Molecules **2015**, *20*, 19221-19235; doi:10.3390/molecules201019221

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

γ-Alumina Nanoparticle Catalyzed Efficient Synthesis of Highly Substituted Imidazoles

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Academic Editor: Derek J. McPhee

Received: 6 September 2015 / Accepted: 14 October 2015 / Published: 21 October 2015

Abstract: γ-Alumina nano particle catalyzed multi component reaction of benzil, arylaldehyde and aryl amines afforded the highly substituted 1,2,4,5-tetraaryl imidazoles with good to excellent yield in less reaction time under the sonication as well as the conventional methods. Convenient operational simplicity, mild conditions and the reusability of catalyst were the other advantages of this developed protocol.

Keywords: benzil; arylaldehydes; γ-Alumina NPs; one pot synthesis; 1,2,4,5-tetraaryl imidazoles

1. Introduction

The imidazole ring system was reported [1] as an active component of several drugs such as Losartan, Olmesartan, Eprosartan and Trifenagrel (Figure 1), and many biologically important compounds like histidine, histamine and biotin. The potency and pertinence of imidazole pharmacophore was largely due to its hydrogen-bond donor acceptor nature as well as its high affinity towards the metals existing in the protein active sites (e.g., Fe, Zn, Mg). The imidazole derivatives were reported to function as

inhibitors of p38 MAP kinase, B-Raf kinase [2], transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5) [3], cyclooxygenase-2 (COX-2) [4] and were also reported to be involved in the biosynthesis of interleukin-1 (IL-1) [5,6]. Appropriately substituted imidazoles were used as glucagon receptors [7], CB1 cannabinoid receptor antagonists [8] and modulators of P-glycoprotein (P-gp) mediated multidrug resistance (MDR) [9]. The imidazole core was also reported to exhibit anti-allergic [10], anti-inflammatory [11], analgesic, antifungal, antimycotic, antibiotic, anti-ulcerative, antibacterial and antitumor activity [12].

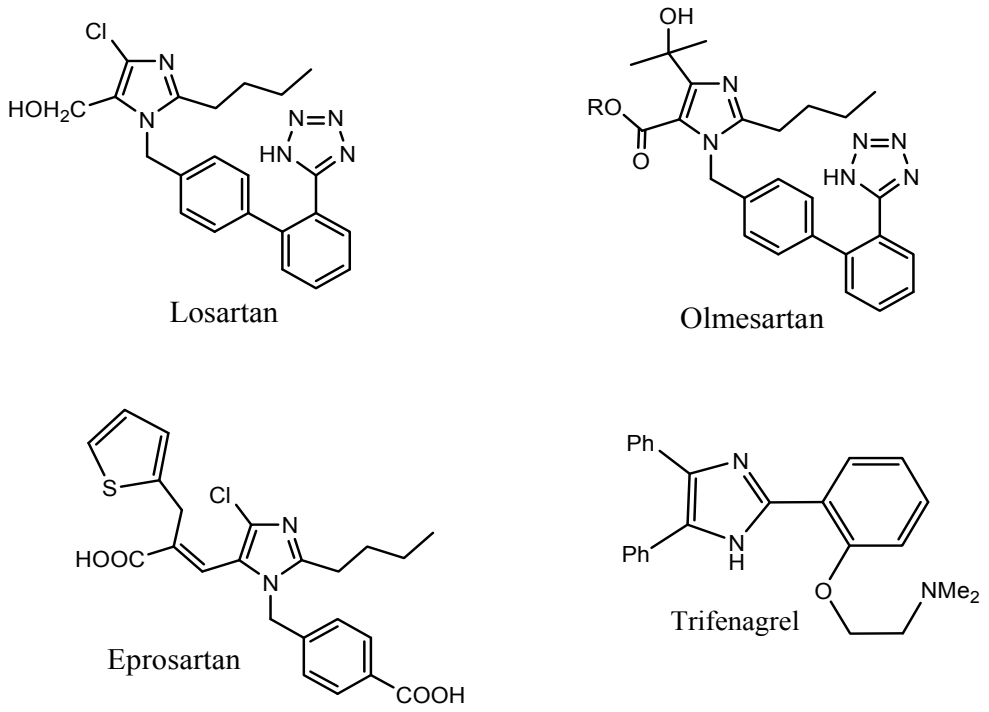


Figure 1. Some of the imidazole based drugs.

A number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles. The catalysts, such as silica gel or Zeolite HY [13], silica gel/$NaHSO_4$ [14], I_2 [15], $K_5CoW_{12}O_{40}$•$3H_2O$ [16], heteropoly acids [17], $HClO_4$-SiO_2 [18], $InCl_3 \cdot 3H_2O$ [19], $ZrCl_4$ [20], BF_3•SiO_2 [21], DABCO [22], PEG-400 [23] and silica-bonded propylpiperazine *N*-sulfamic acid (SBPPSA) [24], were also served for this purpose, all these methods suffered by several disadvantages like the usage of expensive moisture sensitive catalysts, hazardous organic solvents, laborious workup, longer reaction duration, larger volume of catalyst. Hence the development of a mild, simple, more efficient and green procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles was highly desirable.

In recent years, nano catalysts have gained prominence due to their efficiency and selectivity. The easy work up and reusability were the added advantages associated with the usage of this type of catalysts. Alumina is one of the inert biomaterial used in implants due to its biocompatible nature [25–30]. It exists in many metastable forms (γ, δ, θ, κ, ε, η, χ) and in particular γ-Al_2O_3 has significant applications as a catalyst [31]. γ-Al_2O_3 is *iso*-structural with γ-Fe_2O_3 and perhaps the most important nano material used as a support for metal catalysts; in view of its inherent properties like environmental compatibility, greater selectivity, moisture-insensitivity and operational simplicity, we intend to explore the catalytic behavior of γ-Al_2O_3 NPs in the synthesis of imidazoles. We anticipated that the Lewis acid behavior and the smaller

particle size of Al_2O_3 NPs (with large surface area) may efficiently catalyze the chemical reaction. Hence we attempted the γ-Al_2O_3 NPs catalyzed synthesis of tetraaryl imidazoles which is hitherto unreported.

