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Nano Copper Ferrite Catalyzed Sonochemical, One-Pot Three and Four Component Synthesis of Poly Substituted Imidazoles

Paul D. Sanasi*, Ravi K. Majji, Swathi Bandaru, Satyanarayana Bassa, Surekha Pinninti, Sruthi Vasamsetty, Raghu B. Korupolu

Department of Engineering Chemistry, A. U. College of Engineering (A), Andhra University, Visakhapatnam, India
Email: *pauldouglas12@gmail.com

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Abstract

A simple, multi component, one-pot method has been reported for the synthesis of poly substituted imidazoles in presence of magnetically separable and recyclable spinel nano copper ferrite as heterogeneous catalyst by the cyclo-condensation of benzil, aromatic aldehyde, ammonium acetate and substituted amines under ultrasonic irradiation. This method of preparation has many advantages compared to those methods which are previously reported in the literature. This methodology offers simple experimental procedure, milder reaction conditions and environmentally benign approach.

Keywords

Multi Component Reaction, One-Pot Synthesis, Nano Copper Ferrite Catalyst, Poly Substituted Imidazoles, Ultrasonic Irradiation

1. Introduction

One-pot, multi component reactions (MCRs) have significant importance due to formation of a single product with high yields by the combination of two or more components in a single step process [1] [2]. This method is a convenient and great technique for the preparation of some biologically and medicinally active pharmaceutical

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*Corresponding author.

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ingredients.

Imidazole derivatives are very interesting class of Nitrogen containing 5-membered heterocyclic compounds. Because of their wide range of pharmacological importance and significant role in biochemical processes [3] [4], the Biological importance of the poly substituted imidazole ring system has made it a common structure in numerous synthetic compounds, such as fungicides [5], herbicides [5], therapeutic agents [6] and plant-growth regulators [7]. This core also has been utilized in diverse pharmaceutical applications such as anti-inflammatory [8], anti-thrombotic [9] and antitumor [10] agents. Due to their great biological importance of poly substituted imidazole framework, the synthesis of Poly substituted imidazoles has attracted much attention in organic synthesis.

Owing to their enormous collection of pharmacological and biological activities many synthetic strategies has been developed for synthesis of substituted imidazoles such as the hetero-cope rearrangement [11], four component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on wangresin [12] and three component condensation of α-azido chalcones, aromatic aldehyde and substituted aniline in presence of Erbiumtriflate [13]. Later on a first, simple and convenient synthetic methodology has been reported by Radziszewski and japp for the synthesis of 2,4,5-tri phenyl imidazoles by using 1,2 dicarbonyl compounds, ammonia, various aldehydes [14]. Afterward several methods have been reported for the synthesis of tri-substituted imidazoles by cyclo condensation of 1,2 dicarbonyl compounds, various aromatic aldehydes and ammonium acetate using various catalysts such as $NiCl_2 \cdot 6H_2O/Al_2O_3$ [15], MoO_3/SiO_2 [16], Polymer supported zinc chloride [17], trichloro isocyanuric acid (TCCA) [18] under reflux conditions and glyoxalic acid as catalyst under microwave conditions [19] and Zinc (II) (tetra (4-methylphenyl)) porphyrin [20], Magnetic Fe_3O_4 nano particles [21], Sulfamic acid functionalized magnetic nano particles SA-MNP [22], Ionic liquid (EMIM)OAc [23], $Zr(acac)_4$ [24], ceric ammonium nitrate [25] as catalysts under ultra sound assisted conditions. In the same way several methods have been reported for the synthesis of tetra substituted imidazoles by cyclo condensation of 1,2 dicarbonyl compounds, various aromatic aldehydes, ammonium acetate and aromatic/aliphatic amines using various catalysts such as nano $TiCl_4 \cdot SiO_2$ [26], $FeCl_3 \cdot 6H_2O$ [27], $BF_3 \cdot SiO_2$ [28], $HClO_4$-SiO_2 [29], Keggin type heteropoly acid $H_4[PMo_{11}VO_{40}]$ [30] under reflux conditions and Potassium dodecatugstocobaltate trihydrate ($K_5CoW_{12}O_{40} \cdot 3H_2O$) [31], zeolite HY and silica gel [32] as catalyst under microwave conditions and nano crystalline $MgAl_2O_4$ [33] as catalyst under Ultra sound irradiation. In extension with these procedures, several methods have been reported for the synthesis of both tri and tetra substituted imidazoels using various catalysts such as molecular Iodine [34], Sodium dihydrogen phosphate [35], $BiCl_3$ [36], DABCO [37], Sulfonic acid functionalized SBA-15 nanoporous material [SBA-Pr-SO_3H] [38], L-proline [39], nano crystalline sulphated zirconia [40], $InCl_3 \cdot 3H_2O$ [41] under reflux conditions and Well-Dawson heteropolyacid ($H_6P_2W_{18}O_{62} \cdot 24H_2O$) supported on silica [42] under microwave conditions.

According to the literature survey, several synthetic protocols have been reported for the synthesis of substituted imidazoles using various type of copper containing catalyst such as synthesis of imidazoles through the Cu_2O catalyzed cross-cycloaddition between two different isocyanides [43], Synthesis of 1,2,4-trisubstituted imidazoles through the $CuCl_2$-catalyzed oxidative diamination of terminal alkynes by amidines [44], Synthesis of multi substituted imidazoles via CuI-catalyzed [3 + 2] cycloadditions [45]. The above reported methods have its own importance and merits, however most of these methods require harmful catalysts, and difficult work-up and effluent pollution. Therefore, development of environmentally benign, green procedure for preparation of poly substituted imidazoles is highly desirable.

