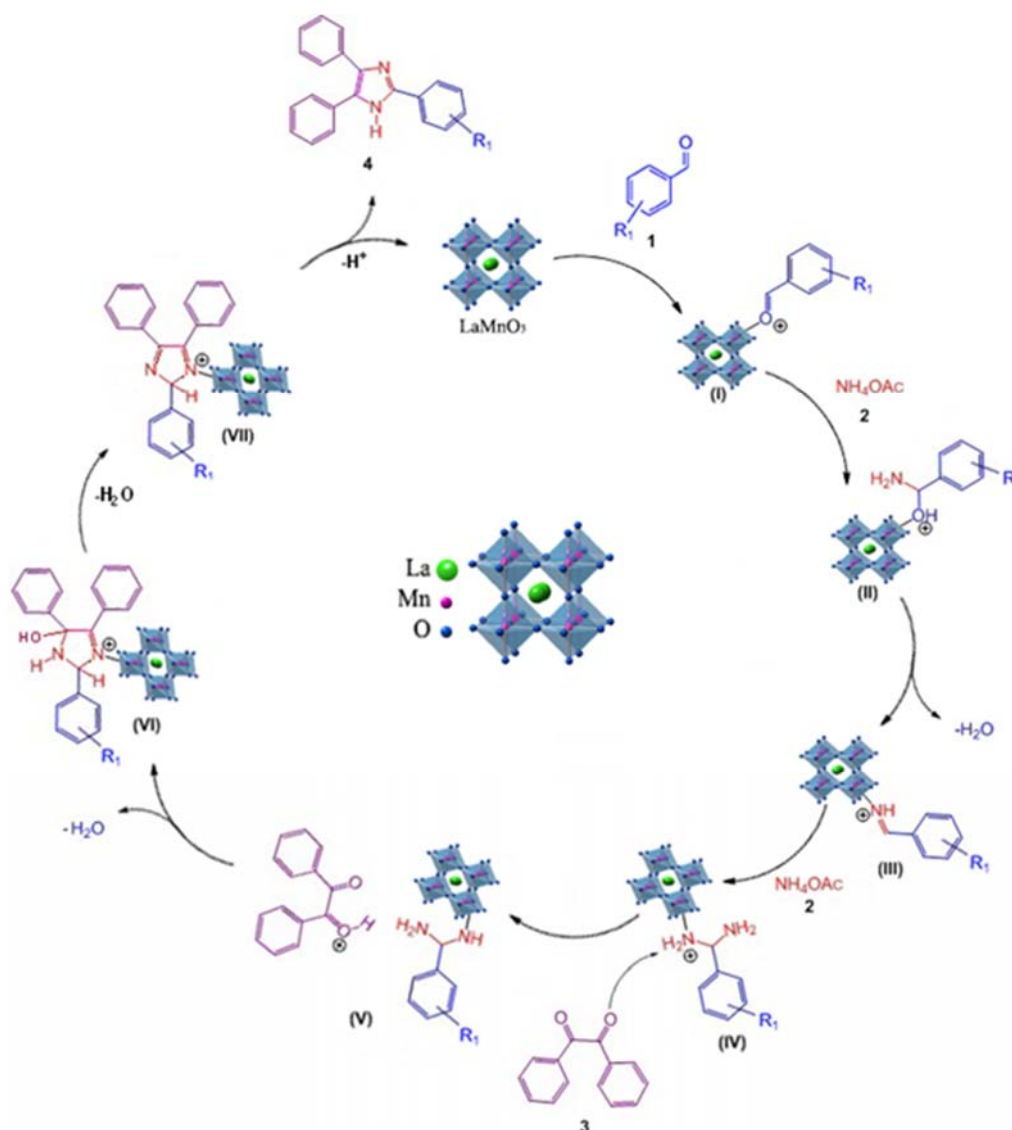
Scheme 2. Plausible mechanism using NP-LaMnO₃.

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