2. Results and Discussion

To the aqueous the solution of $Al(NO_3)_3$•$9H_2O$ (1.72 g dissolved in 460 mL of distilled water) ammonia solution (30 mL) was added in drop wise using peristaltic pump under stirring with a propeller at 500 rpm for 30 min. The resulted turbid solution was warmed at 90 °C (using a temperature controlled water bath) till all the aluminum hydroxide was precipitated. The precipitate was collected by centrifugation and washed with distilled water followed by ethanol and then calcinated at 80 °C for four hours. The overall reaction for the synthesis of Al_2O_3 NPs from $Al(NO_3)_3$ can be depicted as,

$$Al(NO_3)_3 + 3NH_4OH \rightarrow Al(OH)_3 \downarrow + 3NH_4NO_3 \quad (1)$$

$$2Al(OH)_3 \rightarrow 2AlOOH(boehmite) + 2H_2O \quad (2)$$

$$2AlOOH(boehmite) \rightarrow \gamma\text{-}Al_2O_3 + H_2O \quad (3)$$

The synthesized Al_2O_3 NPs were characterized using Power X-ray Diffractometer with Cu Kα radiation (λ = 1.54 Å) over a 2θ range of 10°–90°. The XRD pattern exhibited seven distinct diffraction peaks at 19.79, 32.54, 37.53, 39.01, 45.81, 60.92 and 66.98 which could be assigned to (1 1 1), (2 2 0), (3 1 1), (2 2 2), (4 0 0), (5 1 1) and (4 4 0) of cubic nano γ-Al_2O_3 respectively and found to be in agreement with the database of JCPDS No. 00-010-0425 (Joint Committee on Powder Diffraction Standards) (Figure 2). The images of γ-Al_2O_3 NPs were observed using SEM (Carl Zeiss oxford instrument, (Oxford, UK) at various magnifications (Figure 3). The micrograph at lower magnification revealed the formation of well dispersed rod shaped γ-Al_2O_3 NPs. After confirming the formation of γ-Al_2O_3 NPs it was subjected as a catalyst in the synthesis of tetraaryl imidazoles via multi component reaction (Scheme 1) of benzil (1 mmol), arylaldehyde (1 mmol), ammonium acetate (2.0 mmol), and aniline (1 mmol) in ethanol. The observed yield and reaction duration of γ-Al_2O_3 NPs catalyzed reaction conferred that the γ-Al_2O_3 was an effective and efficient catalyst as anticipated. The observed efficiency may be attributed to Lewis acid behavior of γ-Al_2O_3 NPs and its smaller particle size (larger surface area). For optimization the reaction of benzil (1 mmol), 4-hydroxybenzaldehyde (1 mmol), ammonium acetate (2.0 mmol) and 4-methylaniline (1 mmol) in ethanol was chosen as a representative reaction for the synthesis of 4-(4,5-diphenyl-1-(4-methylphenyl)-1*H*-imidazol-2-yl)phenol. Catalytic efficiency was investigated under sonication and conventional heating methods. In conventional method the reaction mixture was refluxed for 240 min in the absence of catalyst, in this the observed yield was 33% of imidazole **8**, but the same reaction under similar conditions in the presence of 5 mol % of Al_2O_3 NPs could yield 82% of imidazole **8** in 60 min. The increase in mol % of Al_2O_3 NPs from 5 mol % to 10 mol % not only decreased the reaction time from 60 min to 40 min but also increased the yield of imidazole **8** from 82% to 93% (Table 1). Further increase in concentration of γ-Al_2O_3 NPs has no effect on the yield and time of the reaction.

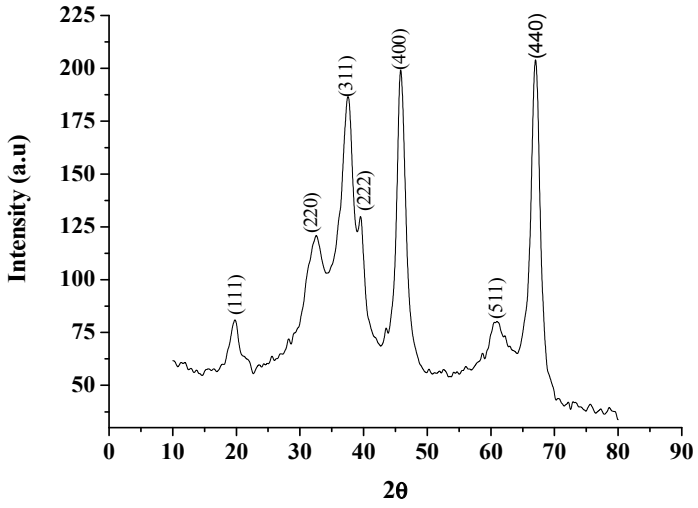


Figure 2. XRD pattern of γ-Al_2O_3 NPs.

