

One Pot Synthesis of Tetra-substituted Imidazole Derivatives by Condensation Reaction Using Zeolite H- ZSM 22 as a Heterogeneous Solid Acid Catalyst

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The present work deals with the synthesis of tetra substituted imidazoles using environmentally benign and green catalyst H-ZSM-22. The synthesized catalyst was characterized by FTIR (Fourier-transform infrared spectroscopy), XRD and the products by FTIR and ¹HNMR. H-ZSM-22 has been used as an efficient catalyst for an improved and rapid synthesis of 1,2,4,5 tetra substituted imidazoles derivatives using reactants: Benzil, Aldehydes, Amines and Ammonium acetate having excellent yield under solvent conditions. Different derivatives of aldehyde have been used in this reaction. For all the synthesized derivatives, ambient reaction time was found to be of 15-30 min. The main advantage of this reaction is small reaction time, high purity yield, easy work up and pollution free.

Keywords: H-ZSM-22; one-pot synthesis; multi-component reaction; tetra-substituted imidazoles.

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1. INTRODUCTION

Multicomponent reactions (MCRs) have been used widely in organic synthesis and medicinal chemistry due to their high synthetic efficiency and atom economy in the preparation of complex compounds from simple substrates [1]. The synthesis of highly substituted imidazoles is a very good application for MCRs. Tetra substituted imidazoles are important heterocycles in pharmaceutical and biochemical processes [2]. They possess fungicidal [3,4], analgesic [5], anti-inflammatory, [6], antibacterial [7] and antitumor activities [8]. In addition many members of this family act as selective inhibitors of P-38 mitogen activated protein (MAP) kinase [9,10], B-Raf kinase [11] and transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5) [12]. Imidazole derivatives are also useful as potential corrosion inhibitors for transition metals such as iron, copper, zinc and their alloys [13].

The prevalence of imidazoles in natural products and pharmacologically active compounds has instituted a diverse array of synthetic approaches to these heterocycles. There are several methods for the synthesis of highly substituted imidazoles. The mostly used methods in last decade are as follows: condensation of diones, aldehydes, primary amines and ammonia [14]; *N*-alkylation of trisubstituted imidazoles [15]; condensation of benzoin or benzoin acetate with aldehydes, primary amines and ammonia in the presence of copper acetate [16]; cyclization of sulfonamides with mesoionic 1,3-oxazolium-5-olates [17]; four-component condensations of diones, aldehydes, primary amines, and ammonium acetate in HOAc under reflux conditions [18]; condensation of carbonyl-*N*-acyl-Nalkylamines with ammonium acetate in refluxing HOAc [19]; conversion of *N*-(2-oxo) amides with ammonium trifluoroacetate under neutral conditions [20].

Here we have presented a novel, and efficient method for the synthesis of 1,2,4,5 tetra substituted imidazoles using H-ZSM-22 as catalyst.

2. EXPERIMENTAL

2.1 Synthesis of Catalyst H- ZSM-22

A typical procedure for the synthesis of ZSM-22 is shown below:

Starting materials of SiO₂ and Al₂O₃ at a ratio of 90: 1 were taken in a 100 ml beaker, 1.0 g of

