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Optical applications of Sol-gel Nano-Composites

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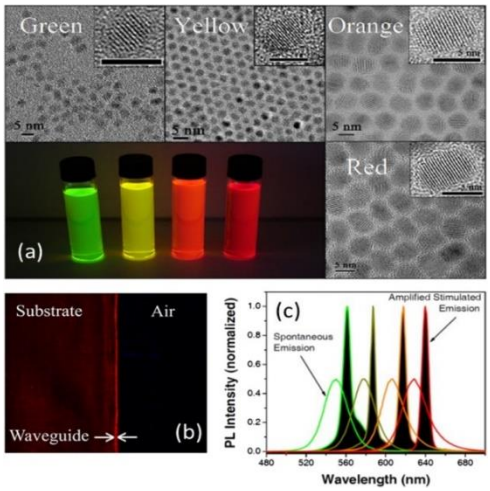

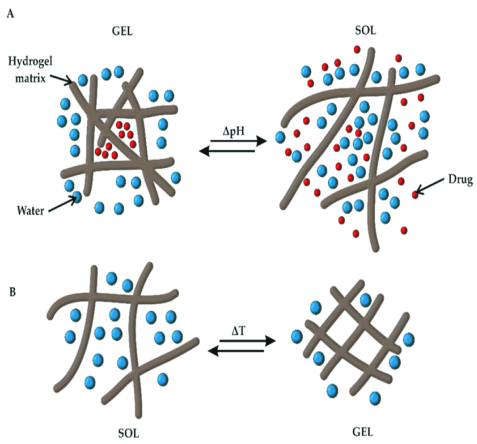

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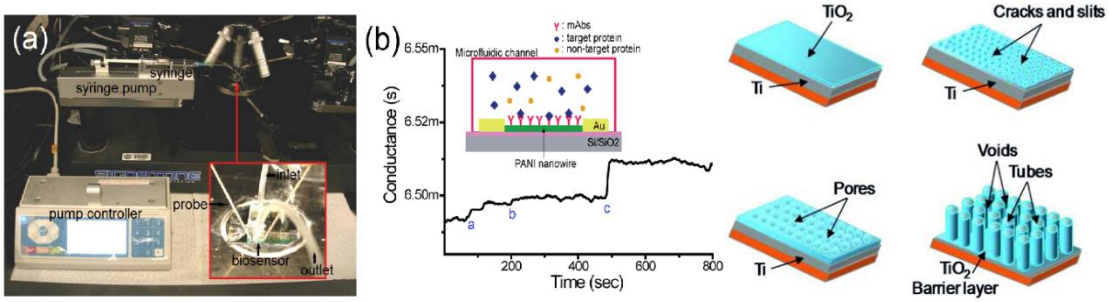

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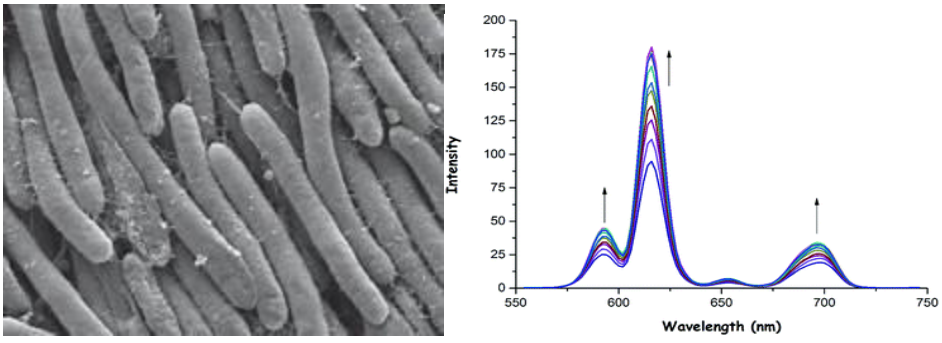

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Optical applications of Sol-gel Nano-Composites

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I. Introduction:

As the number of uses for optical materials grows, so does the demand for new optically functional and transparent materials. In addition to optical demands such as switches and amplifiers, the material should be

integrated into the existing structure such as waveguide and fibre optics. Nanocomposite materials offer a lot of promise since they can provide the necessary stability and processability for these key applications. Sol-gel nanocomposites are made with the sol-gel process for at least one of the phase. They could be obtain in two ways: "in situ" and "ex situ." A first technique has an advantages of producing the matrices as well as dispersion medium from the same batch of precursors, whereas the second method, which is based on dispersing an already synthesised dispersed phases in the matrix sol, provides for better micro structural controls.

Our study was primarily focus on the synthesis of nanomaterials for optical applications. In this work, we examine a most notable achievement in two disciplines of experiments over the last ten years: Photonic and optoelectronic nanocomposite material with semiconductors quantum dots; nanocomposites material for optical gas sensors During the first use, nanoparticles with quantum sizes ranging are placed into matrices to maintain their unique features while interfering with the host materials. The sensitive material was designed for gas sensor applications to maximise the interaction with the target gas in order to increase an variations of the optical characteristics employed for the transducing platforms. To obtain high dispersal homogeneous and treat the material to build the requisite device structures, it's vital to keep track of the matrix's structurals and optical features, as well as overall nanocomposite's.

II. Related work:

In [1], the authors have proposed the optically functional materials have been created using nanocomposite architectures. Many of semiconductor nanoparticles' fascinating optical properties, by incorporating them into polymers, glasses, or ceramics reinforcing material, properties including absorbance, fluorescent, luminescent, and non - linearity can be investigated. Great optical transparency combined with superior heat and chemical resistance make fusing silicon glasses the top choices for optical, photonic, microfluidic devices, and chemistry application [2]. A matrix and a fiber-reinforced reinforcement make up a composite/Nanocomposite material. [3-6]. Sol–gel technologies have paved an way for the developments of novel material in the form of nanoparticles or nanocomposites for a variety of applications [7].

Massimo Guglielmi et al. [6] Material dopant with semiconductors QDs were generated as bulks or thin films by precipitated or developing semiconductor QDs in glass or polymer. Polymer-inorganic composites have piqued the interest of material scientists who want to create efficient material with desirable characteristics such as low price, densities, and electronic properties [8-11]. Optical study on organics/inorganic nanocomposite have progressed towards that variety of goals, including investigating the basic and important spectrometry of dyes isolates obtained in the sol-gel environments, studying dye energy conversion in solid matrix, using luminous molecules as tests of the sol-gel procedure [17°], and eventually developing material with specific optical properties depending on the properties of physical or chemical chromophore [12-18].

Organization:

The rest of the study is laid out as followed. The second section examines the related works. The

proposed method for optical applications is presented in Section 3. In Section 4, the collected experimental results are discussed. This paper's conclusion has been made in Section 5.

III. Proposed methodology:

1. Different nanoparticles can be included into sol-gel nanocomposites.
2. The use of semiconductor quantum dots allow the optical property of nanocomposite to be fine-tuned.
3. The inclusion of sensitive nanoparticle in a porous sol-gel matrices could be used to create optical sensors.
4. Optical sensing devices, photonic and optoelectronic applications, and photonic and optoelectronic applications have all been investigated.

3.1 Nanocomposites film contains semiconductor quantum dots:

Semiconductor quantum dot (QD) are material with size-dependent characteristics due to excitonic confinement. The energy gap between an electrons and hole level widens as the size of the QD shrinks, causing the emission to blueshift. The ability to control the emission wavelength, as well as fluorescence quantum efficiency and photostability, opens up new possibilities for photonic and optoelectronic applications. Separating the matrices precursors batch from the one contains the NPs, then mixed the two equations, could result in much greater controls of the matrices, QDs, and final micro - structural. Journal of Sol-Gel Scientific and Technological describes the "ex situ" technique. A fundamental idea is to avoid any interactions between chemical processes as much as possible. The next sections will examine the key result we've obtained using this technique over the previous ten years, with a focus on how synthetic chemistry, and hence the resulting structural and microstructural, influences material attributes and prospective application.

3.2 Ex situ approach for the incorporation of ODs in sol-gel matrices:

Three basic processes are involved in the ex-situ fabrication of sol-gel thin film contains QDs:

1. Colloidal methods for synthesis of QDs that allow for control of their structural or surface chemical. This is frequently accomplished in solution that are incompatible with the sol-gel alcoholic mediums.
2. Surface modifications of QD to making these solubility in a solvent suitable with an sol-gel matrices, which is often an alcoholic.
3. The QDs dispersions is mixed into the sol-gel solutions, resulting in a last sol that may be used to create thin films.