Due to the effective activity of magnetically separable copper based nano particles [46], several organic transformations [47] are carried out with these particles and reported earlier in the literature. Along with these, nano copper ferrite has earlier been used as magnetically separable catalyst for several organic synthetic reactions such as asymmetric hydrosilylation of Ketones [48], synthesis of diaryl or aryl akyl sulfides via cross coupling process under ligand free conditions [49], synthesis of substituted benzoxazoles via Ullmann-type coupling under ligand free conditions [50], Cross-coupling of aryl halides with diphenyl diselenide [51], green one-pot three component synthesis of spirooxindoles [52], multicomponent synthesis of 1,4-di substituted 1,2,3-triazoles in tap water [53].

Ultrasound-Assisted organic synthesis (UAOS) has been increasingly developed by researchers across the globe for the synthesis of organic molecules since last three decades. Ultrasound irradiation offers an alternative energy source for organic reactions which are ordinarily accomplished by heating. The salient features of Ultrasonic irradiation are enhanced reaction rates, formation of purer products, easier manipulation, energy conservation, waste minimization and this technique is more convenient to taking green chemistry concepts into an account [54] [55].

Ultrasound-assisted reactions proceed by the formation, growth and collapse of acoustic bubbles in the reaction medium. These directly help in shortening the time span of reactions and increasing the yield of products [56]. Moreover a large number of reactions can be carried out in shorter reaction time, higher yield through milder reaction conditions under Ultra sound Irradiation [57]-[59]. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivity [60].

As a part of our ongoing research towards the synthesis of biologically active heterocyclic compounds using magnetically separable nano catalysts, keeping environmental friendly methods in mind, here we report an efficient and simple work-up method for the synthesis of poly substituted imidazoles using magnetic separable nano copper ferrite as heterogeneous catalyst under ultrasonic irradiation.

2. Experimental

2.1. Chemicals and Apparatus

All chemicals are purchased from commercial sources and liquid aromatic aldehydes and liquid aromatic amines are purified by distillation prior to use. Melting points of the products were recorded on an electrochemical apparatus and they were compared with literature values. ^{1}HNMR and ^{13}CNMR spectral data were performed on the Bruker-Avance 400 MHz and 100 MHz spectrometers respectively in DMSO-d_6/$CDCl_3$. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. IR Spectra were recorded in KBr disks with a Bruker α-FTIR Spectrometer. The mass spectrum was recorded using a Perkin-Elmer PE SCIEX-API 2000, equipped with ESI source used online with a HPLC system after the ultraviolet (UV) detector.

Ultrasonication was performed in a Rivotek ultrasonic cleaner with Transducer PZT crystals (Morgan Matrac, UK make) bonded on the base of the tank with welbond technique (frequency of 40 kHz and an output power of 250 W). The Flask containing the reaction mixture was located in the maximum energy area in the water bath where the surface of the reactants (reaction vessel) is slightly lower than the level of the water and the addition and removal of water controlled the temperature of the water bath.

2.2. Catalyst Preparation

The spinel nano copper ferrite has been synthesized by citrate sol-gel precursor method as reported earlier by us [46].

2.3. Catalyst Characterization

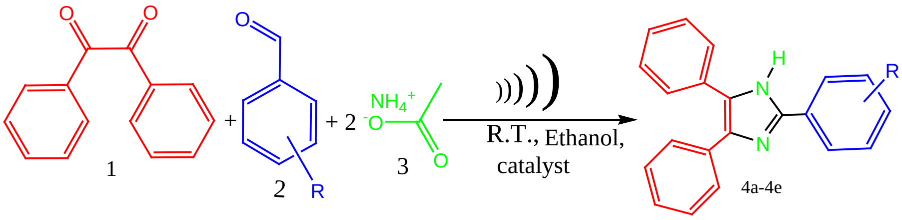
The catalyst has been characterized using FTIR, SEM, TEM, XRD and particle size analyzer as reported earlier [46].

2.4. General Procedure for the Synthesis of 2,4,5-Tri Substituted Imidazoles

Benzil (10 mmol), aromatic aldehyde (10 mmol), ammonium acetate (20 mmol) and Copper ferrite (2 mmol) were taken in a flask and the contents are dissolved in 5 mL of ethanol. Then the reaction mixture was sonicated at room temperature for prescribed time (**Scheme 1**). The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate 4:1). After completion of the reaction the catalyst was separated from the reaction mixture by using an external magnet and then the reaction mixture was concentrated in a rotary evaporator to remove the solvent. Then the dried product was recrystallised from hot ethanol for several times to get the corresponding pure product. The products were confirmed by IR, NMR, Mass spectra and by melting points.

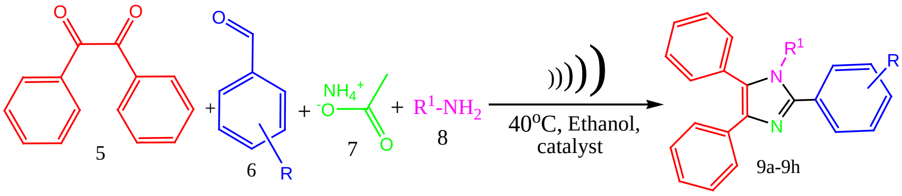
2.5. General Procedure for the Synthesis of 1,2,4,5-Tetra Substituted Imidazoles

Benzil (10 mmol), aromatic aldehyde (10 mmol), ammonium acetate (10 mmol), aromatic amine (10 mmol) and Copper ferrite (2 mmol) were taken in a flask and the contents are dissolved in 5 mL of ethanol. Then the reaction mixture was sonicated at 40˚C for prescribed time (**Scheme 2**). The progress of the reaction was monitored by TLC (n-hexane: ethyl acetate 4:1). After completion of the reaction the catalyst was separated from the reaction mixture by using an external magnet and then the reaction mixture was concentrated in Rotavapour to removal of the solvent. Then the dried product was recrystallised from hot ethanol for several times to get the corresponding pure product. The products were confirmed by IR, NMR, Mass spectra and by melting points.



