One-pot solvent-free synthesis of highly substituted imidazoles catalyzed by zeolite
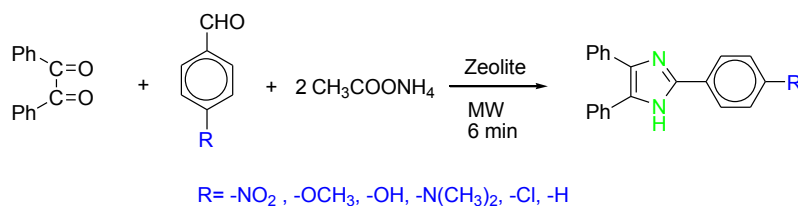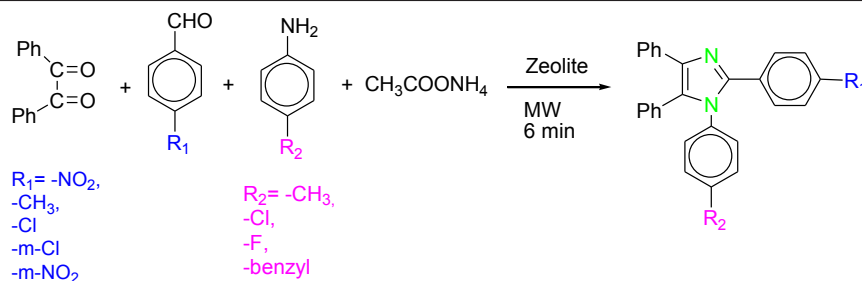
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HIGHLIGHTS

- The synthesis reactions of substituted imidazoles catalyzed by zeolite were solvent free.

- The used natural zeolite was a reusable heterogeneous and an ecofriendly catalyst.

- The reaction times were short and yields were high.

GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

A series of tri- and tetra- substituted imidazoles were synthesized from benzyl, aldehyde and ammonium acetate in the presence of zeolite as an ecofriendly reusable catalyst under microwave irradiation in the absence of solvent. The yields are high to excellent and the use of microwave irradiation reduces reaction times to few minute.

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1. Introduction

Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes. This ability can be attributed to its hydrogen bond donor-acceptor capability as well as its high affinity for metals, which are present in many protein active sites (e.g., Zn, Fe, Mg)[1]. Various substituted imidazoles act as inhibitors of P 38MAP Kinase[2], B-Raf Kinase[3], glucagon receptors[4], plant growth regulators[5], therapeutic agents[6], antibacterial[7], antitumor and also pesticides[8].

Recent development of green chemistry and organometallic chemistry expands the utility of imidazoles as ionic liquids[9] and N-heterocyclic carbenes[10]. They also serve as useful building blocks for the synthesis of other classes of compounds.

Several methods of imidazoles synthesis can be found in the literature, including hetero-Cope rearrangement[11], four-component condensation of arylglyoxals; the combination of primary amines, carboxylic acids, and isocyanides on Wang resin[81], the reaction of N-(2-oxo)-amides with ammonium trifluoroacetate[12], the use of 1,2-amino alcohols in the presence of PCl_5[13], triflate promoted multicomponent reaction of various α-azidochalcones, arylaldehydes, and anilines[14], three-component cyclocondensation of 1,2-dicarbonyl compound, aldehyde and ammonium acetate using L-proline as a catalyst in methanol at moderate temperature[15], the reaction of N-acylated α-aminonitriles with triphenylphosphine and carbon tetrahalide[16], the reaction of 2-(tetrazol-5-yl)-2H-azirines with imines in the presence of Lewis acids[17], the reaction of benzyl, aldehyde and ammonium acetate in the presence of supported zeolite[18], using silica gel-supported sodium bisulfate as a catalytic support by four-component condensation of benzil or benzoin, aldehydes, amines, and ammonium acetate under microwave irradiation or classical heating conditions[19], the reaction of Oximes with benzenecarboximidoyl chlorides[20], thiazolium-catalyzed addition of an aldehyde to an acyl imine[21], the reaction of propargyl amines with sulfonylazides, and terminal alkynes[22], from N-(thiocarbonyl)-N-methylamidines[23], and finally, the combination of diketones, aldehydes, amines, and ammonium acetate in one of four possible media: acetic acid[24], acetic acid or H_2SO_4 with organocatalysts[25], or dimethyl sulfoxide [26].