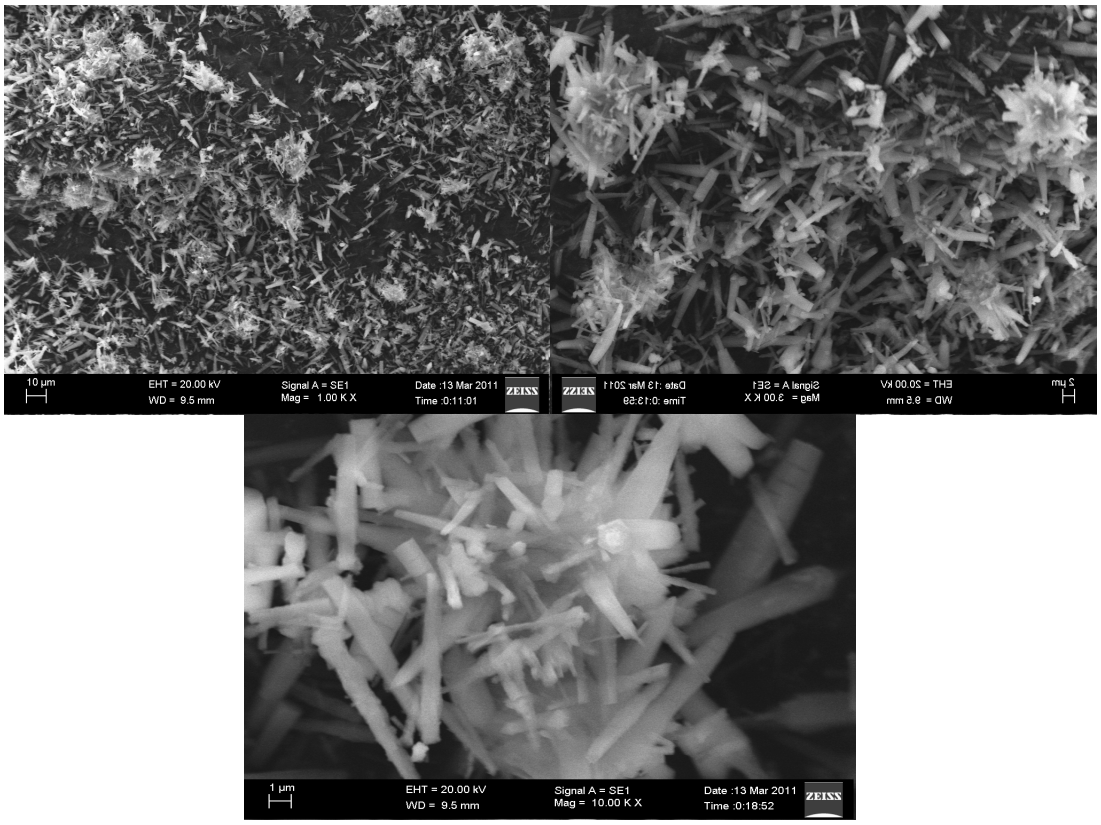
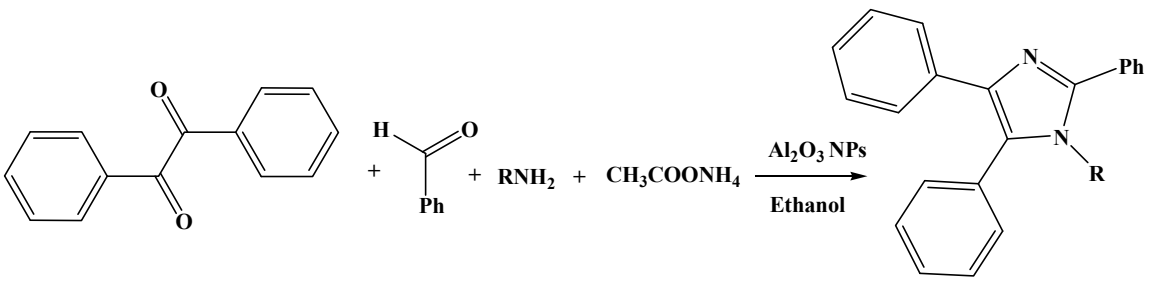


Figure 3. SEM micrographs of synthesized γ-Al_2O_3 NPs at various magnifications.



Scheme 1. Tetraaryl substituted imidazoles using multi-component reaction.

Table 1. Catalytic activity evaluation at 78 °C for synthesis of tetraaryl imidazole **8** in ethanol.

In Conventional Method				Under Ultrasonication			
Entry	**Al_2O_3 (mol %)**	**Time (min)**	**Yield (%) [b]**	**Entry**	**Al_2O_3 (mol %)**	**Time (min)**	**Yield (%) [b]**
1	20	40	93	**1**	20	25	95
2	15	40	93	**2**	15	25	94
3	10	40	93	**3**	10	25	94
4	05	60	82	**4**	05	45	80
5	00	240	33	**5**	00	120	35

[b] Isolated yield.

The effect of temperature on the reaction was investigated by carrying out the representative reaction at different temperatures (RT (25 °C), 50 °C, 80 °C and 100 °C) in solvents like acetonitrile and ethanol separately with 10 mol % of the catalyst and found that the yield was not affected with the increase of temperature (Table 2). To investigate the effects of media, the reaction was carried out in polar and non-polar solvents at RT using 10 mol % γ-Al_2O_3 NPs the catalyst at 80 °C (maximum of 78 °C temperature was maintained when ethanol was used as solvent). The polar solvents were found to be much better than non-polar solvents. Though acetonitrile, dichloromethane or ethanol were found to be good solvents (Table 3), ethanol was opted as a suitable solvent since it is relatively environmental benign and it required only the aqueous work up. The same model reaction was carried under sonication (to compare the general conventional process) and found that the yields were significantly increased under sonication (Table 1); this may be due to the dispersion phenomenon. The required concentration of catalyst under the sonication was investigated by changing its concentration in the synthesis of imidazole **8** and found that 10 mol % was sufficient to afford imidazole with 94% yield in 35 min (Table 1). The excellent yield in lesser time (compared to the conventional process) may be due to the availability of large surface area of catalyst and the sonication assisted dispersion of NPs. The reaction of benzil with various arylaldehydes bearing electron withdrawing groups (such as nitro, halide, *etc.*) or electron releasing groups (methyl, hydroxyl; mono, di, or tri methoxy groups, *etc.*), benzyl amine, aniline derivatives and ammonium acetate were also successfully carried out in the presence of γ-Al_2O_3 NPs. After optimizing the conditions a series of tetraaryl imidazoles from **1**–**22** were synthesized successfully (Table 4). Good to excellent yield of desired products was observed (without the formation of 2,4,5-trisubstituted imidazoles as side products, which were normally observed under the influence of the strong acids [19]). Plausible mechanism of the synthesis of tetraaryl imidazoles given in (Figure 4). The protocol described for the synthesis of tetraaryl imidazoles possesses its scope in the context of ease, generality and the simplicity. Waste generation and side products were largely avoided and hence the products were obtained with high yield and purity. In this experiment, after the completion of reaction, the reusability of the catalyst was assessed by washing the filtered catalyst (Figure 5) thoroughly with ethanol and distilled water followed by activation of the catalyst at 250 °C for 2 h (Figure 6). The separated catalyst was reused efficiently for four cycles with consistent activity (yields were 93%, 93%, 91% and 90%). All these tetraaryl imidazoles **1**–**22** were synthesized using the same methodology and characterized through IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral data and were available as supplementary data.