R= a) m-Br, b) p-F, c) m-$NO_{2,}$ d) p-$NO_{2,}$ e) p-CH_3

Scheme 1. A generalized scheme for synthesis of 2,4,5-tri substituted imidazoles in presence of copper nano ferrite by cyclocondensation of benzil, aromatic aldehyde and ammonium acetate under ultra sound irradiation.

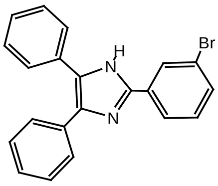
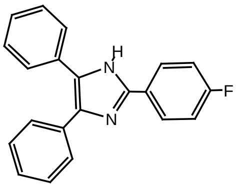
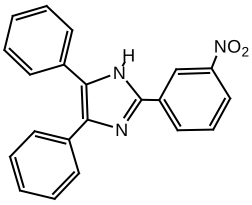


a) R= H, R^1= C_6H_5 b) R= p-OCH_3, R^1= $C_6H_{5,}$ c) R= H, R^1= C_6H_5-CH_2
d) R= p-$OCH_{3,}$ R^1= C_6H_5-CH_2 e) R= p-$CH_{3,}$ R^1= C_6H_5-CH_2 f) R=p-Cl, R^1=C_6H_5-CH_2
g) R=p-Cl, R^1=cyclohexyl h) R=p-CH_3, R^1=cyclohexyl

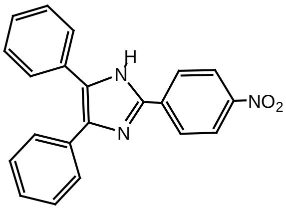
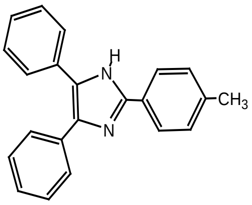
Scheme 2. A generalized scheme for synthesis of 1,2,4,5-tetra substituted imidazoles in presence of catalyst by cyclo condensation of benzil, aromatic aldehyde, ammonium acetate and substituted amine under ultra sonic irradiation.

2.6. Spectra Data

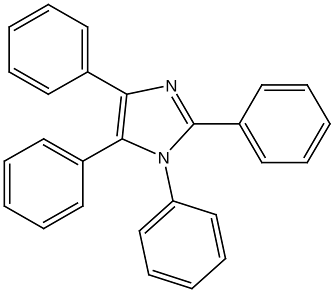
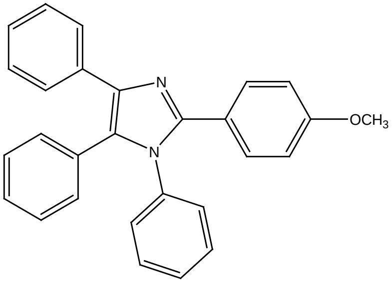
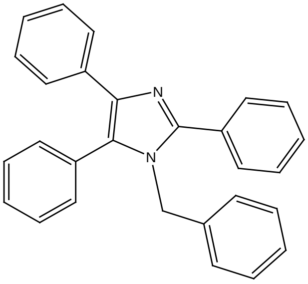
2.6.1. Spectral Data for 2,4,5-Tri Substituted Imidazoles

Compound	Spectral data
2-(3-Bromo phenyl)-4,5,diphenyl-1-H Imidazole: (4a) 	M.P. 300˚C - 302˚C; ^{1}HNMR (Bruker) (400 MHz, $CDCl_3$/DMSO-d_6): δ = 7.22 - 7.48 (m, 10H), 7.65 (s, 1H), 7.42 (d, 1H), 7.39 (d, 1H), 7.21 (t, 1H); ^{13}CNMR (100 MHz, $CDCl_3$/DMSO-d_6); δ = 123.6, 126.5, 127.5, 128.8, 129.3, 132.9, 147. 6 ppm; FTIR (KBr, cm^{-1}); 3432 (N-H), 1600 (C=C), 1482 (C=N), 729 (C-Br): NCMS (*m/z*) (M^+ + 1) 367
2-(4-Flouro phenyl)-4,5,diphenyl-1-H Imidazole: (4b) 	M.P.188˚C - 190˚C; ^{1}HNMR (Bruker) (400 MHz $CDCl_3$/DMSO-d_6): δ = 7.22 - 7.48(m, 10H), 7.46 - 7.42 (d, J = 8.0 Hz, 2H), 7.03 - 6.71 (d, J = 8.6 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$/DMSO-d_6); δ = 126.3, 127.5, 128.9, 129.1, 129.3, 162.9, 133.1 ppm; FTIR(KBr, cm^{-1}); 3432 (N-H), 1600 (C=C), 1482 (C=N), 692 (C-F): NCMS (*m/z*) 315 (M^+ + 1)
2-(3-Nitro phenyl)-4,5,diphenyl-1-H Imidazole: (4c) 	M.P: 300˚C. FTIR (KBr, cm^{-1}): 3448, 3068, 1526, 1350; ^{1}HNMR (Bruker) (400 MHz, $CDCl_3$/DMSO-d_6): δ = 13.10 (s, 1H), 8.95 (s, 1H), 8.53 (d, J1/4 7.5 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.81 (d, J1/4 7.8 Hz, 1H),7.54 - 7.33 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ = 148.4, 143.4, 131.8, 131.2, 130.4, 128.7, 128.4,127.1, 122.6, 119.4; NCMS (*m/z*): 342.3 (M^+ + 1)