Several assisted syntheses of imidazoles from β-diketones and aldehydes in the presence of a variety of catalysts also have been reported. On the other hand, the synthesis of 1,2,4,5-tetrasubstituted imidazoles have been carried out by four-component reactions of a 1,2-diketone, α-hydroxy ketone or α-ketomonoxime of an aldehyde, primary amine and ammonium acetate using microwave[27] or ionic liquids[28]. Most of the above reported synthetic methods for the synthesis of tri-and tetrasubstituted imidazoles suffer from one or more drawbacks, such as acidic condition [29], high temperature, use of toxic metal catalysts [30], poor yields, occurrence of side reactions and expensive reagents. Therefore, the development of a mild generalized method to overcome these shortcomings still remains an ongoing challenge for the synthesis of highly substituted imidazoles for organic chemists. Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are One-Pot processes bringing together three or more components and show high atom economy and high selectivity [31]. MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery [32].The developing of new MCRs and improving known multicomponent reactions are an area of considerable current interest. Considering each of the above methods for this reaction has its own merits, while some of the methods plagued by the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution, here in, we reported a simple, economic and efficient multicomponent one-pot method for the synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles using zeolite (analcime) as an ecofriendly reusable solid catalyst in solvent free conditions in high yields (schemes 1and 2).

Zeolites are extensively used in the fields of heterogeneous catalysis, separations, ion exchange, chemical separation, adsorption, host/guest chemistry, microelectronic devices, optics, and membranes. Similar to other solid acids, zeolites possess both Bronsted and Lewis acid sites, which are typically hydroxyl groups and coordinatively unsaturated cations, respectively. Either Bronsted or Lewis acidity can dominate, depending on the chemical content, crystalline structure, postsynthetic treatments and, last but not the least, the state of hydroxylation under the reaction conditions. In order to draw connections between the acidic properties of zeolites and their catalytic properties, it is essential to obtain quantitative information on the number, nature, location, and strength of the acidic sites [33].
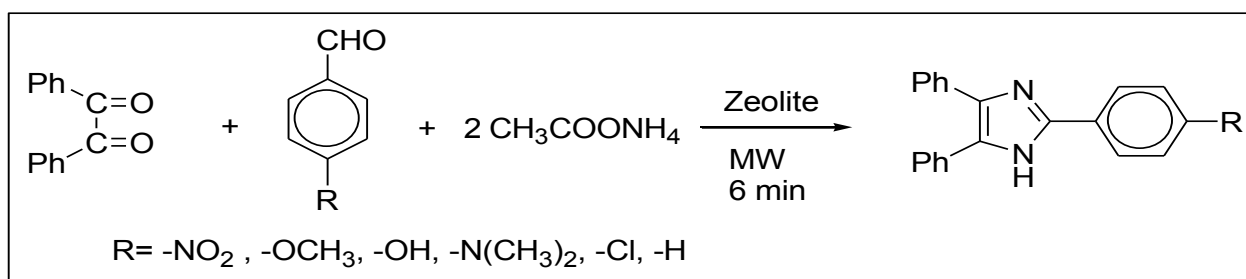
Scheme1. The synthesis of 2, 4, 5- trisubstituted imidazoles
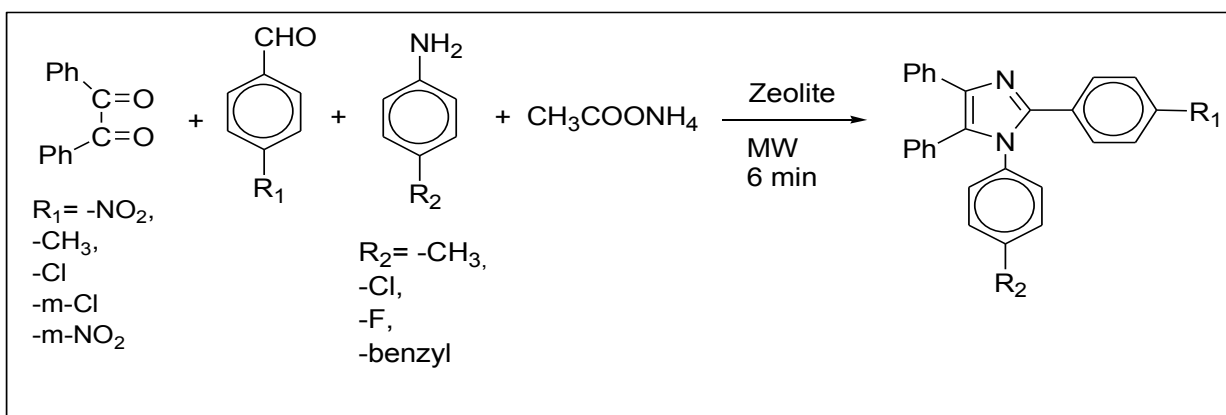
.**Scheme2.** The synthesis of 1, 2, 4, 5- tetrasubstituted imidazoles