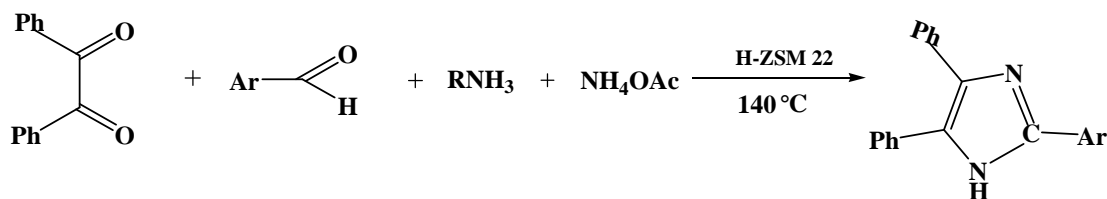
KOH was dissolved in 4.55 g of deionized water to which an aqueous solution of 0.44 g Al₂(SO₄)₃·16H₂O prepared in 4.55 g of deionized water was added, resulting in a clear solution upon thorough mixing. Among the various structure-directing agents (SDAs) that have been used for the synthesis of TON-type Zeolites, 1, 8-diaminooctane was used as the SDA in the present study. Separately, 2.6 g of 1, 8-diaminooctane was dissolved in 18.2 g of deionized water and added into the beaker under constant stirring using a magnetic stirrer. The mixture was then stirred for 30 min further to obtain a clear solution. Colloidal silica (30 wt% SiO₂; Sigma-Aldrich) was used as a silica source. 11.9 g of the colloidal silica mixed with 6.74 g of deionized water was also added under stirring. The final reaction mixture was stirred for 90 min to form a gel; the gel was then kept in a polypropylene bottle for 24 hrs for aging. After aging, the synthesized gel was kept in a Teflon lined autoclave for 2 to 3 days at 160°C for crystallization. The solid phase was then separated by filtration, washed with deionized water, and dried for 12 hrs in an oven at 353 K. The Na- ZSM-22 Zeolite was then converted into H- form by the following procedure:

9.0 of Na-ZSM-22 g, 7.23 g of NH₄Cl and 13.80 ml of deionized water were mixed with 0.1 M HCl solution (5 ml) to reach pH 4. The mixture was stirred at 60°C for 6 hrs. Then the material was filtered under suction and washed with deionized water. After the removal of chloride, the resulting material NH₄⁺-Zeolite was placed in an oven at 60°C for 24 hrs. The ammonium form of Zeolite was converted into H-form by calcination over 60 minutes at 500°C.

2.2 Synthesis of Tetra-Substituted Imidazoles Using ZSM-22 in Refluxing Ethanol

2.2.1 General procedure

A mixture of Benzil (1 mmol), Amine (1 mmol), Aldehyde (1 mmol), Ammonium acetate (5 mmol), and H-ZSM-22 (0.08 g) in ethanol (5 ml) were taken in a 100 ml conical flask and heated on an oil bath (liquid paraffin) at 140°. The progress of the reaction was monitored by TLC (Ethyl acetate, n-hexane 1:3). After completion of reaction, the reaction mixture was cooled at room temperature. The crude product thus obtained was dissolved in ethanol to separate the catalyst by filtration. The solid product was then recrystallized from ethanol.



Synthesis of tetra-substituted imidazoles

2.3 Characterization (Techniques)

Instruments

2.3.1 X-Ray diffraction (XRD)

For x-ray diffraction, the samples were sieved in an ABNT n^o (0.074 nm) sieve and then Placed in an aluminum sample holder for X-ray diffraction analysis using Shimadzu XRD 6000 equipment. The operational details of the technique were set as follows: Copper K α radiation at 40KV/30 ma, with a goniometer speed of 20/min and a step of 0.020 in the 2 θ range scanning from 0 $^{\circ}$ to 60 $^{\circ}$. The only d- spacing of interest in X-ray patterns were the basal spacing's along c axis.

2.3.2 Fourier-transform infrared (FT-IR) spectroscopy

ZSM-22 sample was submitted to physical treatment in accordance with the KBr method, which consists of mixing 0.007 g of the sample and 0.1 g of KBr, grinding and pressing the solid mixture to 5 ton for 30 s in order to form a pastille that allows the passage of light. Characterization was performed using an infrared spectrophotometer SHIMADZU FT-IR in the wavelength ranges from 3000 to 400 cm⁻¹, with increments of 500 cm⁻¹. Characterization of the products was performed on SHIMADZU FT-IR spectrometer, and the sample was prepared with KBr and pressed into wafer/pellet. Spectra were collected in the range of 500–4000 cm⁻¹. NMR of the products was performed on BRUKER ADVANCE II 400 NMR spectrometer.