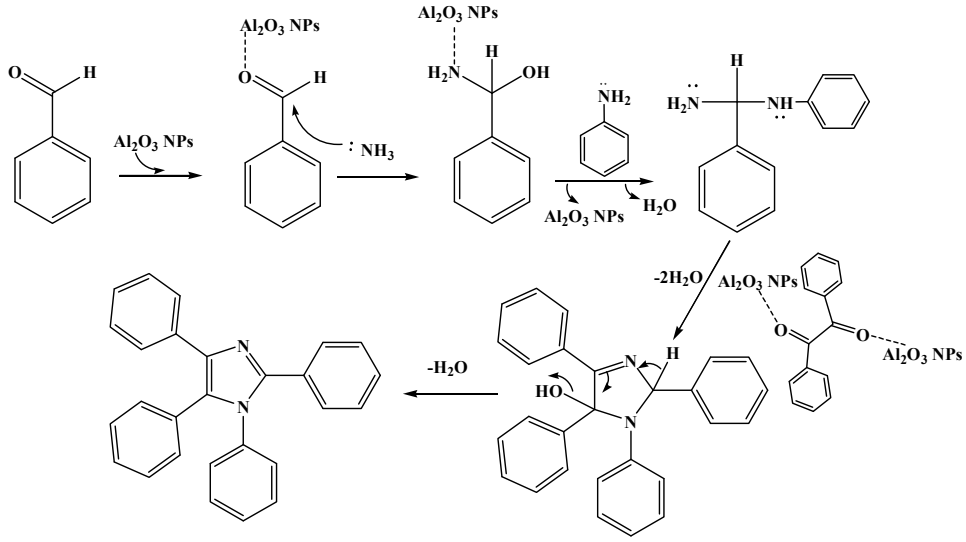


Figure 4. Plausible mechanism for synthesis of tetraaryl imidazoles.

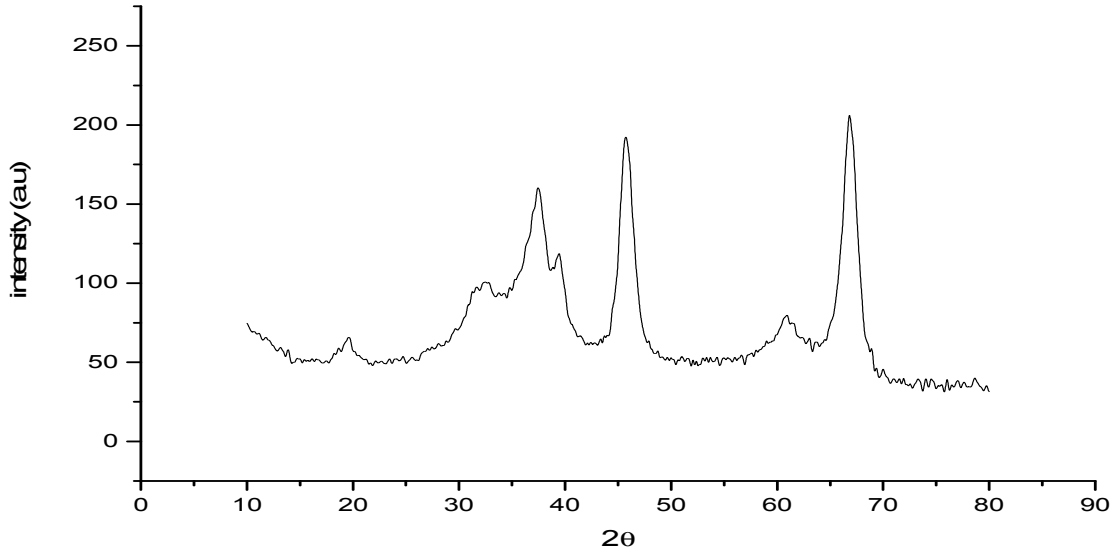


Figure 5. XRD pattern of recovered γ-Al_2O_3 NPs after four runs.

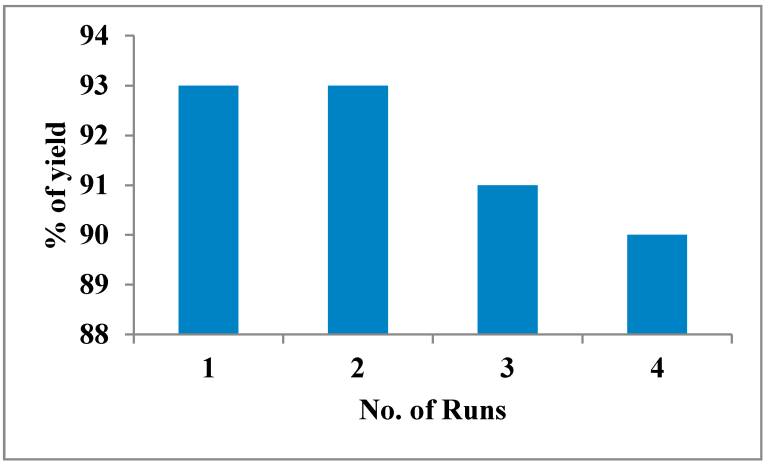


Figure 6. Reusability of catalyst.

Table 2. Temperature evaluation and effect of solvent in the synthesis of tetraaryl imidazole **8**.

Temperature Evaluation [a]			
Entry	**Temperature (°C)**	**Time (min)**	**Yield (%) [c]**
1	25	90	88
2	50	60	90
3	78	40	93

[a] in ethanol and 10 mol % catalyst; [c] Isolated yields.

Table 3. Effect of solvent on the yield of tetraaryl imidazole **8** at 10 mol % catalyst.

Effect of Solvent [b]		
Entry	**Solvent**	**Yield (%) [c]**
1	Ethanol	93
2	Methanol	88
3	Dichloromethane	86
4	Acetonitrile	88

[b] at reflux temp, time 40 min; [c] Isolated yields.

Table 4. Synthesis of tetraaryl imidazoles (**1**–**22**) [a].