2. Experimental

2.1. General

All reagents were purchased from Merck, without further purification. NMR spectra were recorded on 300 MHz NMR spectrometer. The IR spectra were recorded on Varian FT-IR spectrometer. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck60F$_{254}$) UV indicator. Melting points were determined with Buchi B-540 melting point apparatus and are uncorrected.

2.2. General procedure for the synthesis of 2, 4, 5-tri-substituted imidazoles

Benzyl (4 mmol = 841 mg), aldehyde (4 mmol) ammonium acetate (8 mmol = 617 mg) and zeolite (0.1 g) were mixed thoroughly in a mortar. Then the reaction mixture was transferred into a baker and irradiated with 100 W microwaves for 6 minutes. The progress of reaction monitored by TLC using CH$_2$Cl$_2$: EtOAc=90:10 as the eluent. After completion of the reaction, the mixture was cooled and product was extracted with CH$_2$Cl$_2$ (3×20 ml). The organic phase washed with H$_2$O. The solvent was removed by means of rotary evaporator. Further purification by recrystallization in methanol 95% produced the corresponding pure trisubstituted imidazoles (Table 3). All compounds are known and their physical data are given in literature [34- 37].
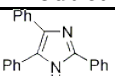
2.3. General procedure for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles

To a solution of Benzyl (1mmol= 210 mg), aldehyde (1mmol), primary amine (1mmol) and ammonium acetate (1mmol) in 3 mL CH$_2$Cl$_2$, zeolite (0.1 g) was added and stirred for 5 minutes. Then the solvent was allowed to evaporate and the dry residue transfered into a baker and irradiated with 100 W microwave oven for 6 minutes. The progress of reaction monitored by TLC using CH$_2$Cl$_2$: EtOAc =90:10 as the eluent. The mixture was cooled at room temperature and then CH$_2$Cl$_2$ (3×20 mL), was added to the reaction mixture and filtered, the organic phase washed with water and n-hexane and dried over MgSO$_4$ and filtered. The solvent was removed by means of a rotary evaporator. Further purification by recrystallization in methanol 95% produced the corresponding pure tetrasubstituted imidazoles(Table 4). All compounds are known and their physical data are given in literature [23, 38].
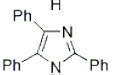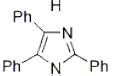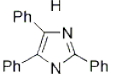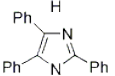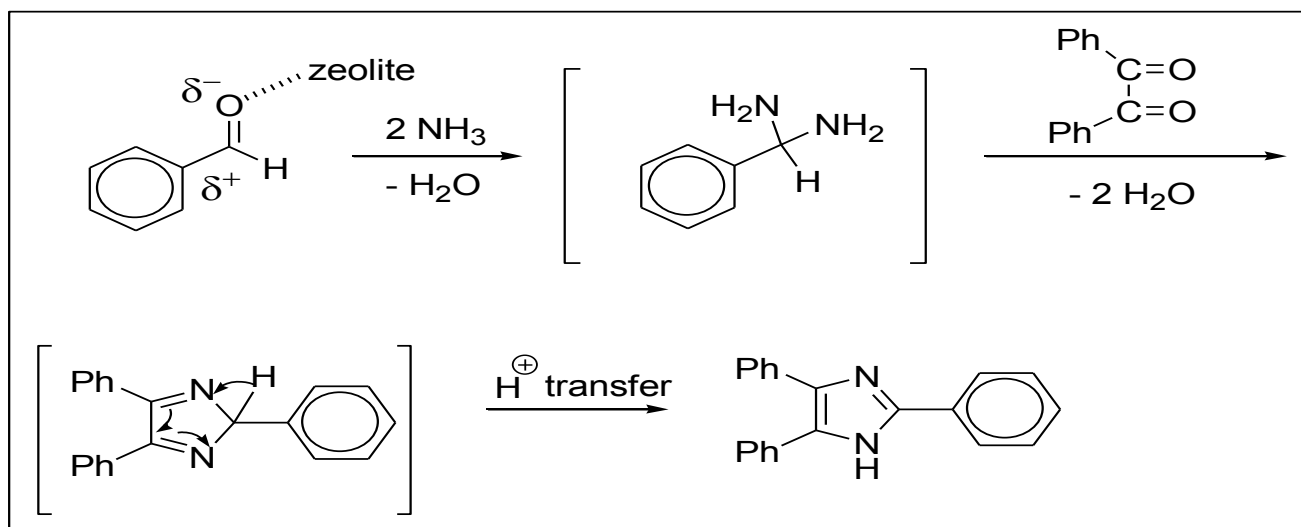
3.   Results and Discussion