Continued

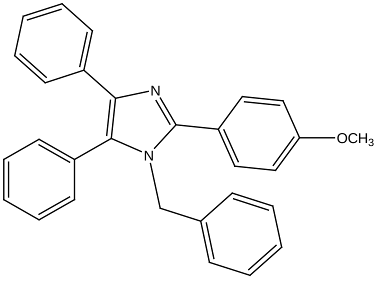
2-(4-Nitro phenyl)-4,5,diphenyl-1-H Imidazole: (4d)  	M.P: 199˚C - 201˚C. FTIR (KBr, cm^{-1}): 3402, 2928, 1598, 1519, 1346, 856; ^{1}H NMR (Bruker) (400 MHz, CDCl$_3$/DMSO-d$_6$): δ = 12.81 (s, 1H), 8.01 - 7.42 (m, 14H); ^{13}C NMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 148.9, 143.7, 131.6, 130.6, 129.7, 128.4, 127.8, 127.4, 126.9, 126.1, 125.4, 124.3, 122.2, 118.5; NCMS (*m/z*): 342.2 (M^{+} + 1).
2-(4-Methyl phenyl)-4,5,diphenyl-1-H Imidazole: (4e)  	M.P: 184˚C - 186˚C. FTIR (KBr, cm^{-1}): 3450 (N-H), 1600 (C=C), 1585 (C=N). ^{1}HNMR (Bruker) (400 MHz, CDCl$_3$/DMSO-d$_6$): 2.30 (s, CH$_3$), 7.10 - 7.60 (m, 10H), 7.70 (d, 2H, J = 10 Hz), 7.30 (d, 2H, J = 10 Hz). ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$), 55.7, 113.4, 122.6, 126.3, 126.6, 128.0, 128.3, 133.4, 145.7, 159.6 ppm: NCMS (*m/z*):311 (M + 1)

2.6.2. Spectral Data for 2,4,5-Tri Substituted Imidazoles

Compound	Spectral data
1,2,4,5 tetra phenyl imidazole (9a)  	M.P: 214˚C - 216˚C: FTIR(KBr) (cm^{-1}): 3055 (C-Haromatic), 1599 (C=Caromatic), 1496 (C=N); ^{1}HNMR(Bruker) (400 MHz, CDCl$_3$/DMSO-d$_6$): 7.16 - 7.49 (m, 20H) ppm; ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$): 128.70, 128.63, 130.05, 130.85, 131.02, 31.55, 132.53, 132.67, 132.92, 133.87, 134.26, 134.81, 135.41, 136.23, 137.11, 138.40, 139.54 ppm; NCMS (*m/z*): 373 (M + 1)
2-(4-methoxy phenyl), 1,4,5 tri phenyl imidazole (9b)  	M.P: 254˚C - 256˚C: FTIR (KBr) (cm^{-1}): 3058 (C-H aromatic), 1601 (C=C aromatic), 1505 (C=N), 1065 (C-O-Ar): ^{1}HNMR (400 MHz, CDCl$_3$/DMSO-d$_6$): 3.24 (s, 3H, CH$_3$), 6.83 (d, J = 7.4 Hz, 2H), 7.23 - 7.41 (m, 15H,), 7.47 (d, J = 7.4 Hz, 2H, H-Ar) ppm; ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 55.57, 114.07, 123.30, 126.83, 128.60, 128.77, 128.89, 129.12, 129.16, 129.24, 130.12, 131.10, 131.29, 131.59, 135.0, 137.07, 137.27, 146.49, 160.0 ppm; NCMS (*m/z*): 403 (M + 1)
1-(benzyl) 2,4,5 tri phenyl imidazole (9c)  	M.P: 166˚C - 168˚C: FTIR (KBr, (cm^{-1}): 3056 (C-H aromatic), 2926, 1600 (C=C aromatic); ^{1}H NMR (400 MHz, CDCl$_3$/DMSO-d$_6$): δ = 7.65 - 7.55 (m, 4H), 7.38 - 7.13 (m, 14H), 6.80 (d, J1/4 7.5 Hz, 2H), 5.11 (s, 2H); ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 148.1, 137.9, 137.3, 134.1, 132.7, 131.0, 130.8, 130.5, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 127.3, 126.9, 126.4, 126.0, 48.2; NCMS (*m/z*): 387.2 (M + 1);

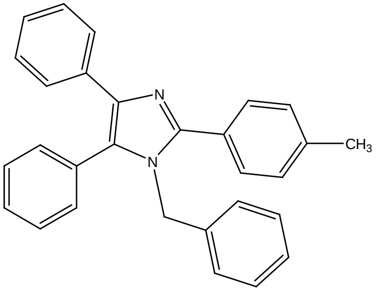
Continued

1-(benzyl), 2(4-methoxy phenyl), 4,5 di phenyl imidazole (9d)



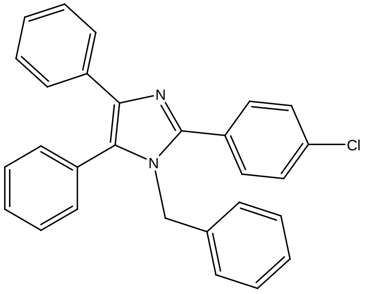
M.P: 158˚C - 160˚C: FTIR (KBr, (cm^{-1}) : 3047 (C-H aromatic), 1604 (C=C aromatic); ^{1}HNMR (400 MHz, CDCl$_3$/DMSO-d$_6$): d 7.58 (d, J1/4 7.8 Hz, 4H), 7.31 - 7.12 (m, 11H), 6.92 - 6.80 (m, 4H), 5.08 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 159.9, 147.9, 137.6, 134.5, 131.0, 130.9, 130.3, 129.7, 129.0, 128.7, 128.5, 127.9, 127.2, 126.7, 126.2, 125.9, 123.3, 113.9, 55.2, 48.1; NCMS (*m/z*): 417.3 (M + 1)