2.3.3 Spectral data of tetra substituted imidazole derivatives

Entry 1: 1, 2, 4, 5-Tetraphenyl-1H-imidazole (C₂₇H₂₀N₂) White powder; m.p. 210–215 $^{\circ}$ C FT-IR (KBr): ν_{max} (in Cm⁻¹) 3058 (C-H aromatic), 1589 (C=C aromatic), 1448 (C=N) 1H NMR (400 MHz, CDCl₃): δ (ppm) 7.11–7.58 (m, 20H, H-Ar) (Figs. 3-4)

Entry 2: 2-(4-Chlorophenyl)-1, 4, 5-triphenyl-1H-imidazole (C₂₇H₁₉ClN₂): Cream crystal; m.p. 151-156 $^{\circ}$ C; FT-IR (KBr): ν_{max} (in Cm⁻¹) 3050 (C-H

aromatic), 1589 (C=C aromatic), 1448 (C=N) 1065 (C-Cl) 1H NMR (400 MHz, CDCl₃): δ (ppm) 7.15–7.37 (m, 17H, H-Ar), 7.5 (d, 2H, H-Ar) (Figs. 5-6)

Entry 3: 2-(4-Nitrophenyl)-1,4,5-triphenyl-1H-imidazole (C₂₇H₁₉NO₂N₂): m.p. 185-190 $^{\circ}$ C; FT-IR (KBr): ν_{max} (in Cm⁻¹) 3058 (C-H aromatic), 1591 (C=C aromatic), 1515 (C=N) 1338 (C-NO₂) 1H NMR (400 MHz, CDCl₃): δ (ppm) 6.6-7.8 (m, 17H, H-Ar), 8.2 (d, 2H, H-Ar) (Figs. 7-8)

Entry 4: 2-(4-Hydroxyphenyl)-1, 4, 5-triphenyl-1H-imidazole (C₂₇H₁₉OHN₂): m.p. 278-280 $^{\circ}$ C FT-IR (KBr): ν_{max} (in Cm⁻¹) 3006 (C-H aromatic), 1577 (C=C aromatic), 1442 (C=N) 1085 (C-OH) 1H NMR (400 MHz, CDCl₃): δ (ppm) 6.5-7.8 (m, 17H, H-Ar), 7.9 (d, 2H, H-Ar) (Figs. 9-10).

3. RESULTS AND DISCUSSION

3.1 Characterization of Zeolites and Products

The x-ray diffraction patterns of H-ZSM-22 are shown in Fig. 1. The XRD analysis shows that the synthesized materials are crystalline in nature. Further it was found that in diffraction signals, the sharp peak value (2 θ) for H-ZSM-22 is 23.6 are already reported [21]. FT-IR spectrum of H-ZSM-22 is shown in Fig 2. In FT-IR analysis H-form of ZSM-22 shows absorption band at 450cm⁻¹ which corresponds due to Si, Al-O bond and those at around 1000 and 790 cm⁻¹ where respectively due to asymmetric and symmetric stretches of the Zeolite framework.

Our main point is to consider the synthesis of tetra-substituted imidazole derivatives. The reaction was carried out by using H-Form of ZSM-22 through a condensation reaction between benzil, aldehydes, amines and ammonium acetate using ethanol as solvent at 140 $^{\circ}$ C and the products are shown in Table 1. The catalyst was found to be highly selective resulting 87% isolating yield of tetra substituted imidazole derivative. It was found that without catalyst the reaction could not occur, thus catalyst plays an important role in

this reaction and dictates the activity of the catalyst. The synthesis of tetra-substituted imidazole derivatives was carried out by using different amounts of H-Form of Zeolite ZSM-22 at temperature 140°C which occurs at a reaction time of 30 minutes and the results are shown in Table 2. It was noticed that the yield increases from 56% - 87% with increase in the weight of the catalyst from 20 to

80 mg respectively. The product yield remains constant with further increase in the amount of catalyst. For the rest of the studies we used the weight of catalyst as 80 mg. Also, it was noticed that with further increasing the amount of catalyst, there is increase in the yield of product, but there is no effect on the reaction time which remains same for all the cases as shown in Table 2.