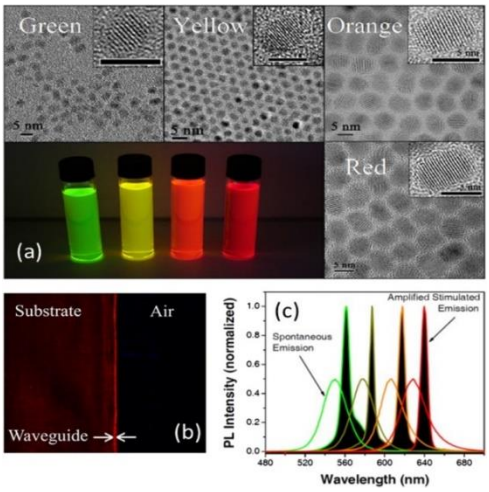
3.2.1 Synthesis of QDs:

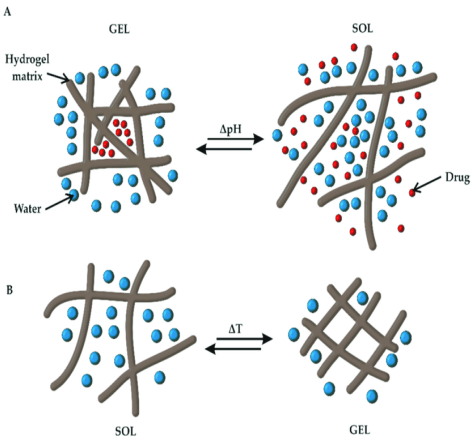
The activity focused on simpler organic - inorganic hybrid systems, such as pure chalcogenide (CdS, PbS, and ZnS), as well as complicated core-shells QDs focused on the CdSe-ZnS systems. CdS NPs was made by reacting a solutions of cadmium acetic dihydrates (CdAc), methanol, or mercaptopropyl- trimethoxysilane

(MTMS) with thioacetamide to produce hybrid organic-inorganic films focused on organically modified silicon-germania and silica-zirconia matrix dop with CdS and PbS QDs (TAA). Core-shells CdSe-ZnS QDs are much more difficult to make. Chemicals and photo durability must have been kept when NPs are disseminated in the solid material. Chemical stabilities could be achieved by going to grow an inorganically shells (ZnS) with appropriate surfaces passive film [19-23].

3.2.2 Sol-gel matrices:

Due to its Journal of Sol-Gel Science and Technologies refractive index and probable interactions with QDs, the nature of the matrix may have a significantly impact on the properties of the final materials. Furthermore, an matrix of these nanocomposite materials must be processable in some way before they may be used to make devices. In the same study, the performance of two large indexing matrices, TiO2 and ZrO2, were studied. Despite the fact that all matrices are proven to be acceptable waveguides materials (Fig: 1b), the zirconia composites had much higher PL intensity than a titania composite. According to several comparisons of conduction-band offset, the differential was caused by electron transport from of the QDs to the matrices in QD-TiO2 film. propylene glycol (median molecular mass: 1000) (PEG) in an equimolar ratio. The isocyanate groups of the silicate molecules reacts with of hydroxyl group of PEG to form this. Material with a tunable optical refractive indices of up to 1.8 as well as stable PL property can be created using this technology. Spray printing and imprinting lithography can also be used to make this material, indicating that it is a viable material for the creation of optical device [24-28].





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3.2 Nanocomposites films for gas sensors:

In the sections that follow, we'll look at our works on synthesising nanomaterial to build gas

sensor using several kinds of transforming platform. We created material for conductometer and surfaces acoustic waves (SAW) gas sensor, however the majority of our work is focused on optical sensors, particularly plasmonic sensors. Electrical gas sensors that detect resistance change are known as conductometric sensors. In SAW sensors, the piezoelectric turns an electrical impulse into the mechanical waves, which then is converted back in to electronic signals. The optical qualities produced by interaction with the sensitive materials include absorbency, luminance, and surface plasmon resonance excitement (SPR). SPR is a coherence oscillation of light-excited surfaces conduction electron that could be supported by material with a small positive imaginary dielectric constants and a negative growth dielectric constant.

IV. Experimental result and discussion:

4.1 Metal oxides:

Metal oxides are used in natural polymers composites in incorporating their properties into the polymer matrices. Metal oxides based biopolymers composites have been created using a variety of metal oxide, like ZnO, TiO2, SnO2, SiO2, ZrO2, among others, in combination with various biopolymer.

4.1.1 TiO2:

The most common crystalline phases of titanium dioxides are anatase and rutile, making this one of the most investigates material for gas sensor application. With TiO2 as the sensitive material, we constructed a range of gas sensors. They developed a TiO2-Au films in which Au NPs is synthesised using colloid techniques and would then dispersed in a titania-based sol-gel solutions after purifications and surface functionalization.

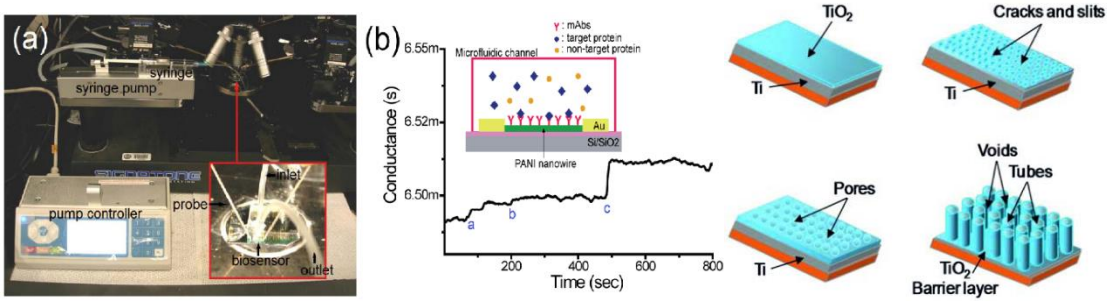

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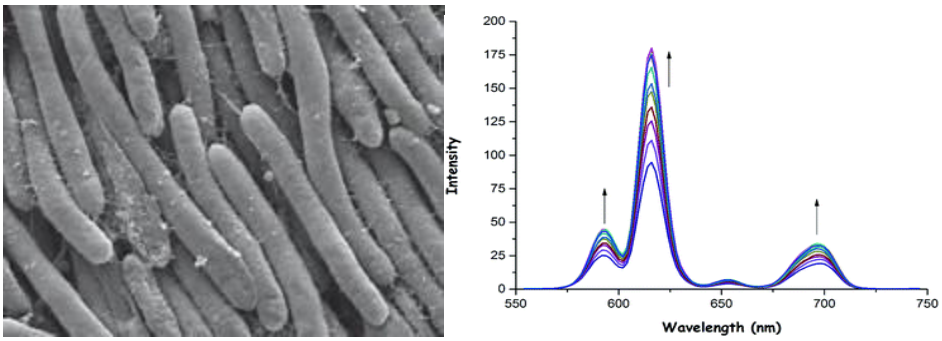
Fig. 3 TiO2-Au films utilized as sensitive material for conductometries and optical gas sensor.

4.1.2 NiO:

NiO must be a p-type semiconductors with a 4.2 eV large band gap which has been used in chemoresistives and optical gas sensing as a sensitive materials. All optical and conductometric gas sensor were made with Solgel NiO film. To make the NiO solution, nickel oxalate tetrahydrates was dissolved in methanol in the presences of diethanolamines. Finally, colloid Au NPs was add to the solution. A conductometric or optical H2, CO, and NO2 sensors was made from pure NiO or NiO-Au film.

4.1.3 ZnO:

Zinc oxides are among the most study material for gas sensing. It is used to detect a wide range of gaseous products, including oxygen, carbon monoxide, hydrogen, ammonia, and a large range of volatile organic compounds (VOCs). It may also be activated by all thermal or UV light, allow low-temperature sensors to be developed. We were able to make ZnO sol-gel films by dissolves zinc acetic acid dihydrates in ethanol in the presences of msonoethanolamine. To this solution, different volumes of tetrachloroauric acid ethanolic solution was then added. A conductivity or optically H2, CO, and NO2 sensors was made from pure ZnO or ZnO-Au films.



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4.2 Hybrid organic-inorganic:

To disperse Au colloid, a hybrid organic-inorganic sol-gel material could be employed. Au colloid was used to create a sub-monolayers on top where by the PSQ sol-gel matrices is obtained, or they were implanted in the PSQ matrices. The PSQ sol-gel matrerials were also coated on complex metallic architectures with nanoprism arrays generated by combining microspheres scanning with thermal oxidation. The multilayer structure was made utilising a simple and basic methodology based on alternating depositions of regenerating silken, and it closely resembles the cuticle structure of Hoplia coerulea. TNSs are sub-stechiometric TiO2 2D crystals synthesised by sol-gel chemistry, which were chose for their minimum sizes, high refracted indexing, and water dispersibility, making silk manufacturing integration very simple.