1-(benzyl), 2(4-methyl phenyl), 4,5 di phenyl imidazole (9e)



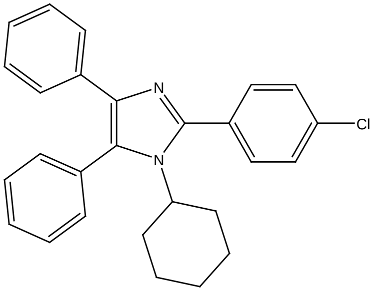
M.P: 168˚C - 170˚C: FTIR (KBr) (cm^{-1}): 3020 (C-H aromatic), 1600 (C=C aromatic), 1484 (C=N), 1448.
^{1}H NMR (400 MHz, CDCl$_3$/DMSO-d$_6$): δ = 2.36 (s, 3H, CH$_3$), 5.09 (s, 2H, CH$_2$), 6.80 - 7.59 (m, 19H, Ar-H) ppm.
^{13}C NMR (100 MHz, CDCl$_3$/DMSO-d$_6$):
δ = 159.9, 147.9, 137.6, 134.5, 131.0, 130.9, 130.3, 129.7, 129.0, 128.7, 128.5, 127.9, 127.2, 126.7, 126.2, 125.9, 123.3, 113.9, 55.2, 48.1: NCMS (*m/z*): 401 (M + 1)

1-(benzyl), 2(4-chloro phenyl), 4,5 di phenyl imidazole (9f)



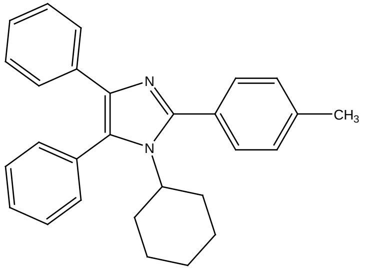
M.P: 162˚C - 164˚C: FTIR (KBr) (cm^{-1}): 1600, 1477, 1447, 1414.
^{1}HNMR (400 MHz, CDCl$_3$/DMSO-d$_6$): δ = 5.08 (s, 2H, CH$_2$), 6.81 - 7.60 (m, 19H, ArH); ^{13}C NMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 48.3, 125.9, 126.5, 126.8, 127.5, 128.1, 128.7, 128.75, 128.8, 128.85, 129.5, 130.2, 130.4, 130.8, 131.0, 134.3, 134.9, 137.3, 138.3, 146.8. NCMS (*m/z*): 421 (M + 1)

1-(cyclohexyl), 2(4-chloro phenyl), 4,5 di phenyl imidazole (9g)



M.P: 152˚C - 154˚C; FTIR (KBr) (cm^{-1}) 1599, 1499, 1481, 1465;
^{1}HNMR (400 MHz, CDCl$_3$/DMSO-d$_6$):
δ = 0.76 - 1.86 (m, 10H, 5(CH$_2$), 3.95 (t, 1H, CH), 7.02 - 7.48 (m, 14 H, Ar-H). ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 21.32 (CH$_3$), 24.99, 26.12, 33.51, 58.24, 125.85, 126.60, 127.77, 128.52, 128.64, 128.93, 129.45, 129.77, 132.16, 132.62, 134.69, 137.63, 138.62, 147.75. NCMS(*m/z*): 413 (M + 1)

1-(cyclohexyl), 2(4-methyl phenyl), 4,5 di phenyl imidazole (9h)



M.P: 163˚C - 165˚C; FTIR (KBr) (cm^{-1}); 1599, 1499, 1481, 1465;
^{1}HNMR (400 MHz, CDCl$_3$/DMSO-d$_6$):
δ = 0.76 - 1.86 (m, 10H, 5(CH$_2$), 2.44 (s, 3H, CH$_3$), 3.95 (t, 1H, CH), 7.02 - 7.48 (m, 14 H, Ar-H). ^{13}CNMR (100 MHz, CDCl$_3$/DMSO-d$_6$): δ = 21.32 (CH$_3$), 24.99, 26.12, 33.51, 58.24, 125.85, 126.60, 127.77, 128.52, 128.64, 128.93, 129.45, 129.77, 132.16, 132.62, 134.69, 137.63, 138.62, 147.75. NCMS (*m/z*): 393 (M + 1)