Entry	**R**	**Ph**	**Reaction Time (min)**		**Yield (%) [b]**		**mp (°C)**
			Conventional	**US**	**Conventional**	**US**	
1	-CH_2Ph	Ph	40	25	92	95	161–163
2	-CH_2Ph	4-ClPh	40	25	92	94	165–167
3	-CH_2Ph	4-OC_2H_5Ph	50	30	92	94	155–157
4	-CH_2Ph	3,5-$(OCH_3)_2$Ph	50	35	92	93	180–182
5	-CH_2Ph	3-Cl Ph	40	25	92	93	144–146
6	4-CH_3Ph	4-OH-3-OC_2H_5Ph	45	25	90	94	180–182
7	4-CH_3Ph	4-C_2H_5Ph	55	30	90	93	212–214
8	4-CH_3Ph	4-OHPh	40	25	93	94	>275
9	4-CH_3Ph	3,5-$(OCH_3)_2$Ph	45	30	91	94	140–142
10	4-CH_3Ph	3,4,5-$(OCH_3)_3$Ph	55	35	93	93	102–104
11	4-CH_3Ph	2-Thienyl	40	25	89	92	200–201
12	4-OCH_3Ph	3,4,5-$(OCH_3)_3$Ph	60	45	91	92	123–125
13	4-ClPh	4-C_2H_5Ph	55	35	92	93	181–182
14	4-ClPh	3,4,5-$(OCH_3)_3$Ph	60	40	91	93	123–125
15	4-ClPh	4-CNPh	60	45	87	89	112–114
16	4-ClPh	AllyloxyPh	60	50	91	91	98–100
17	4-ClPh	4-BrPh	50	35	93	91	80–82
18	4-IPh	2,4-(Cl),Ph	45	25	89	92	109–111
19	4-IPh	4-OH-3-OCH_3Ph	50	30	93	94	96–98
20	4-CH_3Ph	3-OHPh	50	25	93	93	260–162
21	4-ClPh	3-OHPh	45	30	94	92	85–87
22	4-ClPh	4-OH-3-OC_2H_5Ph	40	30	94	94	169–170

[a] Reaction conditions: aldehyde (1 mmol), aniline (1 mmol) and γ-Al_2O_3 NPs (10 mol %), ethanol (10 mL), ammonium acetate (2.0 mmol); [b] Isolated and unoptimized yields.

In summary, the reaction of arylaldehyde, aryl amine and ammonium acetate with benzil in the presence of γ-Al_2O_3 NPs as efficient and effective catalyst provided a simple one-pot entry into the synthesis of biologically active highly substituted imidazoles. The simplicity, efficiency, generality, high yield, eco-friendly procedure, reusability of the catalyst was the promising points of the described methodology.

3. Experimental Section

3.1. Chemicals and Apparatus

Solvents and reagents were commercially sourced and used without further purification. Melting points were recorded on Elchem Microprocessor (Chennai, India) based DT apparatus in open capillary tubes and are uncorrected. IR spectra recorded on Avatar-330 FTIR spectrophotometer (Thermo Nicolet, Madison, WI, USA) using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) has been listed. Sonication was carried out by using E-Chrom ultrasonic horn (10F-8, No. 20, Minchuan W. Road, Taipei 104, Taiwan), 22 kHz frequency. The NMR spectra were recorded on Bruker (Bruker Corporation, Billerica, MA, USA) 400 & 500 MHz spectrometers using TMS as internal standard (chemical shifts δ in ppm). $CDCl_3$ and DMSO-d_6 are used as NMR solvents. Mass spectra were recorded on an HRMS MicromasszQ (San Diego, CA, USA) spectrometer. TLC was performed on preparative plates of silica gel (s.d.fine). Visualization was made with an iodine chamber.

3.2. Preparation of Al_2O_3 NPs

In a typical preparation, $Al(NO_3)_3$•$9H_2O$ (1.72 g) was dissolved in 460 mL distilled water and 30 mL of ammonia solution added drop wise using peristaltic pump under stirring using a propeller at 500 rpm for 30 min. The resulting turbid solution was warmed for two hours using a temperature controlled water bath at 90 °C till all aluminum hydroxide settled. The resulting precipitate was harvested by centrifugation, washed with distilled water followed by ethanol. The precipitate was then calcined at 800 °C for four hours.

*General procedure for the synthesis of 1,2,4,5-tetraaryl imidazoles (***1**–**22***) under the conventional heating:* An aldehyde (1 mmol), aniline (1 mmol) and γ Al_2O_3 NPs (10 mol %) in ethanol (10 mL), were added, stirred for 10 min. To this ammonium acetate (2.0 mmol) followed by 1,2-diketone (1 mmol) were added, then the reaction mixture was heated at 80 °C until completion of the reaction. Completion of the reaction was monitored by TLC. The reaction mixture was cooled to RT and catalyst was filtered, the solvent was removed by rotary evaporator. The crude product was dissolved in ethyl acetate and water (3 × 10 mL:10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and then the solvent was distilled under reduced pressure to get crude product. The crude product was purified by column chromatography to afford the corresponding imidazoles in good to excellent yield.

*General procedure for the synthesis of 1,2,4,5-tetraaryl imidazoles (***1**–**22***) under the ultrasonication:* To ethanol (10 mL), aldehyde (1 mmol), aniline (1 mmol) and γ Al_2O_3 NPs (10 mol %) in ethanol (10 mL) were added and stirred for 10 min. To this ammonium acetate (2.0 mmol) followed by 1,2-diketone (1 mmol) were added, then the reaction mixture was kept under sonicationup to the completion of the reaction (Table 4). Completion of the reaction was monitored by TLC. The reaction mixture was cooled to RT and catalyst was filtered, the solvent was removed by rotary evaporator. The crude product was

dissolved in ethyl acetate and water (3 × 10 mL:10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and then the solvent was distilled under reduced pressure to get crude product. The crude product was purified by column chromatography to afford the corresponding imidazoles in good to excellent yield. The identity as well as purity of the product was confirmed by ^{1}H-, ^{13}C-NMR, and mass spectra.

4. Spectral Data

1-Benzyl-2,4,5-triphenyl-1H-imidazole (**1**): Yield: 95%. m.p.: 161–163 °C; IR (KBr, cm^{-1}): 2956, 1613, 1560, 1416. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.11 (s, 2H), 6.80 (d, *J* = 7.4 Hz, 3H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.2–7.4 (m, 10H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 3H), 7.18–7.24 (m, 8H), 7.28–7.34 (m, 3H) 7.63 (d, *J* = 6.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 31.03, 48.41, 76.84, 77.16, 77.47, 115.85, 116.06, 116.15, 116.38, 124.60, 124.63, 126.00, 126.11, 126.46, 126.61, 126.88, 127.61, 128.18, 128.23, 128.67, 128.69, 128.80, 128.88, 128.97, 129.14, 130.01, 130.25, 130.33, 130.62, 130.85, 131.14, 133.03, 133.08, 133.11, 134.36, 135.02, 137.35, 138.39, 146.73, 146.75, 161.55, 164.00, 194.70, 207.12. HRMS (*m*/*z*): Calcd. for $C_{28}H_{22}N_2$: 386.1783. Found: 386.1788 (M^+).