This study describes a successful approach for the synthesis of tri and tetra-substituted imidazoles using a laboratory MW reactor. This MW technology does not require linking-cleaving chemistry and afford the products immediately. A solvent-free cyclization reaction for synthesis of imidazoles is developed, which require MW irradiation of 1, 2-diketone, aromatic aldehydes and ammonium acetate in the presence of zeolite.

This allows for easy separation of the solid catalyst by simple filtration, and in optimal conditions the catalyst can be reused 5 times at least (Table 1). The ready and exclusive formation of cyclized imidazoles occurs in high yields. The reaction under thermal conditions affords lower yields (Table2).

Hence, it is clear from yield comparison plot of classical and MW assisted synthesis of the substituted imidazoles that MW irradiation has been found to be easier, convenient, eco-friendly and yields are more than good as compare with the classical method. In general, synthesis of substituted imidazole under thermal conditions may occur in two steps, formation of Schiff base and its cyclization. In this procedure, carbonyl groups coordinated to the zeolite catalyst firstly and then nucleophile attacks on activated carbonyl and the reaction is continued (schemes 3 and 4). The structure of substituted imidazoles was deduced from their H-NMR, IR spectra data and also their melting points. The reaction under MW condition was carried out in 6 min and melting points of the synthesized substituted imidazoles are given in Tables 3 and 4

Table 1.
Recovery of zeolite in the synthesis of 2, 4, 5- trisubstituted imidazoles.

Run	Product	Time/min	Yield (%)
1	Ph, Ph, Ph imidazole	6	96
2	Ph, Ph, Ph imidazole	6	92
3	Ph, Ph, Ph imidazole	6	94
4	Ph, Ph, Ph imidazole	6	93
5	Ph, Ph, Ph imidazole	6	94