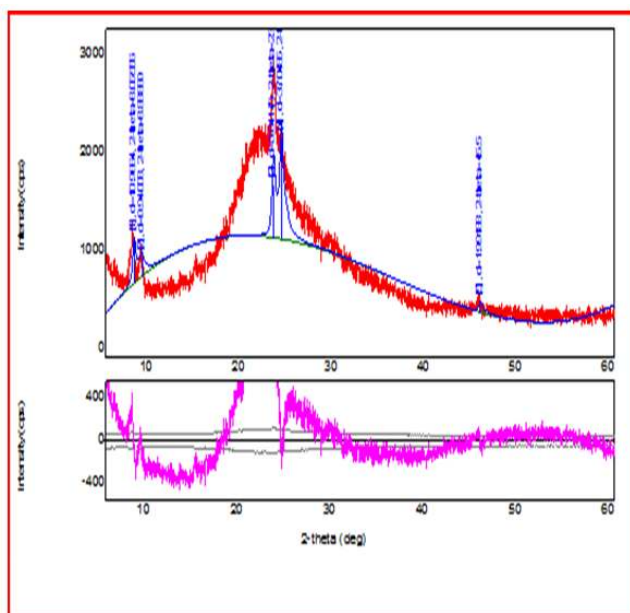


Fig. 1. XRD spectrum of H-ZSM-22

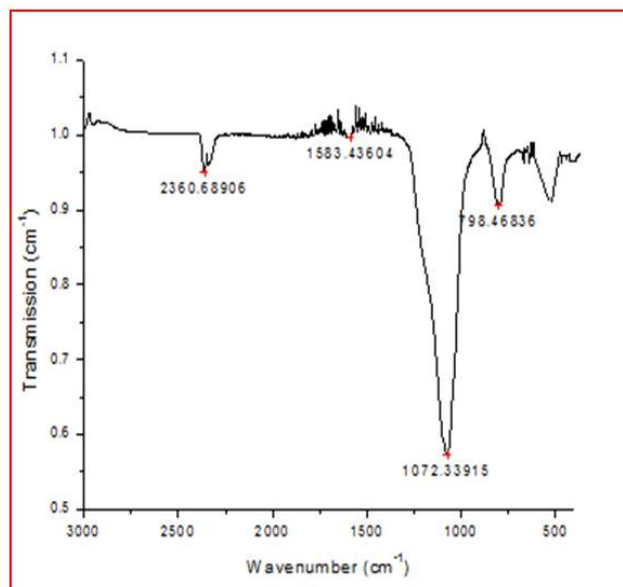
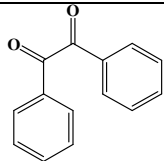
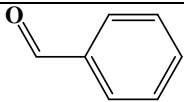
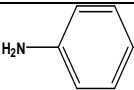
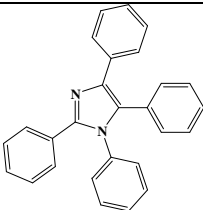
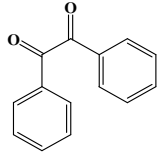
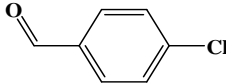
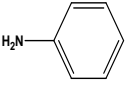
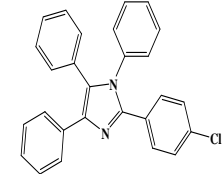
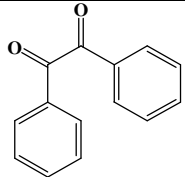
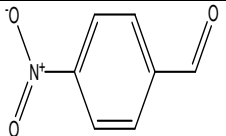
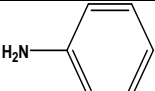
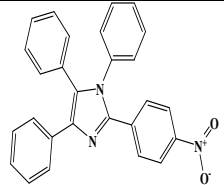
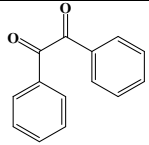
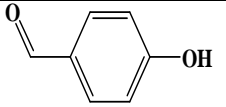
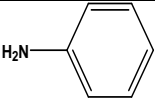
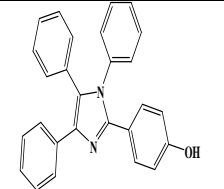