3. Results and Discussion

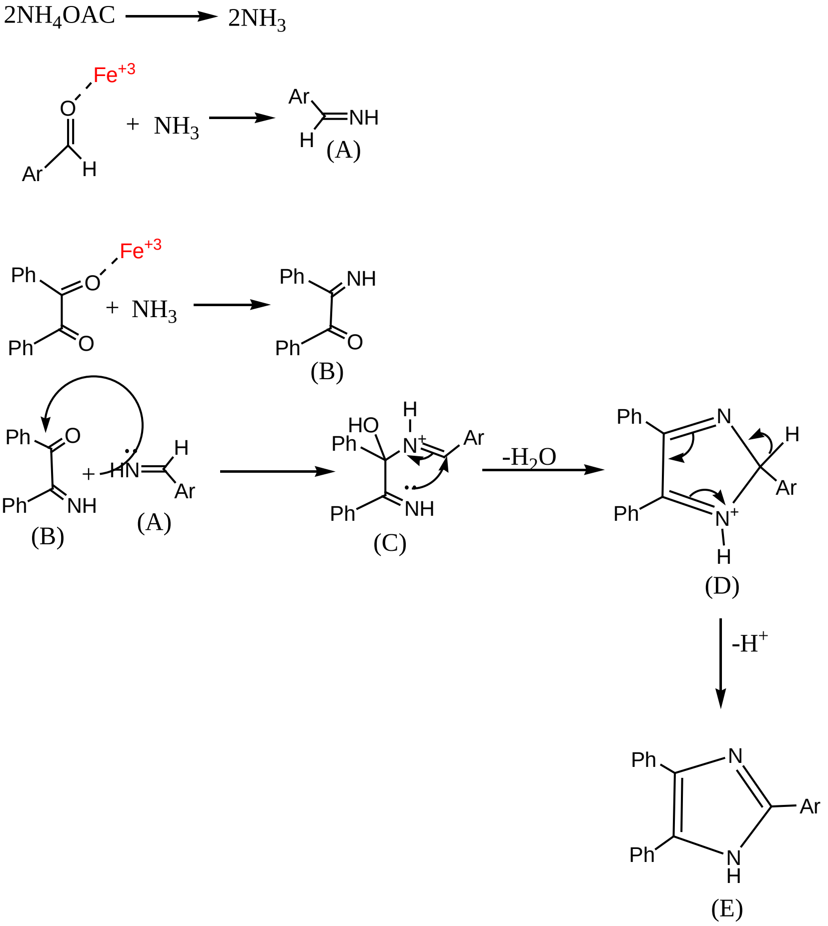
3.1. Plausible Mechanism for the Formation of Products under Nano Copper Ferrite

The plausible mechanism for the synthesis of 2,4,5-tri substituted imidazoles [46] with the copper nano ferrite in the reaction may be shown in **Scheme 3**. Ammonia molecules are obtained from Ammonium acetate. The Aldehyde and 1, 2-diketone are first activated by ferrite nano particles (Fe^{3+}) to afford (A) and (B) respectively. The imine intermediate (A), condenses further with the carbonyl carbon or 1,2 diketone imine (B) and formation of carbocation (C) followed by attack of imine nitrogen to positive centre and dehydration to afford the imo-imidazole (D), which rearranges via 1,5 sigmatropic shift followed by deprotonation gives tri substituted imidazole (E) (**Scheme 3**).

The plausible mechanism for the synthesis of 1,2,4,5-tetra substituted imidazoles [33] with the copper nano ferrite in the reaction may be shown in **Scheme 4**. Ammonium acetate is the source of ammonia molecule. Aldehyde and 1, 2-diketone are first activated by ferrite nano particles (Fe^{3+}). Then, aldehyde, ammonia and Substituted amine undergo reaction to form germinal di-amino intermediate (A). Further reaction of activated 1,2-diketone (B) with germinal di amino intermediate (A) by the loss of water molecule to form an intermediate (C) on cyclization gives intermediate (D) which on loss of one more water molecule gives tetra substituted imidazole (E) (**Scheme 4**).

3.2. Optimization of Reaction Conditions

Since few years as a part of our ongoing investigation in developing an efficient and green synthesis for synthesis of poly substituted imidazoles, here we report an efficient method for the synthesis of poly substituted

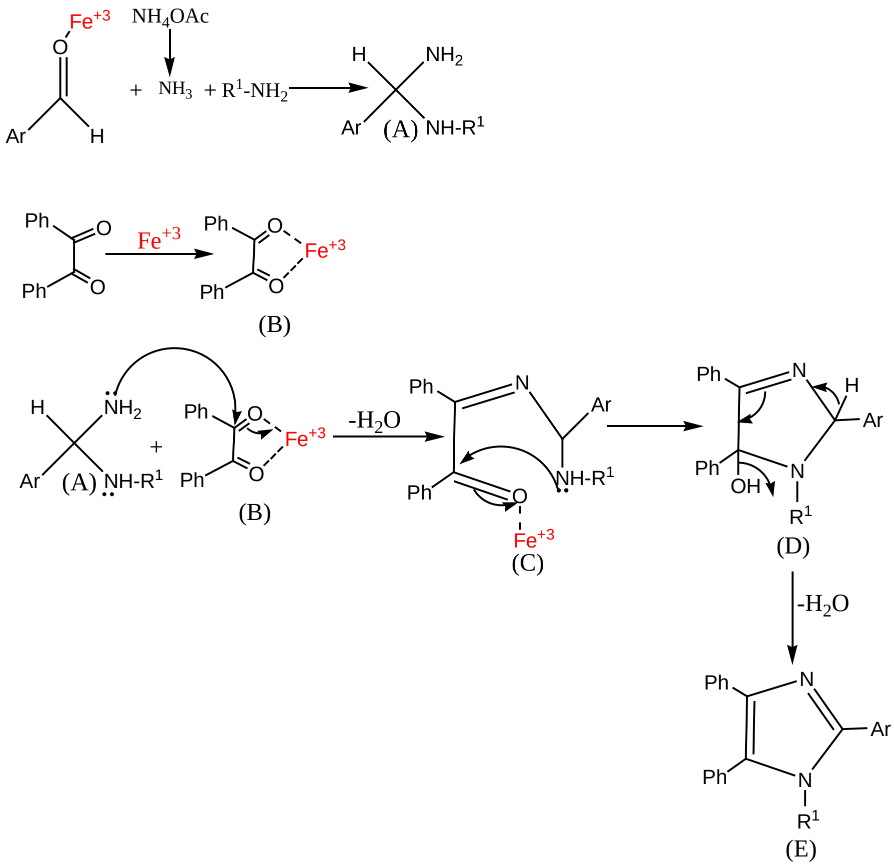


Scheme 3. Plausible mechanism for the formation of 2,4,5-tri substituted Imidazoles.

imidazoles by cyclo condensation of benzil, aromatic aldehydes, ammonium acetate and substituted amines in ethanol in presence of copper nano ferrite under ultrasound irradiation.