V. Conclusion:

Nanocomposites multifunctional material based on the incorporations of QDs in inorganic or hybrid organic-inorganic matrix have been analysed, demonstrating such a stabilising optical property, good chemical stability, and easy processability is being achieved and used the sol-gel technique in combinations with colloidal method by carefully selecting materials and synthesis procedures. SPR-based optical gas sensor have great promise for better understanding chemical reactions at the nanoscales as well as the development of real-world device. SPR or absorbances-based optical gas sensor, as well as conductometer and surface acoustic wave

sensor, have all utilised nanocomposites sol-gel films material as sensitive materials. We showed that by carefully controlling the film structure, a highly selective gas sensor with customised microstructure may be created.

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RESEARCH ARTICLE

NANO COPPER FERRITE AS HETEROGENEOUS CATALYST FOR THE ONE-POT SYNTHESIS OF ACRIDINE DERIVATIVES

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ABSTRACT

A simple, multi component, one-pot synthesis of benzo (b) acridines deriviatives by the condensation of β-napthyl amine (naphthalene 2-amine), dimedone (5,5 dimethyl cyclohexane 1,3 dione) and aromatic aldehyde through knovenogel condensation catalyzed by nano copper ferrite particles under reflux conditions has been achieved and reported. This methodology leads shorter reaction times, formation of good to excellent yields of products, recyclability and reuse of the heterogeneous catalyst which makes the present conversion as an environmentally benign approach

Keywords: *Nano copper ferrite, knovenagel reaction, Michael addition, acridines, one-pot synthesis, dimedone, β-napthyl amine, heterogeneous catalyst.*

Introduction

Because of the production of single high yielding product through the condensation of two or more components in a one step process[1], one-pot multi-component reactions now attract much interest in organic synthesis, such multi-component reactions are convenient and efficient methods for synthesizing biologically and medically active pharmaceutical ingredients[2].

There is always a need for both industry and scientists to establish new methods for synthesizing biologically active organisms. Multi-component reactions are the most powerful and efficient way to synthesize a wide variety of useful compounds sustainably and diversely including pharmaceuticals, such as biologically active

heterocyclic compounds. The result in Multi-component reaction is depends on reaction conditions like temperature, solvent, catalyst, concentration, the kind of starting materials and functional groups. Such considerations play a vital role in the design and discovery of novel multi-component reactions[3].

Acridine derivatives have significant biological and pharmacological activities that can be used as antimalarial agent[4], antibacterial agent[5], antinoplastic agent[6], antiparasitic agent[7] and fluorinated acridones can be used as anti-cancer agents[8-11]. It should be noted that acridines biological activity is due to the acridine moiety's ability to intercalate through π-π interaction between base pairs of double stranded DNA. In cellular machinery, this induces changes[12].

Due to the high biological and pharmacological significance of acridine derivatives, earlier various methods for the synthesis of acridine derivatives have been reported, such as three component condensation of aromatic aldehyde, naphthalene 1-amine and 5,5 dimethyl cyclohexane 1,3 dione, using functionalized sulphonic acid SBA-15 (SBA-Pr-SO3H)[13], succinamide N-sulphonic acid[14], TEBAC (triethyl bezyl ammonium chloride)[15], BNBTS(N,N'-Dibromo-N,N'-1,2-ethanediylbis(p-toluenesulfonamide)[16]. The other previously mentioned methods of synthesis for acridine derivatives include condensation of aromatic aldehyde, 5,5 dimethyl cyclohexane 1,3 dione, substituted aromatic/aliphatic amines or ammonium acetate by the use of water-mediated oxalic acid[17], Zinc chloride[18], Cu-doped ZnO[19], ceric ammonium nitrate under sonic condition[20], Vitamin B_1[21], SDS (sodium 1-dodecanesulfonic acid)[22]. These methods have their own qualities and shortcomings such as prolonged reaction time, elevated reaction temperature, complicated work-up for catalyst synthesis, and difficulty in recovering the catalyst from the reaction mixture. It is therefore unavoidable that an effective method for the preparation of benzo(b) acridine derivatives using magnetically separable heterogeneous catalyst should be developed to overcome these limitations.

Due to performance, economic and environmental considerations, and simple recoverability from the reaction mixture, heterogeneous catalysts have attracted great attention from chemists in recent years. Interestingly, nano particles, relative to their bulk analogues, have a high surface-to-volume ratio and coordination sites, which have a greater number of active sites per unit area[23]. Nano particles, especially ferrite nano particles, have attracted considerable interest in chemistry and material sciences due to their potential applications in catalysis[24]. The paramagnetic and insoluble properties of ferrite nano particles enable the catalyst to be readily separated by a strong external magnet. Previously, copper and cobalt nano ferrites were synthesized and used for various organic transformations[25-31]. As part of our ongoing research copper and cobalt ferrite nano particles were synthesised, characterised and used in the preparation of 2,4,5-tri substituted imidazoles under reflux conditions[32]. In extension to this Copper ferrite was used as heterogeneous catalyst for the synthesis of poly substituted imidazoles under ultra sound irradiation[33], nickel cobalt ferrite was used as heterogeneous catalyst for one-pot multi-component synthesis of β-acetamido ketones[34], nano copper ferrite was used as heterogeneous catalyst for the synthesis of poly substituted pyridine derivatives in one-pot manner[35] and nano cobalt ferrite was used as heterogeneous catalyst for synthesis of pyranoquinoline derivatives under microwave irradiation[36]. Now Copper ferrite nano particles were used as magnetically separable catalyst for the one-

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pot synthesis of benzo (b) acridines deriviatives by the condensation of β-napthyl amine (naphthalene 2-amine), dimedone (5,5 dimethyl cyclohexane 1,3 dione) and aromatic aldehyde through knovenogel condensation, which was represented in **scheme 1**. This current reported method involves shorter reaction time, mild reaction temperature and easy separation of the catalyst from the reaction mixture. With no significant loss of its catalytic activity, the recycled catalyst can be reused for the next five consecutive cycles. In this research, nano copper ferrite was used for the synthesis of benzo (b) acridines deriviatives as a mild and effective catalyst.

2. Experrimental:

2.1 Material and Methods:

All the chemical samples are brought from commercial sources and liquid aromatic aldehydes are purified prior to use by distillation. Solvent evaporation is performed by using superfit rotary evaporator. Characterization of the desired products was done by IR, ^{1}HNMR, MASS spectral analysis. ^{1}HNMR spectral data was recorded under Bruker-Avance 400MHz spectrophotometer by using $CDCl_3$ as a solvent and tetra methyl silane as a reference sample. Values of chemical shift were recorded on δ scale, in parts per million (ppm). IR spectra have been recorded on SHIMADZU FT-IR, prestige-21 edition. MASS data was reported on Perkin-elmer PE SCIEX-API 2000, Equipped with an ESI source used online with a HPLC system after the ultraviolet detector.

2.2 Preparation of Copper ferrite:

As previously reported by us, the spinel nano copper ferrite was produced by sol-gel citrate precursor method [32].

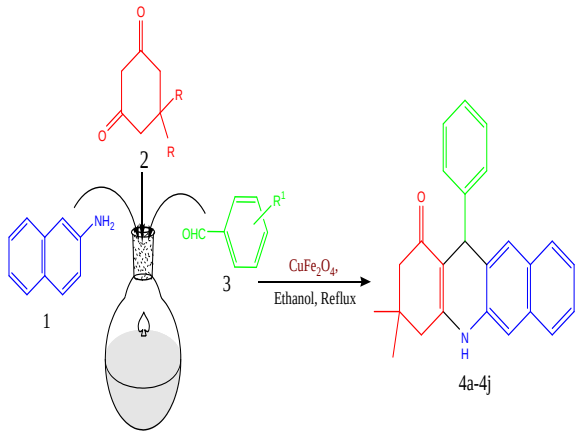
2.3 Characterization of Copper ferrite:

As previously reported by us, nano copper ferrite was characterized by FTIR, SEM, TEM, XRD and particle size analyzer [32].