Fig. 2. FTIR spectrum of H-ZSM-22

Table 1. Synthesis of tetra substituted imidazole derivatives using H-ZSM-22 through a condensation reaction between Benzil, Aldehyde, Amine and Ammonium acetate

Entry	Benzil	Aldehyde	Amine	Ammonium acetate	Product	Time min	Yield %
1.	 benzil	 benzaldehyde		NH4OAc	 1,2,4,5-tetra-phenyl-1H-imidazole	30	81
2.	 benzil	 p-chloro benzaldehyde		NH4OAc	 2-(4-chlorophenyl)-1,4,5-triphenyl-1H-imidazole	15	86
3.	 benzil	 p-nitrobenzaldehyde		NH4OAc	 2-(4-nitrophenyl)-1,4,5-triphenyl-1H-imidazole	17	87
4.	 benzil	 p-hydroxy benzaldehyde		NH4OAc	 2-(4-hydroxyphenyl)-1,4,5-triphenyl-1H-imidazole	20	76

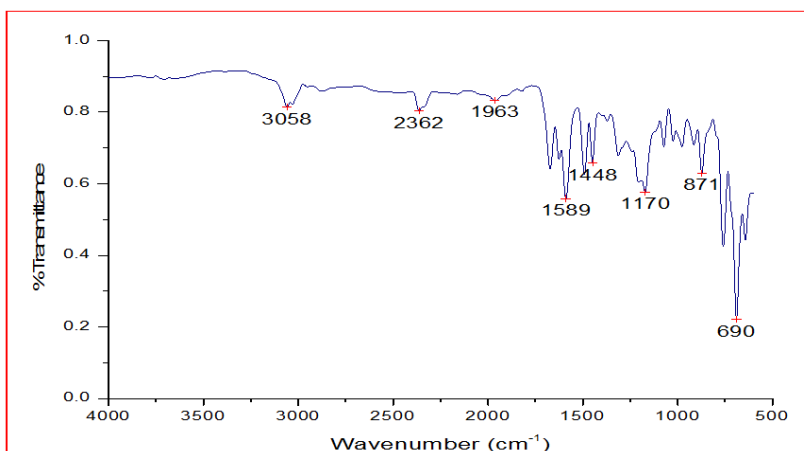


Fig. 3. FTIR spectrum of 1, 2, 4, 5-Tetra Phenyl 1H-Imidazole

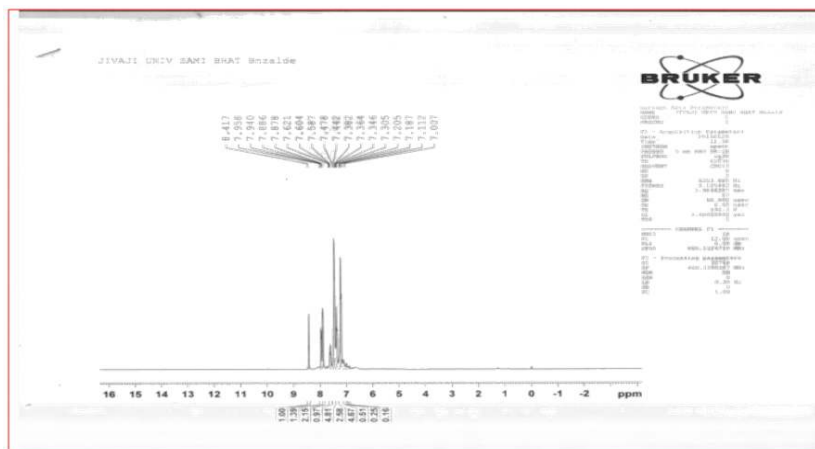


Fig. 4. 1H-NMR spectrum of 1, 2, 4, 5 -Tetraphenyl-1H-imidazole

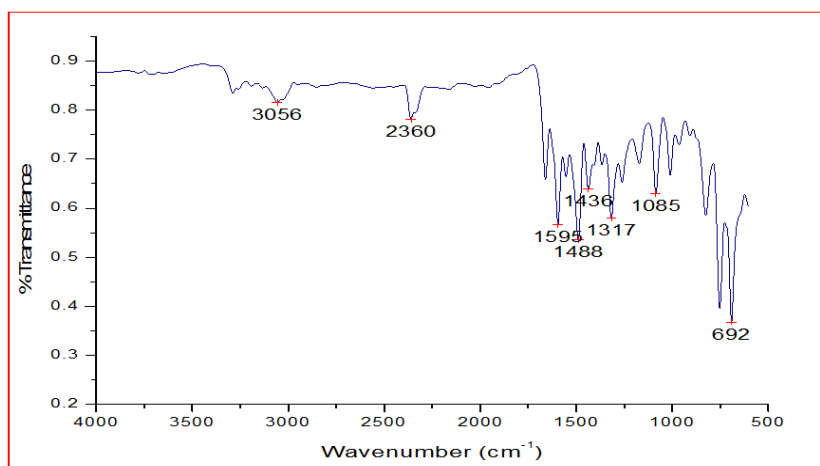


Fig. 5. FTIR spectrum of 2-(4-chlorophenyl) 1, 4, 5-triphenyl -1H-imidazole

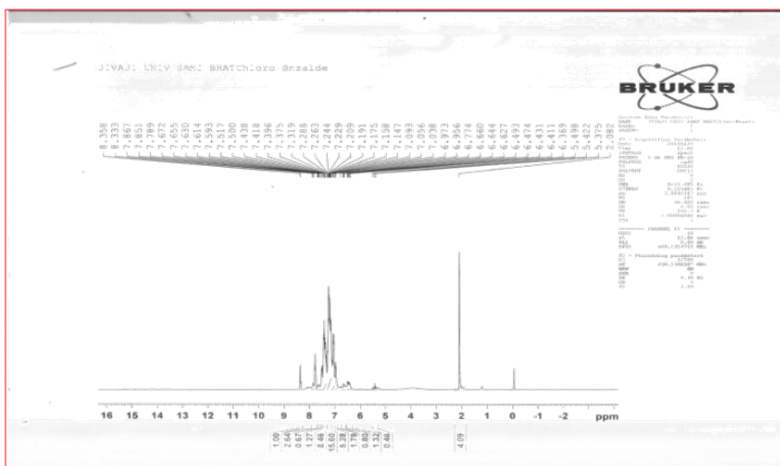