Scheme3. The possible reaction mechanism for the synthesis of tri-substituted imidazoles [23].
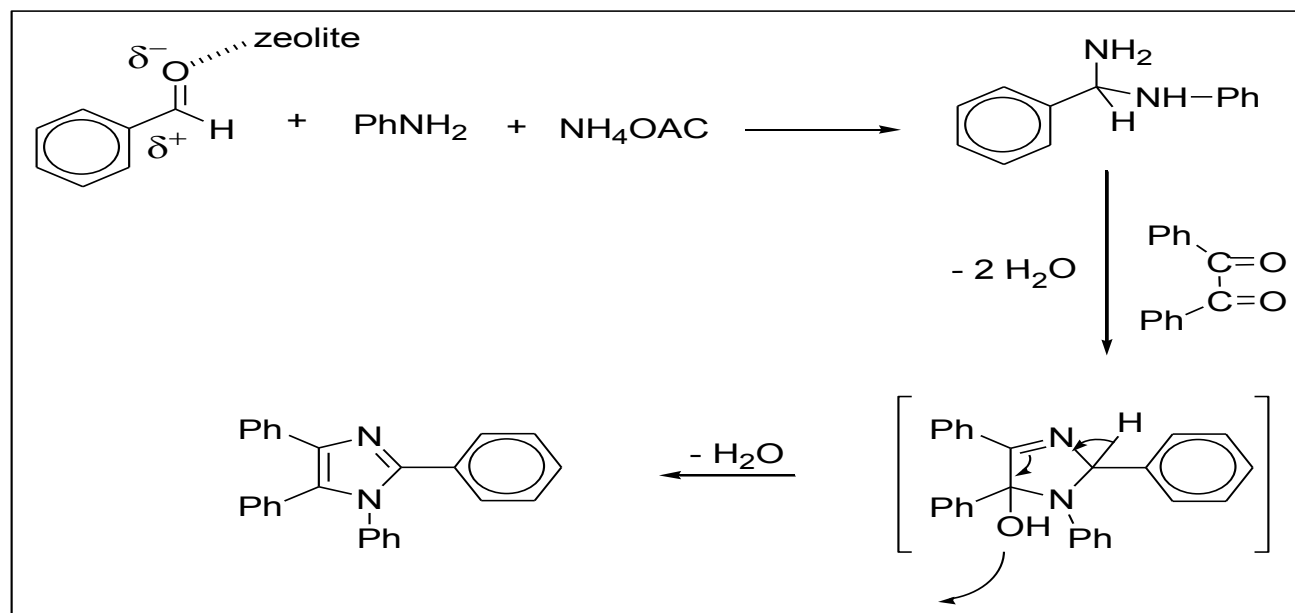
Scheme4. The possible reaction mechanism for the synthesis of tetra-substituted imidazoles [33].

Table 2.
The synthesis of trisubstituted imidazoles using benzyl, Ammonium acetate and substituted Aldehydes under different conditions.
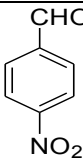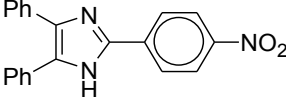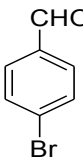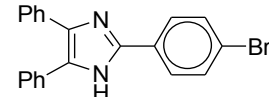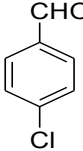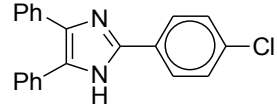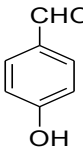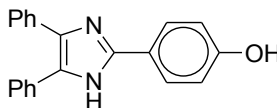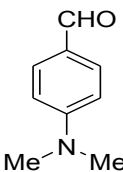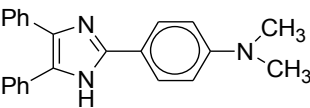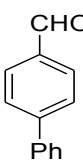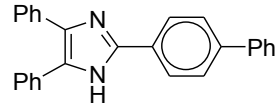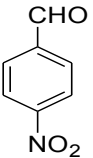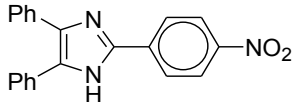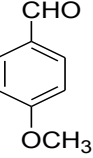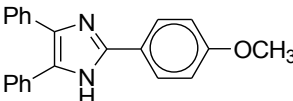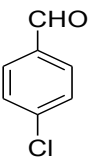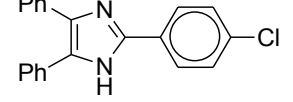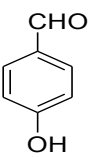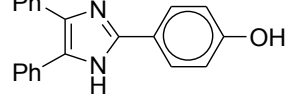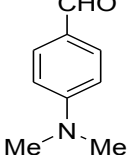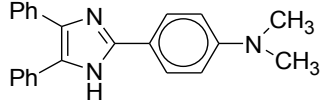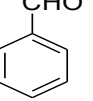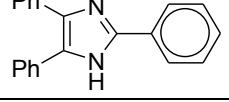
Entry	ArCHO	Product	Microwave Method		Thermal Method	
			Reaction Time (min)	Yield (%)	Reaction Time (h)	Yield (%)
1			6	90	4	59
2			6	90	4	56
3			6	88	4	54
4			6	91	4	61
5			6	92	4	65
6			6	85	4	52

Table 3.
The synthesis of trisubstituted imidazoles using Benzyl, Ammonium acetate and substituted Aldehydes.