1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (**2**)*:* Yield: 94%. m.p.: 165–167 °C; IR (KBr, cm^{-1}): 2986, 1618, 1563, 1417, 802. ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 5.12 (s, 2H), 6.83 (d, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.20–7.40 (m, 6H), 7.52 (d, *J* = 7.6 Hz, 3H), 7.56 (t, *J* = 7.6 Hz, 3H), 7.69 (d, *J* = 6.8 Hz, 3H). ^{13}C-NMR (125 MHz, DMSO) δ_C: 48.30, 125.88, 126.03, 126.36, 126.50, 126.80, 127.35, 127.52, 128.07, 128.13, 128.23, 128.57, 128.58, 128.61, 128.72, 128.76, 128.78, 128.83, 128.86, 128.90, 129.03, 129.09, 129.90, 130.07, 130.43, 130.98, 131.05, 131.10, 134.30, 134.48, 135.00, 137.34, 137.56, 138.11, 138.32, 138.50, 146.86. HRMS (*m*/*z*): Calcd. for $C_{28}H_{21}ClN_2$: 420.1393. Found: 420.1387 (M^+).

1-Benzyl-2-(4-ethoxyphenyl)-4,5-diphenyl-1H-imidazole (**3**): Yield: 94%. m.p.: 155–157 °C; IR (KBr, cm^{-1}): 2965, 1629, 1598, 1423, 1134. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.41 (t, *J* = 7.2 Hz, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 2H), 6.79 (d, *J* = 7.4 Hz, 2H), 6.89 (d, *J* = 7.4 Hz, 2H), 7.23–7.56 (m, 10H), 7.54 (d, *J* = 7.4 Hz, 2H), 7.97 (d, *J* = 7.2 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 14.91, 29.50, 48.38, 63.64, 114.70, 123.33, 126.17, 126.42, 126.94, 127.45, 128.19, 128.67, 128.71, 128.89, 129.17, 129.23, 129.87, 130.06, 130.57, 131.24, 131.30, 134.67, 137.82, 137.94, 148.22, 159.65. HRMS (*m*/*z*): Calcd. for $C_30H_{26}N_2O$: 430.2045. Found: 430.2033 (M^+).

1-Benzyl-2-(3,5-dimethoxyphenyl)-4,5-diphenyl-1H-imidazole (**4**): Yield: 93%. m.p.: 180–182 °C; IR (KBr, cm^{-1}): 2945, 1685, 1531, 1492, 1176. ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 3.67 (s, 3H), 3.87 (s, 3H), 5.08 (s, 2H), 6.87 (d, *J* = 6.8 Hz, 3H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.14 (s, 1H), 7.18–7.24 (m, 8H), 7.28–7.34 (m, 3H), 7.56 (d, *J* = 6.8 Hz, 2H). ^{13}C-NMR (125 MHz, DMSO) δ_C: 48.31, 55.71, 55.99, 111.05, 112.29, 121.69, 123.56, 125.99, 126.44, 126.91, 127.44, 128.17, 128.73, 128.77, 128.92, 130.02, 131.13, 134.57, 137.89, 138.01, 148.06, 148.84, 149.67. HRMS (*m*/*z*): Calcd. for $C_{30}H_{26}N_2O_2$: 446.1994. Found: 446.1980 (M^+).

1-Benzyl-2-(3-chlorophenyl)-4,5-diphenyl-1H-imidazole (**5**): Yield: 93%. m.p.: 144–146°C; IR (KBr, cm^{-1}): 2980, 1610, 1521, 1410, 1122, 790. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 5.12 (s, 2H), 6.82 (s, 2H), 7.19–7.29 (m, 8H), 7.34–7.41 (m, 8H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 48.30, 125.87, 126.02, 126.40, 126.53, 126.81, 127.38, 127.54, 128.11, 128.16, 128.26, 128.59, 128.62, 128.64, 128.73, 128.80, 128.82, 128.85, 128.89, 128.95, 129.08, 129.41, 129.90, 130.11, 130.26, 130.48, 130.76, 130.93, 131.03, 131.08, 134.31, 134.47, 134.98, 137.32, 137.53, 138.06, 138.28, 138.48, 146.85, 148.09, 148.45. HRMS (*m*/*z*): Calcd. for $C_{28}H_{21}ClN_2$: 420.1393. Found: 420.1399 (M^+).

4-(4,5-Diphenyl-1-(4-methylphenyl)-1H-imidazol-2-yl)-2-ethoxyphenol (**6**): Yield: 94%. m.p.: 180–182 °C; IR (KBr, cm^{-1}): 2956, 1613, 1560, 1416, 1139. ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 1.32 (t, 3H, *J* = 7.6 Hz), 2.30 (s, 3H), 3.90 (q, 2H, *J* = 7.6 Hz), 6.84 (d, 1H, *J* = 7.6 Hz), 6.75 (s, 1H), 6.91 (d, 2H, *J* = 7.6 Hz), 7.00–7.06 (m, 3H), 7.10–7.25 (m, 6H), 7.58 (d, 2H, *J* = 7.6 Hz), 7.97 (d, 2H, *J* = 7.6 Hz). ^{13}C-NMR (125 MHz, DMSO) δ_C: 14.89, 21.23, 31.06, 64.42, 112.70, 114.13, 122.46, 122.79, 126.60, 127.53, 127.93, 128.23, 128.35, 128.41, 129.16, 129.79, 130.03, 130.65, 130.94, 131.26, 133.10, 134.66, 134.84, 135.03, 137.92, 138.20, 145.41, 146.13, 147.14, 194.72, 207.16. HRMS (*m*/*z*): Calcd. for $C_{30}H_{26}N_2O_2$: 446.1994. Found: 446.1981 (M^+).

2-(4-Ethylphenyl)-4,5-diphenyl-1-(4-methylphenyl)-1H-imidazole (**7**): Yield: 93%. m.p.: 212–214 °C; IR (KBr, cm^{-1}): 2967, 1694, 1523, 1461, 1245. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (s, 3H), 2.31 (s, 3H), 2.61 (m, 2H), 6.90 (d, *J* = 7 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 2H), 7.15–7.42 (m, 6H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 8 Hz, 2H), 8.00 (d, *J* = 8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 15.36, 21.31, 28.70, 31.06, 125.47, 126.59, 127.53, 127.70, 127.92, 127.98, 128.11, 128.23, 128.27, 128.40, 128.45, 128.68, 128.95, 129.16, 129.78, 130.04, 130.84, 130.99, 131.27, 133.11, 134.72, 135.04, 138.17, 144.43, 147.24. HRMS (*m*/*z*): Calcd. for $C_{30}H_{26}N_2$: 414.2096. Found: 414.2090 (M^+).