To evaluate the effect of ultrasound on **Scheme 1** initially reaction was performed with same conditions in absence of ultrasound irradiation, which results in low to moderate yields of formation of products and but under ultra sonication results good yields of products using the optimized reaction conditions. The formation of moderate yields in absence of sonication is due to effect of copper nano ferrite. The results are tabulated in **Table 1**.

This process was demonstrated by taking wide range of substituted aromatic aldehydes to synthesize the corresponding products in good yields. Aromatic aldehydes bearing electron releasing groups leads some better results than electron withdrawing groups. This methodology was compared with the other ultrasonic methods which are performed in presence of different catalyst at different reaction temperatures. The results are tabulated in **Table 2**.



Scheme 4. Plausible mechanism for the formation of 2,4,5-tri substituted Imidazoles.

Table 1. Effect of ultrasound on **Scheme 1** (compound 4a).

S. No.	Condition	Time (min)	Yield (%)[(a)]
1	No sonication	30	45
2	No sonication	45	55
3	Sonication at R.T.	10	60
4	Sonication at R.T.	20	80
5	Sonication at R.T.	30	96

[(a)] Reaction conditions: Benzil (10 mmol), m-bromo benzaldehyde (10 mmol), Ammonium acetate (10 mmol), Copper ferrite (2 mmol) and Ethanol (5.0 mL).

Table 2. One-pot Synthesis of various 2,4,5-tri substituted imidazole derivatives under ultrasound irradiation.

S. No.	U.S./ Catalyst	R	Temp (˚C)	Time (min)	Yield (%)	M.P. (˚C)$_{rep}$/M.P. (˚C)$_{lit}$
1	U.S./SA-MNPs [22]	m-Br	40	30	95	302-304/301-303 [22]
2	U.S./[EMIM]OAc [23]	m-Br	-	-	-	Not reported
3	U.S./$CuFe_2O_4$	m-Br	R.T.	30	96 (4a)	300-302/301-303 [22]
4	U.S./SA-MNPs [22]	p-F	-	-	-	Not reported
5	U.S./[EMIM]OAc [23]	p-F	-	-	-	Not reported
6	U.S./$CuFe_2O_4$	p-F	R.T.	25	92 (4b)	188-190/190(19)
7	U.S./SA-MNPs [22]	p-CH_3	40	40	92	187-189/186-188 [22]
8	U.S./[EMIM]OAc [23]	p-CH_3	-	-	-	Not reported
9	U.S./$CuFe_2O_4$	p-CH_3	R.T.	30	94 (4e)	184-186/186-188 [22]
10	U.S./SA-MNPs [22]	m-NO_2	40	30	92	268-270/269-271 [22]
11	U.S./[EMIM]OAc [23]	m-NO_2	R.T.	90	87	317-319/313-315 [23]
12	U.S./$CuFe_2O_4$	m-NO_2	R.T.	30	88 (4c)	310-312/313-315 [23]
13	U.S./SA-MNPs [22]	p-NO_2	-	-	-	Not reported
14	U.S./[EMIM]OAc [23]	p-NO_2	R.T.	70	70	239-242/235-238 [23]
15	U.S./$CuFe_2O_4$	p-NO_2	R.T.	30	86 (4d)	232-234/235-238 [23]

S. Nos. 1-9 contain electron releasing groups where as SNos.10-15 contain electron withdrawing groups on the aldehyde

U.S. = Ultra Sonication; SA-MNPs = Sulfamic acid-functionalized magnetic nano particles; [EMIM] OAc = 1-ethyl-3-methylimidazole acetate; $CuFe_2O_4$ = copper ferrite nano particles (present work). Reaction conditions: Benzil (10 mmol), Aromatic aldehyde (10 mmol), Ammonium acetate (10 mmol), Copper ferrite (2 mmol) and Ethanol (5.0 mL). As mentioned above some of the tri substituted imidazole products with the respective catalysts were not reported with the mentioned aromatic aldehyde.

In extension to our work here we report an efficient method for the synthesis of tetra substituted imidazoles by cyclo condensation of benzil, aromatic aldehydes, ammonium acetate and substituted amines in ethanol in presence of copper nano ferrite under ultrasound irradiation. The results are tabulated in **Table 3**.

In order to examine the effect of catalyst concentration on **Scheme 2** (product 9c) we perform the reaction with various concentrations of the catalyst in ethanol at 40˚C. The use of 2 mmol and above concentrations of the catalyst gave good yields of the desired products. The results are tabulated in **Table 4**.

In order to examine the effect of solvent on **Scheme 2** we perform the reaction in presence of various solvents including ethanol, CH_3CN, CH_2Cl_2 and water at different time at 40˚C. The use of ethanol as solvent afforded good yields of the desired products. The results are tabulated in **Table 5**.