Entry	ArCHO	Product	mp (°C)	
			Found	Lit.
1	CHO ... NO₂	Ph, Ph imidazole–C₆H₄–NO₂	235-238	[236-237][36]
2	CHO ... OCH₃	Ph, Ph imidazole–C₆H₄–OCH₃	253-255	[255][37]
3	CHO ... Cl	Ph, Ph imidazole–C₆H₄–Cl	263	[266-268][38]
4	CHO ... OH	Ph, Ph imidazole–C₆H₄–OH	269-270	[209][35]
5	CHO ... N(Me)₂	Ph, Ph imidazole–C₆H₄–N(CH₃)₂	260-261	[259.5-260][35]
6	CHO	Ph, Ph imidazole–C₆H₅	275-276	[276-278][39]

Spectroscopic data of the synthesized trisubstituted imidazoles are given below:

Entry1; 2-(4-Nitrophenyl)-4, 5-diphenyl-1H-imidazole; IR (KBr): 3400 (N-H), 1580 (C=N), 1515 (NO2), 1335 (NO2) Cm^{-1} ;^{1} H- NMR (CDCl3): 7.15-7.70 (m, 10H, Ph), 7.90- 8.25 (AB, 4H, J 9 Hz, Ar) ppm.

Entry2;2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole; IR (KBr): 3428(N-H), 2893, 2465, 1636, 1216 Cm^{-1} ;^{1} H- NMR (CDCl3/DMSO-d6): 3.85 (s, 3H), 6.93–6.96 (d, J 8.8 Hz, 2H), 7.25–7.59 (m, 10H),8.02– 8.05 (d, J 8.8 Hz, 2H) 12.52 (brs, 1H) ppm.

Entry3; 2-(4-chlorophenyl)-4, 5-diphenyl-1H-imidazole; IR (KBr): 3452, 3065, 1635, 1323; 1H-NMR (DMSO-d6): 12.78 (s, 1H), 8.11 (d, 2H), 7.56-7.23(m, 12H).

Entry4;2-(4-Dimethylaminophenyl)-4,5-diphenyl-1H-imidazole ; IR (KBr): 3590, 3454, 3284, 3064, 1701, 1283 cm^{-1};^{1} H-NMR (DMSO-d6): 12.40 (s, 1H), 9.70 (s, 1H), 7.90 (d, J 8.4 Hz, 2H), 7.54–7.21 (m, 10H), 6.86 (d, J 8.4 Hz, 2H) ppm.

Entry5;2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole; IR (KBr): 3050 (C-H), 2850 (C-H), 1615 (C=C), 1600(C=N), 1360 (C-N) Cm^{-1} ;^{1} H-NMR (CDCl3): 2.90 (s, 2CH3), 6.60 (d, 2H, J .8.9 Hz, Ar), 7.10-7.60 (m, 10H, Ph), 7.70 (d, 2H, J 8.9 Hz, Ar) ppm.

Entry6; 2, 4, 5-Triphenyl-1H-imidazole; IR (KBr): 3428(N-H), 2893, 2465, 1636, 1216 Cm^{-1} ;^{1} H- NMR (CDCl3): 7.15-8.00 (m, 15H, Ph), 9.20 (brs, NH) ppm.

Spectroscopic data of the synthesized tetrasubstituted imidazoles are given below:

Entry1;2-(4-Nitrophenyl)-4,5-diphenyl-1-p-tolyl-1H-imidazole; IR (KBr): 1591, 1507, 1334 Cm^{-1} ;^{1} H- NMR (DMSO-d6) 2.15(s, CH3) 6.97–8.12(m, 18H Ar) ppm.

Entry2;2-(4-Chlorophenyl)-1-(4-fluorophenyl)-4,5-diphenyl-1Himidazole; IR (KBr): 1594, 1479, 1418 Cm^{-1} ;^{1} H- NMR (DMSO-d6) 7.17–7.49 (m, 18H Ar) ppm.

Entry3;1,2-Bis(4-chlorophenyl)-4,5-diphenyl-1H-imidazole; IR (KBr): 1599, 1497, 1412; 1H-NMR (DMSO-d6): 2.20 (s, CH3), 6.92– 7.63 (m, 18H Ar) ppm.