Fig. 6. 1H-NMR spectrum of 2-(4-chlorophenyl) 1, 4, 5-triphenyl imidazole

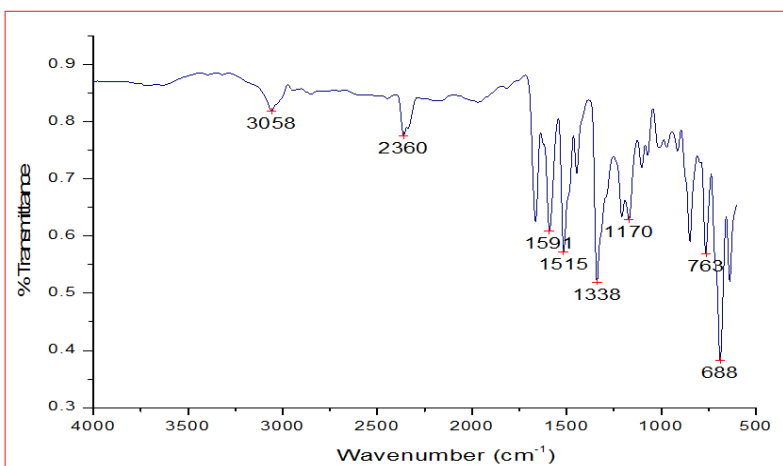


Fig. 7. FTIR spectrum of 2-(4-nitrophenyl) 1, 4, 5-triphenyl 1H- imidazole

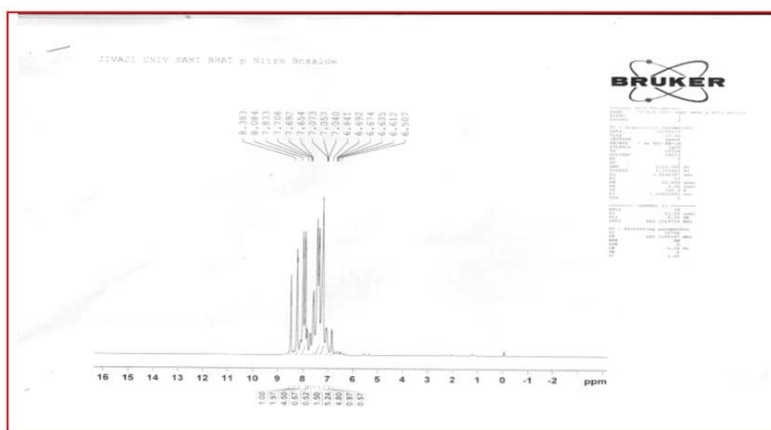


Fig. 8. 1H-NMR spectrum of 2-(4-nitrophenyl) 1, 4, 5-triphenyl 1H- imidazole

The use of smaller amounts of catalyst gave a low yield and the much more amount could not enhance the yield of the product. The result and catalytic efficiency of H- ZSM-22 for the synthesis of tetra-substituted imidazoles using various derivatives of Aldehydes, Benzil, Amines and Ammonium acetate are shown in Table 1. In all these cases the reactions are highly efficient and completed within 20-30 minutes. The catalyst shows a good performance in all these cases and the product yield of various derivatives of tetra-substituted imidazoles are 76% - 87%. The product yield of tetra-substituted imidazole derivatives depends on the nature of the functional group on the aromatic ring of the aldehyde. Aldehydes with electron-withdrawing groups afford more pure products compared with electron-donor groups. In all these cases the reaction work is very simple and easy. The catalyst was recycled using ethanol as solvent which was evaporated. The efficiency of the recovered catalyst was verified by the reaction of Aldehydes, Benzil, Amine and Ammonium acetate and was found between 79-87% as shown in Table 3. The efficiency of the recovered catalyst decreased after three reaction cycles due to the loss of catalyst or catalyst structure

during recovering process. The efficiency of various catalysts in the synthesis of imidazole derivatives has been compared in Table 4.

Table 2. Effect of weight of H-ZSM-22 on the synthesis of tetra substituted imidazole derivatives

Weight of catalyst mg	Reaction time min	Yield %
20	30	56
40	30	62
60	30	68
80	30	87

Reaction conditions: Substrate: Benzil, Aldehydes, Amines and Ammonium acetate, reaction temperature: 140°C, solvent: ethanol

Table 3. Effect of catalyst recycling on percentage yield of tetra substituted imidazole derivative