2.4 General Procedure for the Synthesis of Benzo(b) Acridine Derivatives:

In a 50mL round bottom flask, β-napthyl amine (10mmol), aromatic aldehyde (10mmol), 5,5 dimethyl cyclohexane 1,3dione (10mmol) and copper ferrite (500mg) (which is prior activated in microwave oven for 2 minutes) were taken and 5mL of ethanol was applied to dissolve the contents in the flask. The reaction mixture was then refluxed for a prescribed period of time. TLC (n-hexane: ethyl acetate 4:1) was used to monitor the reaction progress. After the reaction was completed, an external strong Neodyneium35 magnet was used to separate the catalyst from the reaction mixture. Then 20mL of ethanol was added and concentrated under the rotary evaporator. The solid product was recrystallised several times with hot ethanol after evaporation of the solvent to obtain the corresponding pure product. IR, ^{1}H NMR and MASS spectral analysis have confirmed the products.

Scheme 1:



4a) R=CH_3, R^1=H, 4b) R=CH_3, R^1=p-OCH_3, 4c)R=CH_3, R^1=p-CH_3, 4d) R=CH_3, R^1=p-Br, 4e) R=CH_3, R^1=p-OH, 4f) R=CH_3, R^1=p-NO_2, 4g) R=H, R^1=p-OH,m-OC_2H_5, 4h) R=H, R^1=p-OCH_3,m-OH, 4i) R=H, R^1=p-OCH_3,m-OCH_3, 4j) R=H, R^1=p-Cl

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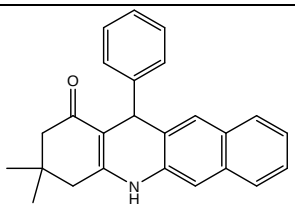
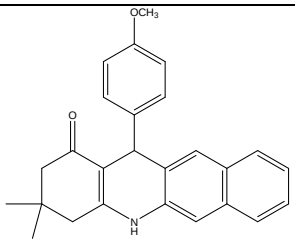
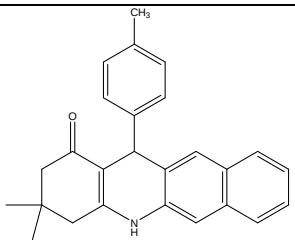
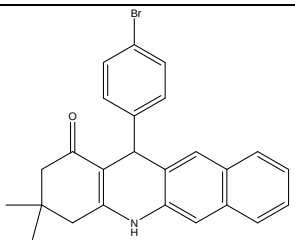
Compound	Spectral data
 3,3-dimethyl-12-phenyl-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4a)	White solid: IR(KBr, cm^{-1}): 3300, 3285, 3073, 2985, 1700, 1674, 1610, 1420, 1384, 1230, 785, 715. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 4.0 (s, 1H), 4.74 (s, 1H), 7.06-7.14 (m, Ar-H, 5H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 353 (M^+) m/z.
 12-(4-methoxyphenyl)-3,3-dimethyl-3,4-dihydro benzo[*b*]acridin-1(2*H*,5*H*,12*H*)-one (4b)	White solid: IR(KBr, cm^{-1}): 3310, 3275, 3050, 2980, 1705, 1670, 1614, 1435, 1375, 1280, 1225, 885. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 3.73 (s,3H), 4.0 (s,1H), 4.74 (s, 1H), 6.65 (d, J=8Hz, 2H), 6.95 (d, J=8Hz, 2H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 385 (M+2) m/z.
 3,3-dimethyl-12-*p*-tolyl-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4c)	White solid: IR(KBr, cm^{-1}): 3295, 3270, 3060, 2990, 1710, 1675, 1620, 1430, 1375, 1225, 845. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 2.35 (s,3H), 4.0 (s,1H), 4.74 (s, 1H), 6.84 (d, J=8Hz, 2H), 6.95 (d, J=8Hz, 2H), 6.73-7.52 (m, Ar-H, 6H), ESI-MS: 368 (M+1) m/z, 391 (M+Na) m/z.
 12-(4-bromophenyl)-3,3-dimethyl-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4d)	White solid: IR(KBr, cm^{-1}): 3310, 3265, 3070, 2980, 1703, 1664, 1615, 1385, 1225, 865, 750. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 4.0 (s,1H), 4.74 (s, 1H), 6.95 (d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 431 (M^+) m/z, 433(M+2) m/z.

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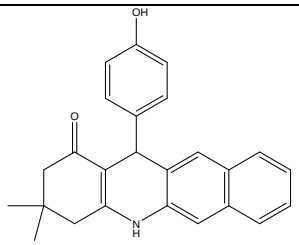
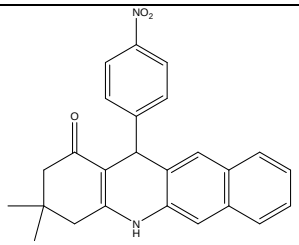
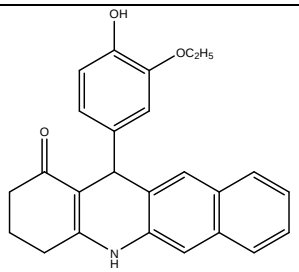
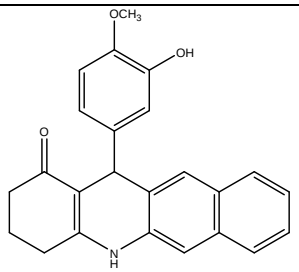
 12-(4-hydroxyphenyl)-3,3-dimethyl-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4e)	White solid: IR(KBr, cm^{-1}): 3500, 3305, 3275, 3070, 2980, 1705, 1670, 1615, 1380, 1228, 1210, 875. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 4.0 (s,1H), 4.74 (s, 1H), 5.0(s,1H), 6.61 (d, J=8Hz, 2H), 6.89 (d, J=8Hz, 2H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 370(M+1) m/z.
 3,3-dimethyl-12-(4-nitrophenyl)-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4f)	Pale yellow solid: IR(KBr, cm^{-1}): 3290, 3275, 3065, 2980, 1702, 1670, 1605, 1550, 1355, 1380, 1229, 855. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.11 (s, 6H), 1.88 (s, 2H), 2.86 (s, 2H), 4.0 (s,1H), 4.74 (s, 1H), 7.32 (d, J=8Hz, 2H), 8.07 (d, J=12Hz,2H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 399(M+1) m/z.
 12-(3-ethoxy-4-hydroxyphenyl)-3,4-dihydro benzo[*b*]acridin-1(2*H*,5*H*,12*H*)-one (4g)	White solid: IR(KBr, cm^{-1}): 3510, 3290, 3275, 3068, 2980, 1710, 1670, 1615, 1380, 1228, 1225, 865, 735. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.33 (t,3H), 1.44 (m, 2H), 1.96 (t, 2H), 2.94 (t, 2H), 3.9 (q, 2H), 4.0 (s,1H), 4.74 (s, 1H), 5.0(s,1H), 6.40 (s, 1H), 6.45 (d, J=8Hz,1H), 6.50 (d, J=8Hz,1H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 386(M+1) m/z.
 12-(3-hydroxy-4-methoxyphenyl)-3,4-dihydro benzo[*b*]acridin-1(2*H*,5*H*,12*H*)-one (4h)	White solid: IR(KBr, cm^{-1}): 3500, 3310, 3290, 3070, 2985, 1700, 1670, 1615, 1420, 1380, 1230, 1210, 835, 765. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.44 (m, 2H), 1.96 (t, 2H), 2.94 (t, 2H), 3.73 (s,3H), 4.0 (s,1H), 4.74 (s, 1H), 5.0(s,1H), 6.42 (s, 1H), 6.48 (d, J=8Hz, 1H), 6.51 (d, J=8Hz, 1H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 372(M+1) m/z.