4-(4,5-Diphenyl-1-(4-methylphenyl)-1H-imidazol-2-yl)phenol (**8**): Yield: 94%. m.p.: >280 °C; IR (KBr, cm^{-1}): 2956, 1619, 1562, 1414, 1287. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.26 (s, 3H), 6.65 (d, *J* = 7.4 Hz, 2H), 7.08–7.24 (m, 7H), 7.32 (d, *J* = 7.4 Hz, 3H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.68 (t, *J* = 7.2 Hz, 2H), 7.81 (t, *J* = 7 Hz, 3H), 7.95 (d, *J* = 5.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 21.09, 115.40, 121.86, 126.69, 126.77, 128.53, 128.71, 128.87, 128.93, 129.97, 130.01, 130.05, 130.23, 131.08, 131.20, 131.60, 132.74, 134.79, 135.12, 135.99, 136.83, 138.33, 158.01. HRMS (*m*/*z*): Calcd. for $C_{28}H_{22}N_2O$: 402.1732. Found: 402.1720 (M^+).

2-(3,5-Dimethoxyphenyl)-4,5-diphenyl-1-(4-methylphenyl)-1H-imidazole (**9**): Yield: 94%. m.p.: 140–142 °C; IR (KBr, cm^{-1}): 2923, 1609, 1567, 1495, 1165. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.20 (s, 3H), 3.60 (s, 6H), 5.55 (d, 1H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 7.2 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.40–7.60 (m, 6H), 7.97 (d, *J* = 7.2 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 29.83, 56.14, 106.16, 126.70, 127.56, 128.02, 128.28, 128.46, 128.49, 129.17, 129.83, 130.06, 130.86, 131.28, 133.14, 135.03, 138.02, 138.32, 146.63, 147.04. HRMS (*m*/*z*): Calcd. for $C_{30}H_{26}N_2O_2$: 446.1994. Found: 446.1980 (M^+).

4,5-Diphenyl-1-(4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)-1H-imidazole (**10**): Yield: 93%. m.p.: 102–104 °C; IR (KBr, cm^{-1}): 2934, 1693, 1567, 1436, 1173. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.30 (s, 3H), 3.61 (s, 6H), 3.81 (s, 3H), 6.70 (s, 3H), 6.90 (d, *J* = 8 Hz, 3H), 7.10 (d, *J* = 8 Hz, 2H), 7.30–7.50

(m, 5H), 7.50 (t, *J* = 6.8 Hz, 2H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.70 (d, *J* = 6.8 Hz, 1H), 8.00 (d, *J* = 7.4 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 21.16, 55.88, 60.96, 106.28, 125.91, 126.72, 127.51, 128.04, 128.26, 128.39, 128.44, 129.13, 129.83, 130.01, 130.72, 131.01, 131.21, 133.08, 134.51, 134.87, 135.01, 138.08, 138.11, 138.37, 146.74, 152.77. HRMS (*m*/*z*): Calcd. for $C_{31}H_{28}N_2O_3$: 476.2100. Found: 476.2109 (M^+).

4,5-Diphenyl-2-(thiophen-2-yl)-1-(4-methylphenyl)-1H-imidazole (**11**): Yield: 92%. m.p.: 200–201 °C; IR (KBr, cm^{-1}): 2959, 1643, 1562, 1414, 1165. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 2.30 (s, 3H), 6.9 (d, *J* = 7.6 Hz, 2H), 7.1 (d, *J*= 7.6 Hz, 2H), 7.3–7.5 (m, 6H), 7.51 (t, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 6.8 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 4H), 8.47 (d, *J* = 7.4 Hz, 1H), 8.59 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 14.24, 126.89, 123.12, 126.99, 127.41, 128.10, 128.23, 128.33, 128.51, 129.13, 130.01, 130.14, 130.41, 131.16, 131.75, 133.07, 134.02, 134.29, 135.01, 136.07, 138.87, 138.92, 144.14, 149.00, 149.51. HRMS (*m*/*z*): Calcd. for $C_{27}H_{22}N_2S$: 406.1501. Found: 406.1501 (M^+).

1-(4-Methoxyphenyl)-4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-1H-imidazole (**12**): Yield: 92%. m.p.: 123–125 °C; IR (KBr, cm^{-1}): 2909, 1667, 1549, 1492, 1174. ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 3.68 (s, 6H), 3.78 (s, 3H), 3.84 (s, 3H), 6.71 (s, 2H), 6.82 (d, *J* = 6 Hz, 3H), 7.00 (d, *J* = 7.2 Hz, 2H), 7.19–7.32 (m, 7H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 6 Hz, 3H) ^{13}C-NMR (125 MHz, DMSO) δ_C: 55.48, 55.88, 60.86, 106.23, 114.29, 125.90, 126.61, 127.39, 127.95, 128.16, 128.37, 129.03, 129.58, 129.91, 130.15, 130.69, 131.08, 131.13, 133.02, 134.46, 134.89, 137.94, 138.10, 146.74, 152.73, 159.25. HRMS (*m*/*z*): Calcd. for $C_{31}H_{28}N_2O_4$: 492.2049. Found: 492.2040 (M^+).

1-(4-Chlorophenyl)-2-(4-ethylphenyl)-4,5-diphenyl-1H-imidazole (**13**): Yield: 93%. m.p.: 181–182 °C; IR (KBr, cm^{-1}): 2996, 1687, 1564, 1436, 802. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.41 (t, *J* = 6.8 Hz, 3H), 4.03 (d, *J* = 6.8 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.94 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8 Hz, 2H), 7.31 (m, 3H), 7.52 (d, *J* = 8 Hz, 2H), 7.55 (m, 3H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 63.57, 114.34, 121.15, 122.73, 126.78, 127.52, 128.24, 128.30, 128.65, 129.17, 129.44, 129.78, 130.06, 130.35, 130.53, 130.64, 131.26, 133.14, 134.14, 134.45, 135.04, 135.93, 138.37, 147.16, 159.30.HRMS (*m*/*z*): Calcd. for $C_{29}H_{23}ClN_2$: 434.1550. Found: 434.1558 (M^+).