Runs	% Yield
1 st run	87
2 nd run	86.4
3 rd run	83.3
4 th run	79.6

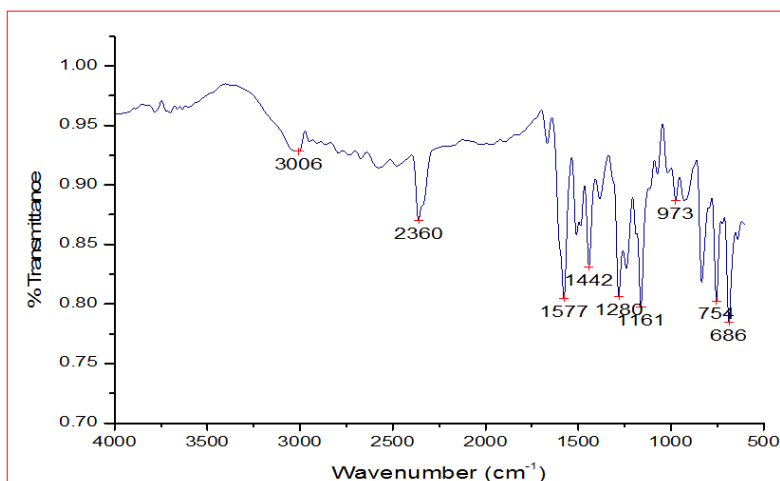


Fig. 9. FTIR spectrum of 2-(4-Hydroxyphenyl) 1, 4, 5-triphenyl 1H- imidazole

Table 4. The efficiency comparison of various catalysts in the synthesis of tetra substituted imidazoles

Entry	Catalyst	Solvent	Condition	Yield	Time(h)	Ref.
1	BF ₃ .SiO ₃	-	140°C	80-96	2	22
2	MCM-41	-	140°C	74-82	1.92-2.25	23
3	MCM-41	AcOH	140°C	75-85	23-35 min	23
4	P-TsOH	EtOH	Reflux	73-83	13-23 min	23
5	ZSM-22	EtOH	140°C	76-87	15-30 min	This work

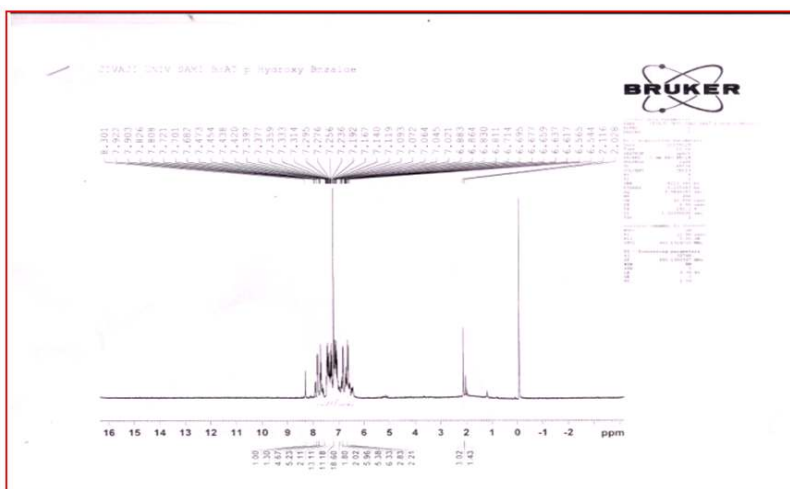


Fig. 10. ¹H-NMR spectrum of 2-(4-Hydroxyphenyl) 1,4,5-triphenyl 1H-imidazole

4. CONCLUSION

H-ZSM-22 has been introduced as an efficient catalyst for the synthesis of tetra-substituted imidazoles. This catalyst provides an alternate way for the above synthesis in terms of small reaction time, better product yield, minimum waste production, reusability of the catalyst as compared to other catalysts. In conclusion, we have demonstrated a simple method for the synthesis of tetra-substituted imidazoles using H-ZSM-22 as an eco-friendly, inexpensive and efficient catalyst.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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