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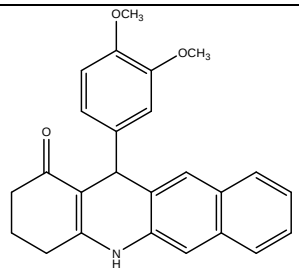
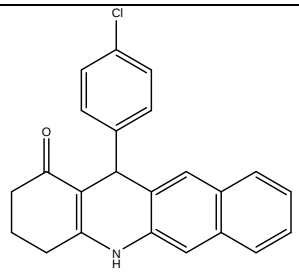
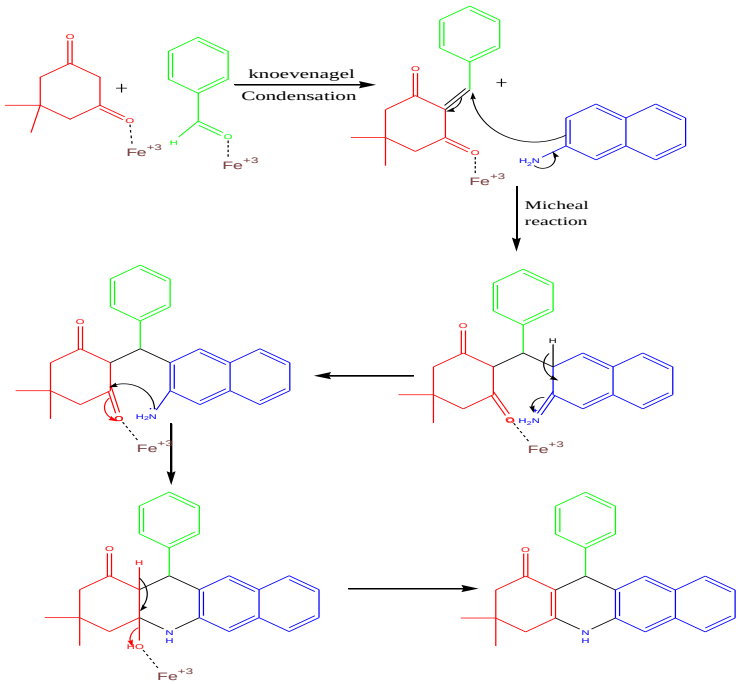
 12-(3,4-dimethoxyphenyl)-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4i)	White solid: IR(KBr, cm^{-1}): 3310, 3290, 3070, 2980, 1710, 1684, 1615, 1410, 1384, 1230, 1215, 840, 765. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.44 (m, 2H), 1.96 (t, 2H), 2.94 (t, 2H), 3.73 (s,6H), 4.0 (s,1H), 4.74 (s, 1H), 6.46 (s, 1H), 6.51 (d, J=8Hz,1H), 6.54 (d, J=8Hz,1H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 386(M+1) m/z.
 12-(4-chlorophenyl)-3,4-dihydrobenzo[*b*] acridin-1(2*H*,5*H*,12*H*)-one (4j)	White solid: IR(KBr, cm^{-1}): 3295, 3280, 3075, 2980, 1705, 1670, 1615, 1380, 1235, 870, 790. ^{1}HNMR(400MHz, $CDCl_3$) δ in ppm: 1.44 (m, 2H), 1.96 (t, 2H), 2.94 (t, 2H), 4.0 (s,1H), 4.74 (s, 1H), 7.0(d, J=8Hz, 2H), 7.15 (d, J=8Hz, 2H), 6.73-7.52 (m, Ar-H, 6H). ESI-MS: 360(M+1) m/z.

3.2 Plausible reaction mechanism for the formation of products:

According to literature survey[13,18,19,20,32] the possible reaction pathway for the formation of desired products is given below.



Scheme 2: Catalytic reaction pathway for the formation of products

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3.3 Effect of various substituents on synthesis of substituted benzo (b) Acridine derivatives.

The reaction was performed with various substituted aromatic aldehydes and two types of cyclohexane 1,3 dione derivatives. All the reactions are investigated at same temperature and same amount of catalyst. The results reveals that geminal methyl groups on cyclohexane 1,3 dione was not appreciably effect for the formation of Acridine derivatives. Both the cyclohexane 1,3dione derivatives gave almost similar results. The results are tabulated in table 1.

Table 1: Optimisation of reaction conditions on the formation of products.

S. No.	R in 1, 3diketone	R^1 in Aromatic Aldehyde	Temp (^{0}C)	Time (min)	Yield (%)	Product
1)	CH_3	H	70^{0}C	50	88	4a
2)	CH_3	4-OCH_3	70^{0}C	55	80	4b
3)	CH_3	4-CH_3	70^{0}C	65	85	4c
4)	CH_3	4-Br	70^{0}C	75	76	4d
5)	CH_3	4-OH	70^{0}C	70	75	4e
6)	CH_3	4-NO_2	70^{0}C	85	70	4f
7)	H	4-OH,3-OC_2H_5	70^{0}C	80	78	4g
8)	H	4-OCH_3, 3-OH	70^{0}C	75	80	4h
9)	H	4-OCH_3, 3-OCH_3,	70^{0}C	75	85	4i
10)	H	4-Cl	70^{0}C	70	80	4j

3.4 Effect of catalyst loading on the formation of products:

The present reaction was also investigated under different catalytic amounts. The result shows that 0.5g of catalyst is adequate to achieve reasonable product yields. Increasing the catalyst quantity further would not lead to a major change in the product yield. Therefore, 0.5g of catalyst was taken for the reaction to perform. The condensation of benzaldehyde, 5,5 dimethyl cyclohexane 1,3-dione, β-napthyl amine (naphthalene 2-amine) in ethanol was selected as the model reaction for this analysis (scheme 1). In table-2, the results are tabulated.

Table-2: Effect of catalyst loading

S.No.	Catalyst loading in (grams)	Time (min)	Yield (%)*
1.	0.2	50	35
2.	0.3	50	55
3.	0.4	50	75
4.	0.5	50	85
5.	0.6	50	88
6.	0.7	50	88

*Reaction conditions: Benzaldehyde (10mmol), 5,5-dimethyl,cyclohexane1,3-dione (10mmol), β-napthyl amine (naphthalene 2-amine) (10mmol) in ethanol (5mL), reflux at 70^{0}C.

3.5 Effect of solvent on the synthesis of benzo(b) Acridine derivatives.

In the presence of polar solvents rather than non-polar solvents, the Knovenagel reaction is favourable, according to the literature survey[15,17,37]. With different classical solvents selected as the medium for the comparison, the present reaction was investigated. The condensation of benzaldehyde, 5,5 dimethyl cyclohexane 1,3-dione, β-napthyl amine (naphthalene 2-amine) in ethanol was selected as the model reaction for this analysis (scheme 1). The findings were contrasted with literature showing that polar solvents such as ethyl alcohol and ethyl acetate were found to be better than non-polar solvents. Bad yields are obtained in the presence of non-polar solvents including toluene and cyclohexane. The findings could be interpreted as the stronger solubility of the reactants in polar solvents. Based on the findings ethyl alcohol was chosen as a suitable

solvent for this transformation. Even though water is polar solvent, trace amounts of yields were obtained due to aggregation of the hydrophobic catalyst. The results are presented in table-3.

Table-3: Effect of solvent on the synthesis of benzo(b) Acridine derivatives.

S.No.	Solvent	Yield (%)*
1.	Ethyl alcohol	85
2.	Ethyl acetate	70
3.	Acetonitrile	58
4.	Water	trace
5.	Toluene	30
6.	Cyclohexane	25

*Reaction conditions: Benzaldehyde (10mmol), 5,5-dimethyl,cyclohexane1,3-dione (10mmol), β-napthyl amine (naphthalene 2-amine) (10mmol) and catalyst (0.5gr) in solvent (5mL), reflux at 70^0C

3.6 Recycling of the Catalyst:

In heterogeneous catalysis, catalyst recyclability and reusability are of considerable concern. Recycling of the catalyst was accomplished by magnetically fixing the catalyst with a heavy Neodymium35 magnet at the bottom of the flask, after which the solution was extracted with a pipette, the solid washed twice with acetone, and the fresh substrate dissolved in the same solvent, enabling the reaction to begin for the next run. Without any apparent loss of its catalytic activity, the catalyst was successively reused five times. These catalysts are highly magnetic and it is found that their magnetization saturation values are 32.45 emu/g, which is much higher than other magnetic catalysts recorded. Therefore an external strong Neodymium35 magnet used for complete isolation of heterogeneous catalyst conveniently.

4. Conclusion

We have reported an effective, inexpensive and modified process for the synthesis of benzo(b) Acridine derivatives using nano copper ferrrite as a heterogeneous reusable catalyst. Low catalyst loading, shorter reaction times and simple work-up procedures are found to be involved in the process. All these features make it an environmentally benign approach for this method.

Acknowledgements: The authors of thankful to the authorities of CSIR-IICT, Hyderabad and Advanced Analytical Laboratories, Andhra University, Visakhapatnam for characterization studies and Dr. SPD is thankful to Principal, AUCE-A and TEQIP-III, AU College of Engineering for the financial assistance to procure chemicals.

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RESEARCH ARTICLE

NANO COPPER FERRITE CATALYZED ONE-POT SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES THROUGH MULTI-COMPONENT HANTZSCH CONDENSATION

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ABSTRACT

A simple, multi component, one-pot synthesis of polyhydro quinoline derivatives (4a-4t) by the condensation of aromatic aldehyde, 1,3-di keto compound, active methylene compound and ammonium acetate catalyzed by nano copper ferrite under reflux conditions has been achieved and reported. This methodology leads shorter reaction times, formation of good to excellent yields of products, recyclability and reuse of the heterogeneous catalyst which makes the present conversion as friendly to the environment.