3.3. Recycling of the Catalyst

Catalyst reusability is of major concern in heterogeneous catalysis. The recovery and reusability of the catalyst was investigated in this reaction with benzaldehyde (**4a**). Catalyst recycling was achieved by fixing the catalyst magnetically at the bottom of the flask with a strong magnet, after which the solution was taken off with a pipette and concentrated in rotary evaporator then the solid washed twice with chloroform. The fresh substrate dissolved in the same solvent was introduced into the flask, allowing the reaction to proceed for the next run.The catalyst was consecutively reused five times without any noticeable loss of its catalytic activity. These catalysts are highly magnetic and their saturation magnetization values [46] are much higher than other reported magnetic catalysts. Therefore, they could be easily and almost completely separated by an external magnet which is of a great advantage for a heterogeneous catalyst.

Table 3. One-pot Synthesis of various 1,2,4,5-tetra substituted imidazole derivatives under ultrasound irradiation.

S. No.	U.S./Reflux Under Catalyst	R	R^1	Temp (˚C)	Time (min)	Yield (%)	M.P.(˚C)$_{rep}$/M.P.(˚C)$_{lit}$
1	$HClO_4$-SiO_2/reflux [29]	H	C_6H_5	140	10	91	216 [29]
2	$MgAl_2O_4$/U.S. [33]	H	C_6H_5	60	15	91	216-218 [33]
3	$CuFe_2O_4$/U.S.	H	C_6H_5	40	15	92(9a)	214-216/216 [29]
4	$HClO_4$-SiO_2/reflux [29]	p-OCH_3	C_6H_5	-	-	-	Not reported
5	$MgAl_2O_4$/U.S. [33]	p-OCH_3	C_6H_5	60	18	93	253-254 [33]
6	$CuFe_2O_4$/U.S.	p-OCH_3	C_6H_5	40	15	94(9b)	254-256/253-254 [33]
7	$HClO_4$-SiO_2/reflux [29]	H	C_6H_5-CH_2	140	6	96	165-167 [29]
8	$MgAl_2O_4$/U.S. [33]	H	C_6H_5-CH_2	-	-	-	Not reported
9	$CuFe_2O_4$/U.S.	H	C_6H_5-CH_2	40	10	95(9c)	166-168/165-167 [29]
10	$HClO_4$-SiO_2/reflux [29]	p-OCH_3	C_6H_5-CH_2	140	10	96	157-160 [29]
11	$MgAl_2O_4$/U.S. [33]	p-OCH_3	C_6H_5-CH_2	-	-	-	Not reported
12	$CuFe_2O_4$/U.S.	p-OCH_3	C_6H_5-CH_2	40	15	94(9d)	158-160/157-160 [29]
13	$HClO_4$-SiO_2/reflux [29]	p-CH_3	C_6H_5-CH_2	140	6	90	165-168 [29]
14	$MgAl_2O_4$/U.S. [33]	p-CH_3	C_6H_5-CH_2	-	-	-	Not reported
15	$CuFe_2O_4$/U.S.	p-CH_3	C_6H_5-CH_2	40	20	96(9e)	168-170/165-168 [29]
16	$HClO_4$-SiO_2/reflux [29]	p-Cl	C_6H_5-CH_2	140	8	94	162-164/162-165 [29]
17	$MgAl_2O_4$/U.S. [33]	p-Cl	C_6H_5-CH_2	-	-	-	Not reported
18	$CuFe_2O_4$/U.S.	p-Cl	C_6H_5-CH_2	40	15	92(9f)	160-162/162-163 [26]
19	$HClO_4$-SiO_2/reflux [29]	p-Cl	Cyclohexyl	-	-	-	Not reported
20	$MgAl_2O_4$/U.S. [33]	p-Cl	Cyclohexyl	-	-	-	Not reported
21	$CuFe_2O_4$/U.S.	p-Cl	Cyclohexyl	40	20	90(9g)	152-154/-
22	$HClO_4$-SiO_2/reflux [29]	p-CH_3	Cyclohexyl	140	18	90	164 [29]
23	$MgAl_2O_4$/U.S. [33]	p-CH_3	Cyclohexyl	-	-	-	Not reported
24	$CuFe_2O_4$/U.S.	p-CH_3	Cyclohexyl	40	20	92(9h)	162-164/164 [29]

U.S. = Ultra Sonication, $CuFe_2O_4$ = copper ferrite nano particles (present work). Reaction conditions: Benzil (10 mmol), Aromatic aldehyde (10 mmol), Ammonium acetate (10 mmol), substituted amine (10 mmol), Copper ferrite (2 mmol) and Ethanol (5.0 mL). As mentioned above some of the tri substituted imidazole products with the respective catalysts were not reported with the mentioned aromatic aldehyde.

Table 4. Effect of catalyst concentration on the synthesis of 1,2,4,5-tetra substituted imidazoles[a].

S. No.	$CuFe_2O_4$ Concentration mmol	Yield (%)
1	5	95
2	2	95
3	1	80
4	0.5	70

[a] Reaction conditions for Product 9c: Benzil (10 mmol), Benzaldehyde (10 mmol), Ammonium acetate (10 mmol), Benzyl amine (10 mmol), Ethanol (5.0 mL), 40˚C.

Table 5. Effect of solvent on the synthesis of 1,2,4,5-tetra substituted imidazoles[b].

S. No.	Solvent	Yield (%)
1	Ethanol	95
2	CH_3CN	65
3	CH_2Cl_2	35
4	Water	Trace

[b] Reaction conditions: Benzil (10 mmol), Benzaldehyde (10 mmol), Ammonium acetate (10 mmol), Benzyl amine (10 mmol), Copper ferrite (2 mmol), Ethanol (5.0 mL), 40˚C.

4. Conclusion

In conclusion, we have reported an efficient, convenient and environmentally benign ultrasound assisted one-pot greener synthesis of poly substituted imidazole derivatives using nano copper ferrite. The notable features offered by this methodology are mild reaction conditions, simple procedure, cleaner reactions and good yields of products.

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