Entry4; 1-Benzyl-4, 5-diphenyl-2-p-tolyl-1H-imidazole; IR (KBr): 1601, 1497, 1452 cm^{-1};^{1} H-NMR (DMSO-d6): 2.31 (s, CH3), 5.14 (s, CH2), 6.73–7.56 (m, 19 Ar) ppm.
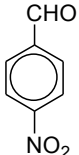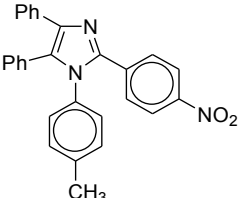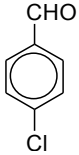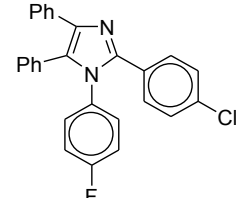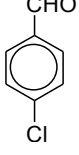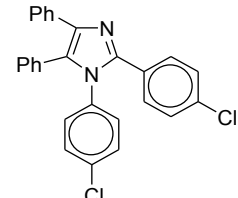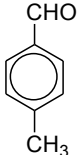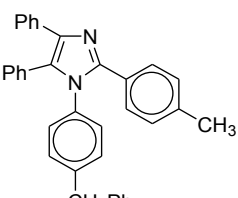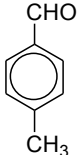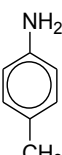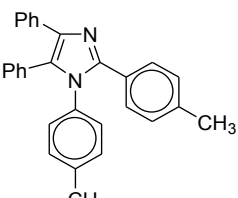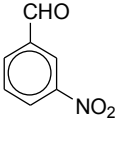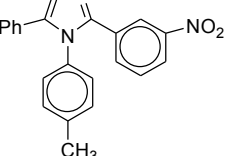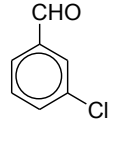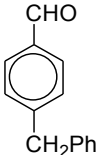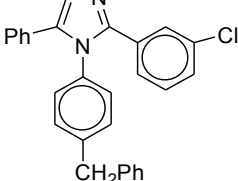
Entry5; 4, 5-Diphenyl-1, 2-di-p-tolyl-1H-imidazole; IR (KBr): 1595, 1508, 473, 1438 Cm^{-1} ;^{1} H-NMR (DMSO-d6) 2.32 (s, 2 CH3), 6.91–7.61 (m, 18H Ar) ppm.

Entry6;2-(3-Nitrophenyl)-4,5-diphenyl-1-p-tolyl-1H-imidazole; IR (KBr): 3428, 1599, 1497, 1412 Cm^{-1} ;^{1} H- NMR (DMSO-d6): 2.26 (s, CH3), 7.15–8.95 (m, 18H Ar) ppm.

Entry7;1-Benzyl-2-(3-chlorophenyl)-4,5-diphenyl-1H-imidazole; IR (KBr): 1599, 1497, 1412Cm^{-1} ;^{1} H- NMR (DMSO-d6) 5.16 (s, CH2), 6.76–7.69 (m, 19H Ar) ppm.

Table 4.
The synthesis of tetrasubstitured imidazoles using benzyl, primary amine, substituted aldehydes and ammonium acetate.

Entry	ArCHO	Primary Amine	Product	Yield(%)	mp (°C)	
					Found	Lit.
1				90	218-219	[219-220][33]
2				91	198-199	[196-198][33]
3				96	190-192	[187-189][33]
4				95	151-154	[155-157][33]
5				91	185-187	[188-191][33]
6				90	150-153	[149-151][39]
7				91	140-142	[144-146][33]

4. Conclusions

In this study, we reported a highly efficient MW assisted rapid and solvent-free synthesis of tri or tetra-substituted imidazoles in the presence of natural zeolite as an efficient reusable solid catalyst. In addition, MW chemistry is a green chemical method that improves reaction conditions and product yields, while reducing solvent amounts and reaction times. One-pot nature of the present procedure makes it an acceptable alternative to multistep approaches. It also simplified the laborious procedures and offers considerable advantages, such as: elimination of solvents, use of substances without any modification or activation, high yields, short reaction times, employment of reusable solid catalysts, and environmentally friendly character over the existing methodologies.

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