Keywords: *Single step synthesis, nano copper ferrite, poly hydro quinoline derivatives, Hantzsch condensation, Hetero generous catalyst, recyclability.*

Introduction

In organic synthesis, one-pot multi-component reactions now attract a great deal of attention now a days due to the creation of a single high-yielding product through the condensation of two or more reactants in a one step method[1], such multi-component reactions are convenient and efficient tools for synthesizing biologically and medically active pharmaceutical ingredients[2]. In the design and preparation of important biologically active pharmaceutical groups used in cardiovascular disease treatment[3], hypertension[3], Alzheimer's disease[4] and as a chemosensitizer in tumour therapy[4], polyhydroquinoline derivatives containing 1,4-dihydro pyridine nucleus play a critical role. Heterocyclic compounds containing

polyhydro quinoline moiety are also employed as bronchodilators[5], geroprotective[5] and hepatoprotective agents[5]. Dihydro pyridine moieties present in polyhydro quinoline derivatives have been used for the synthesis of alkaloids[6] and in several organic transformations such as asymmetric reductive amination of aldehydes[7] and hydrogenation of α,β-unsaturated aldehydes and ketones[8,9].

Polyhydroquinoline derivatives received considerable interest from organic chemists in view of the medical, biological and synthetic values. Hence earlier several synthetic strategies reported like carbon transfer reactions of functionalized oxazolidines and their open chain enamine tautomers to enamine nucleophiles[10], reaction of 3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8,9,10-decahydro acridine-1,8-diones with lithium aluminium hydride (LAH)[11] and competative reactions of β-di carbonyl and β-amino vinyl carbonyl compounds with aldehydes[12] for synthesis of substituted polyhydro quinoline derivatives containing 1,4-dihydro pyridine nucleus. Furthur a simple and facile Hantzsch type condensation (which involves the cyclo condensation between aromatic aldehyde, 1,3-di carbonyl compound, active methylene compound and ammonium acetate for the formation of polyhydro quinoline derivatives) has been developed under the influence of different catalysts such as $Yb(OTf)_3$[13], HY-Zeolite[14], Baker's yeast[15], 1,3-Di (bromo or chloro)-5,5-dimethylhydantoin (DBH or DCH)[16], L-proline[17], $Sc(OTf)_3$[18], 1-(4-Sulfonicacid)butyl-3-methylimidazolium hydrogen sulfate ($[(CH_2)_4SO_3HMIM][HSO_4]$)[19], thiamine N-heterocyclic carbine[20], carbon-based solid acid (amorphous carbon consisting of polycyclic aromatic carbon sheets with attached SO_3H groups)[21], poly(ethylene glycol)-linked dicationic acidic ionic liquids (PEG-DAILs)[22], magnetic ferrite (Fe_3O_4) nano particles[23], FeF_3[24], nano-γ-Fe_2O_3-SO_3H[25], Hafnium (IV) bis (perfluoro octanesulfonyl) imide complex ($Hf(NPf_2)_4$ in $C_{10}F_{18}$)[26], silica gel-supported polyphosphoric acid (PPA-SiO2)[27], molecular iodine[28], La_2O_3[29], Montmorillonite K10 Clay ($(Na,Ca)_{0.33}(Al,Mg)_2(Si_4O_{10})(OH)_2 \cdot nH_2O$)[30] , Nafion-H (a superacidic perfluorinated resin sulfonic acid)[31], $ZrCl_4$[32], ceric ammonium nitrate (CAN)[33]. While existing methods are effective in their aspects above, many of these existing synthetic strategies suffer from their own limitations, such as prolonged reaction time[13,14,15,17,18,24,26,31], elevated temperature[16,21,22,23,24,30], complicated work-up for catalyst synthesis[18,23], and difficulty in recovering the catalyst from the reaction mixture[15,17,18,24,28,31,33]. It is therefore unavoidable that an effective method for the preparation of polyhydroquinoline derivatives using magnetically separable heterogeneous catalyst should be developed to overcome these limitations.

Due to performance, economic and environmental considerations, and simple recoverability from the reaction mixture, heterogeneous catalysts have attracted great attention from chemists in recent years. Interestingly, nano particles, relative to their bulk analogues, have a high surface-to-volume ratio and coordination sites, which have a greater number of active sites per unit area[34]. Nano particles, especially ferrite nano particles, have attracted considerable interest in chemistry and material sciences due to their potential applications in catalysis[35]. The paramagnetic and insoluble properties of ferrite nano particles enable the catalyst to be readily separated by a strong external magnet. Previously, copper and cobalt nano ferrites were synthesized and used for various organic transformations[36-42]. As part of our ongoing research copper and cobalt ferrite nano particles were synthesised, characterised and used in the preparation of 2,4,5-tri substituted imidazoles

under reflux conditions[43]. In extension to this Copper ferrite was used as heterogeneous catalyst for the synthesis of poly substituted imidazoles under ultra sound irradiation[44], nickel cobalt ferrite was used as heterogeneous catalyst for one-pot multi-component synthesis of β-acetamido ketones[45], nano copper ferrite was used as heterogeneous catalyst for the synthesis of poly substituted pyridine derivatives in one-pot manner[46] and nano cobalt ferrite was used as heterogeneous catalyst for synthesis of pyranoquinoline derivatives under microwave irradiation[47]. Now Copper ferrite nano particles were used as magnetically separable catalyst for the one-pot synthesis of polyhydro quinoline derivatives by the condensation of aromatic aldehyde, 1,3-di keto compound, active methylene compound and ammonium acetate under reflux conditions, which was represented in **scheme 1and 2**. This current reported method involves shorter reaction time, mild reaction temperature and easy separation of the catalyst from the reaction mixture. With no significant loss of its catalytic activity, the recycled catalyst can be reused for the next five consecutive cycles. In this research, nano copper ferrite was used for the synthesis of polyhydro quinoline derivatives as a mild and effective catalyst.

2. Experimental:

2.1 Material and Methods:

All chemicals are obtained from commercial sources, liquid aromatic aldehydes are purified by distillation prior to use. Solvent evaporation is done in the superfit Rotavap (800mL). The desired products were confirmed by IR, ^{1}H NMR and MASS spectral data. ^{1}H NMR spectral data was recorded on the Bruker-Avance 400MHz spectrophotometer 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. FTIR spectra were recorded on SHIMADZU FT-IR with IR prestige-21 version. Using a Perkin-Elmer PE SCIEX-API 2000, equipped with an ESI source, the MASS spectra were reported using an online HPLC device following an ultraviolet (UV) detector.

2.2 Preparation of Copper ferrite:

As previously reported by us, the spinel nano copper ferrite was produced by sol-gel citrate precursor method[43].

2.3 Characterization of Copper ferrite:

As previously reported by us, nano copper ferrite was characterized by FTIR, SEM, TEM, XRD and particle size analyzer[43].

2.4 General Procedure for the Synthesis of Polyhydro quinoline Derivatives:

In a 50mL round bottom flask, 1,3-di-ketone (10mmol), aromatic aldehyde (10mmol), active methylene compound (10mmol), ammonium acetate (10mmol) and Copper ferrite (500mg) (previously activated for 2 minutes in the microwave oven) were taken and 5mL of ethanol was applied to dissolve the contents in the flask. The reaction mixture was then refluxed for a prescribed period of time. TLC (n-hexane: ethyl acetate 4:1) was used to monitor the reaction progress. After the reaction was completed, an external strong Neodyneium35 magnet was used to separate the catalyst from the reaction mixture. Then 20mL of ethanol was added and concentrated under the rotary evaporator. The solid product was recrystallised several times with hot ethanol after evaporation of the solvent to obtain the corresponding pure product. IR, ^{1}H NMR and MASS spectral analysis have confirmed the products.