1-(4-Chlorophenyl)-4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-1H-imidazole (**14**): Yield: 93%. m.p.: 123–125 °C; IR (KBr, cm^{-1}): 2990, 1667, 1513, 1454, 782. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.64 (s, 3H), 3.75 (s, 6H), 3.87 (s, 3H), 6.68 (s, 2H), 6.80 (d, *J* = 8.2 Hz, 3H), 7.00 (d, *J* = 8.2 Hz, 2H), 7.01–7.03 (m, 4H), 7.50 (t, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.96 (d, *J* = 8 Hz, 1H), 7.98 (d, *J* = 8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.61, 56.00, 61.00, 106.30, 114.40, 126.01, 126.74, 127.51, 128.07, 128.29, 128.50, 129.16, 129.70, 130.04, 130.24, 130.78, 131.19, 131.25, 133.11, 134.55, 135.04, 138.04, 138.16, 146.87, 152.84, 159.35. HRMS (*m*/*z*): Calcd. for $C_{30}H_{25}ClN_2O_3$: 496.1554. Found: 496.1540 (M^+).

4-(1-(4-Chlorophenyl)-4,5-diphenyl-1H-imidazol-2-yl)benzonitrile (**15**): Yield: 89%. m.p.: 112–114 °C; IR (KBr, cm^{-1}): 2947, 1698, 1512, 1498, 805.^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 6.98 (d, 1H, *J* = 7.2 Hz)

7.11 (d, 1H, *J* = 7.2 Hz), 7.21–7.31 (m, 4H), 7.51–7.56 (m, 6H), 7.66 (t, 2H, *J* =7.4 Hz), 7.97 (d, 4H, *J* =7.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 111.89, 118.68, 121.14, 127.24, 127.41, 128.44, 128.72, 128.82, 129.11, 129.14, 129.17, 129.56, 129.90, 130.05, 131.14, 132.12, 133.11, 133.82, 134.56, 135.05, 135.27, 136.62, 139.42, 144.77, 168.43, 194.75, 207.20. HRMS (*m*/*z*): Calcd. for $C_{28}H_{18}ClN_3$: 431.1189. Found: 431.1180 (M^+).

2-(4-(Allyloxy)phenyl)-1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (**16**): Yield: 91%. m.p.: 98–100 °C; IR (KBr, cm^{-1}): 2956, 1613, 1560, 1416, 1187. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 4.51 (s, 2H), 5.27 (d, *J* = 7.6 Hz, 1H), 5.38 (d, *J* = 7.6 Hz, 1H), 6.03 (t, *J* = 8 Hz, 1H), 6.80 (d, *J* = 8 Hz, 2H), 6.95 (d, *J* = 8 Hz, 2H), 7.18 (d, *J* = 8 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.4–7.6 (m, 6H), 7.97 (d, *J* = 7.2 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 68.88, 114.61, 117.97, 121.15, 123.05, 126.80, 127.51, 128.26, 128.30, 128.65, 129.08, 129.17, 129.45, 129.77, 130.05, 130.39, 130.51, 130.60, 131.25, 133.07, 133.13, 134.18, 134.41, 135.04, 135.89, 138.39, 147.05, 158.93. HRMS (*m*/*z*): Calcd. for $C_{30}H_{23}ClN_2O$: 462.1499. Found: 462.1490 (M^+).

2-(4-Bromophenyl)-1-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (**17**): Yield: 91%. m.p.: 80–82 °C; IR (KBr, cm^{-1}): 2956, 1665, 1560, 1489, 783. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 6.98 (d, *J* = 7.4 Hz, 2H), 7.13 (d, *J* = 7.4 Hz, 2H), 7.41–7.55 (m, 6H), 7.68 (t, *J* = 7.2 Hz, 4H), 7.99 (d, *J* = 7.2 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 24.58, 121.21, 123.08, 127.02, 127.48, 128.37, 128.48, 128.72, 129.06, 129.17, 129.64, 130.03, 130.50, 131.18, 131.62, 133.12, 134.11, 134.61, 135.04, 135.51, 136.69, 138.85, 168.53. HRMS (*m*/*z*): Calcd. for $C_{27}H_{18}BrClN_2$: 484.0342. Found: 484.0349 (M^+).

2-(2,4-Dichlorophenyl)-1-(4-iodophenyl)-4,5-diphenyl-1H-imidazole (**18**): Yield: 92%. m.p.: 109–111 °C; IR (KBr, cm^{-1}): 2945, 1609, 1554, 1417, 786. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 6.66 (d, *J* = 7.2 Hz, 1H) 7.14 (d, *J* = 7.2 Hz, 1H), 7.17–7.33 (m, 3H), 7.46–7.58 (m, 7H), 7.66 (t, *J* = 7.4 Hz, 2H), 7.97 (d, *J* = 7.4 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 93.86, 121.75, 127.05, 127.24, 127.54, 128.35, 128.49, 128.82, 128.99, 129.16, 129.47, 129.72, 129.92, 130.03, 131.00, 133.07, 133.66, 133.95, 135.05, 135.54, 135.86, 136.33, 137.93, 138.07, 138.59, 143.92, 168.57. HRMS (*m*/*z*): Calcd. for $C_{27}H_{17}Cl_2IN_2$: 565.9813. Found 565.9819 (M^+).

5. Reusability of the Catalyst

In the experiment, after the reaction was completed, the γ-Al_2O_3 NPs catalyst was isolated from the reaction mixture by filtration in the work-up stage. The reusability of the catalyst was assessed by washing thoroughly by ethanol and distilled water followed by activating the catalyst at 250 °C for 2 h. The separated catalyst was reused efficiently for four cycles with consistent activity and yields are 93%, 93%, 91% and 90% (Figure 6).

6. Conclusions

In conclusion, the reaction of aldehyde, aryl amine and ammonium acetate with benzyl in ethanol in the presence of γ Al_2O_3 NPs as an efficient and effective catalyst provides a simple one-pot entry into the synthesis of highly substituted imidazole derivatives. The promising points of the present methodology

were efficiency, generality, high yield, eco-friendliness, reusability of the catalyst and simplicity process for the preparation of 1,2,4,5-tetrasubstituted imidazoles.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/10/19221/s1.

Acknowledgments

The Project was full financially supported by king Saud University, through Vice Deanship of Research Chairs.

Author Contributions

Authors B.P.R. M.V.A. and V.V. conceived, designed and performed the experiments; Authors V.V. and N.A.A. wrote the paper.

Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds are available from the authors.