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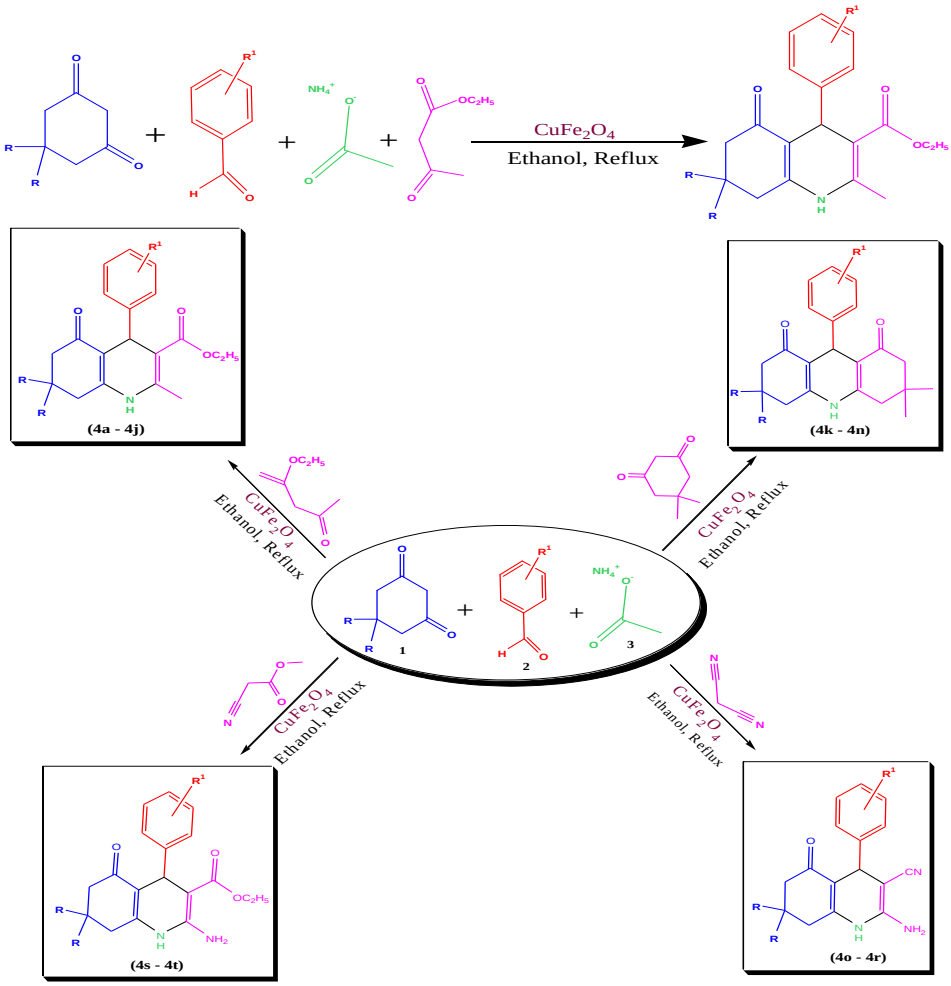
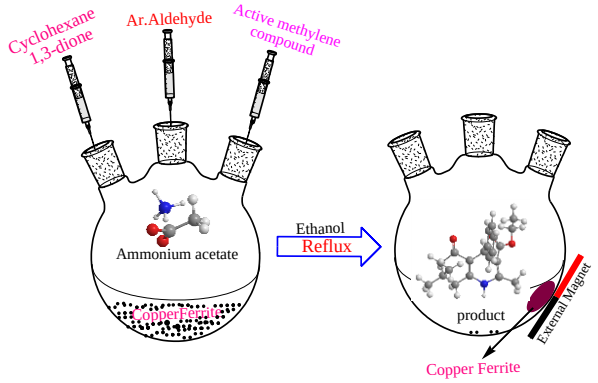
Scheme 1:



4a) R=H, R^1=H, 4b) R=H, R^1= p-OCH_3, 4c) R=H, R^1= p-F, 4d) R=H, R^1= p-CH_3, 4e) R=H, R^1= p-NO_2, 4f) R=CH_3, R^1= p-Br, 4g) R=CH_3, R^1= m-OC_2H_5, p-OH, 4h) R=CH_3, R^1= p-OH, 4i) R=CH_3, R^1= m-OH, p-OCH_3, 4j) R=CH_3, R^1= m-OCH_3, p-OCH_3, 4k) R=CH_3, R^1=H, 4l) R=CH_3, R^1= O-OCH_3, 4m) R=CH_3, R^1= m-OC_2H_5, p-OH, 4n) R=CH_3, R^1= m-OCH_3, p-OCH_3, 4o) R=CH_3, R^1= p-OCH_3, 4p) R=CH_3, R^1= p-Cl, 4q) R=CH_3, R^1= m-OH, p-OCH_3, 4r) R=CH_3, R^1= m-OC_2H_5, p-OH, 4s) R=CH_3, R^1=H, 4t) R=CH_3, R^1= p-Cl

Scheme 2: Schematic representation of synthesis of various polyhydro quinoline derivatives using $CuFe_2O_4$

2.5 Graphical Abstract:



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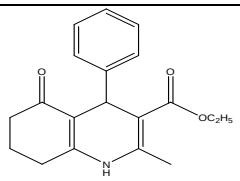
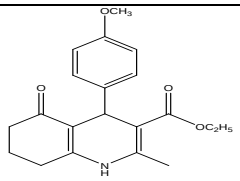
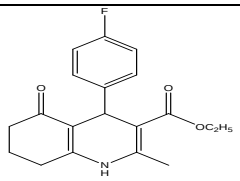
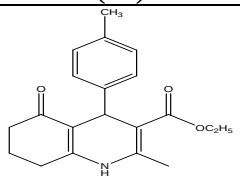
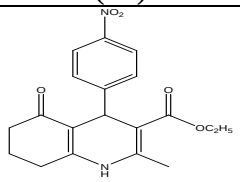
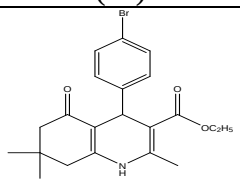
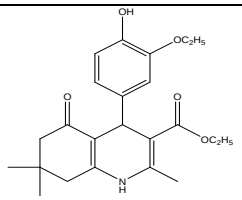
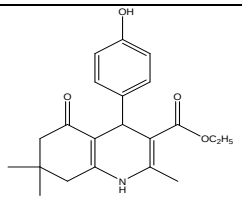
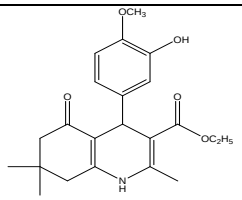
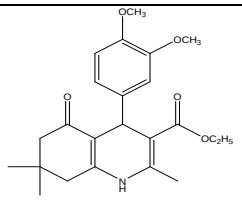
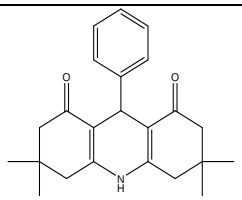
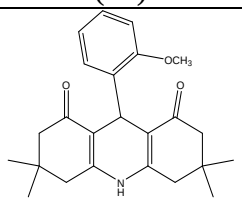
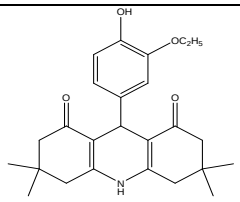
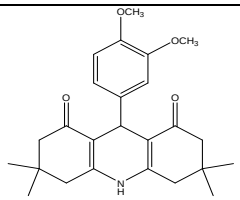
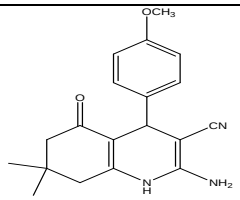
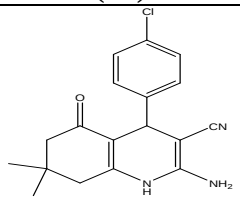
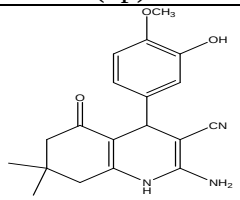
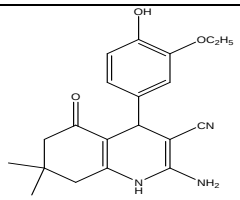
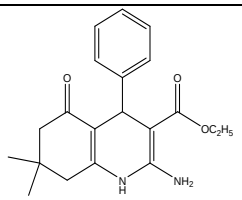
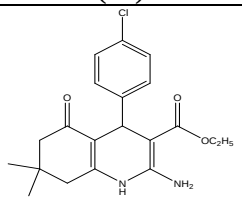
2.6 Spectral data:

Product	Spectral data
 ethyl 2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4a)	White solid, IR (KBr, cm^{-1}): 3300, 3073, 2985, 1700, 1674, 1610, 1420, 1384, 1280, 1230, 885, 715. ^{1}HNMR (400MHz, $CDCl_3$) δ (ppm) : 1.3(t,3H), 1.44 (m,2H), 1.71(s,3H), 1.96 (t,2H), 2.94(t,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 7.06 (d, J=8Hz, 2H), 7.07(t, J=7.6Hz,1H), 7.14 (dd, 2H), ESI-MS: 312(M+1) m/z.
 ethyl 4-(4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4b)	White solid, IR (KBr, cm^{-1}): 3295, 3083, 2990, 1695, 1684, 1618, 1420, 1394, 1320, 1284, 1224, 825, 710. ^{1}HNMR (400MHz, $CDCl_3$) δ (ppm) : 1.3(t,3H), 1.44 (m,2H), 1.71(s,3H), 1.96 (t,2H), 2.94(t,2H), 3.73(s,3H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 6.95 (d, J=8Hz, 2H), 7.65(d,J=7.6Hz,2H),. ESI-MS: 343(M+1) m/z.
 ethyl 4-(4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4c)	White solid: IR (KBr, cm^{-1}): 3290, 3218, 3078, 2980, 1703, 1674, 1614, 1410, 1362, 1280, 1230, 980, 850. ^{1}H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.3(t,3H), 1.44 (m,2H), 1.71(s,3H), 1.96 (t,2H), 2.94(t,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 6.85 (d, J=8Hz, 2H), 7.04 (d, J=8Hz, 2H). ESI-MS: 330 (M+1) m/z.
 ethyl 2-methyl-5-oxo-4-*p*-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4d)	White solid: IR (KBr, cm^{-1}): 3283, 3233, 3073, 2985, 1693, 1684, 1610, 1415, 1394, 1280, 1230, 830. ^{1}H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.28 (t, 3H), 1.45 (m, 2H), 1.71(s,3H), 1.96 (t,2H), 2.35(s,3H), 2.94(t,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 6.94 (d, J=8Hz, 2H), 6.85 (d, J=8Hz, 2H); ESI-MS: 326 (M+1) m/z.
 ethyl 2-methyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4e)	Pale yellow solid: IR (KBr, cm^{-1}): 3296, 3248, 3076, 2936, 1704, 1657, 1636, 1517, 1390, 1348, 1283, 820. ^{1}H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.3 (t, 3H), 1.48(m, 2H), 1.71(s,3H), 1.96 (t,2H), 2.94(t,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 7.32 (d, J=7.6 Hz, 2H), 8.10 (d, J=7.6 Hz, 2H). ESI-MS: 357 (M+1) m/z.
 ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f)	White solid: IR (KBr, cm^{-1}): 3274, 3191, 2966, 2936, 1703, 1647, 1600, 1377, 1367, 1242, 830, 810. ^{1}H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.3 (t, 3H), 1.71(s,3H), 1.88 (s,2H), 2.86(s,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 6.95 (d, J=8 Hz, 2H), 7.31 (d, J=8 Hz, 2H); ESI-MS: 418 (M+1) m/z.

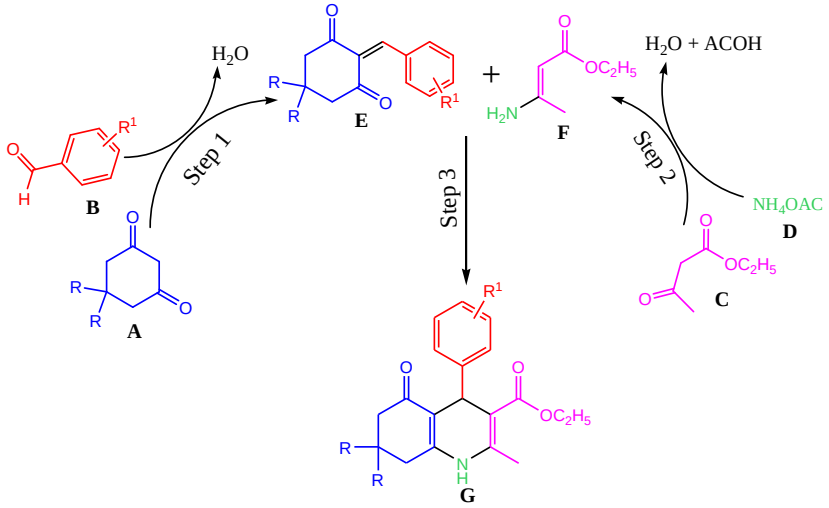
 ethyl 4-(3-ethoxy-4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4g)	White solid: IR (KBr, cm^{-1}): 3493, 3287, 3200, 2966, 2958, 1687, 1647 1613, 1410, 1381, 1368, 1270, 1310, 1217, 850, 780. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.10(s,6H), 1.28 (t, 3H), 1.33 (t, 3H), 1.71(s,3H), 1.88 (s,2H), 2.86(s,2H), 3.9(q, 2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 5.0(brs, 1H), 6.4 (s, 1H), 6.45 (d, J=8 Hz, 1H), 6.5 (d, J=8 Hz, 1H). ESI-MS: 400 (M+1) m/z.
 ethyl 4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4h)	White solid: IR (KBr, cm^{-1}): 3439, 3280, 3208, 2964, 2812, 1679, 1652, 1611, 1395, 1379, 1369, 1308, 1270, 830, 750. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.3 (t, 3H), 1.71(s,3H), 1.88 (s,2H), 2.86(s,2H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 5.0(brs, 1H), 6.61 (d, J=8 Hz, 2H), 6.89 (d, J=8 Hz, 2H). ESI-MS: 356 (M+1) m/z.
 ethyl 4-(3-hydroxy-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4i)	White solid: IR (KBr, cm^{-1}): 3388, 3243, 2953, 2911, 1700, 1643, 1601, 1420, 1385, 1368, 1307, 1275, 1211, 886, 782; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12(s,6H), 1.3 (t, 3H), 1.71(s,3H), 1.88 (s,2H), 2.86(s,2H), 3.73(s, 3H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 5.0(brs, 1H), 6.42 (s, 1H), 6.48 (d, J=8 Hz, 1H), 6.51 (d, J=8 Hz, 1H). ESI-MS: 386 (M+1) m/z.
 ethyl 4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4j)	White solid: IR (KBr, cm^{-1}): 3279, 2957, 2912, 1695, 1645, 1604, 1391, 1379, 1267, 1216, 820, 788. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.3 (t, 3H), 1.71(s,3H), 1.88 (s,2H), 2.86(s,2H), 3.73(s, 6H), 4.0(brs,1H), 4.19 (q,2H), 4.43(s,1H), 6.46 (s, 1H), 6.51 (d, J=8 Hz, 1H), 6.54 (d, J=8 Hz, 1H). ESI-MS: 400 (M+1) m/z.
 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4k)	White solid: IR (KBr, cm^{-1}): 3233, 3190, 2930, 1690, 1595, 1602, 1410, 1375, 1368, 1268, 777, 750. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,12H), 1.88 (s,4H), 2.86(s,4H), 4.0(brs,1H), 4.43(s,1H), 7.06 (d, J=8 Hz, 2H), 7.1 (dd, J=8 Hz, 1H), 7.14(m, 2H); ESI-MS: 350 (M+1) m/z.
 9-(2-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4l)	Pale yellow solid: IR (KBr, cm^{-1}): 3342, 3220, 2957, 1721, 1641, 1608, 1394, 1348, 1248, 1210, 775. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,12H), 1.88 (s,4H), 2.86(s,4H), 3.73(s,3H) 4.0(brs,1H), 4.43(s,1H), 6.65-6.96 (m, Ar, 4H). ESI-MS: 380 (M+1) m/z.

 9-(3-ethoxy-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4m)	Pale Yellow solid: IR (KBr, cm^{-1}):3275, 3257, 3202, 2938, 1680, 1620,1608,1395, 1365, 1274, 1228, 1220, 885, 750. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,12H), 1.88 (s,4H), 1.33(t, 3H), 2.86(s,4H), 3.98(q,2H) 4.0(brs,1H), 4.43(s,1H), 5.0(s,1H), 6.4 (s, 1H), 6.45 (d, J=8 Hz, 1H), 6.5 (d, J=8 Hz, 1H). ESI-MS: 410 (M+1) m/z.
 9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2*H*,5*H*,9*H*,10*H*)-dione (4n)	Pale Yellow solid: IR (KBr, cm^{-1}): 3273, 3198, 2962, 1662, 1642, 1589, 1425, 1380, 1369, 1235, 1223, 850, 720. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,12H), 1.88 (s,4H), 1.33(t, 3H), 2.86(s,4H), 3.73(s,6H) 4.0(brs,1H), 4.43(s,1H), 6.46 (s, 1H), 6.51 (d, J=8 Hz, 1H), 6.54 (d, J=8 Hz, 1H). ESI-MS: 410 (M+1) m/z.
 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4o)	White solid: IR (KBr, cm^{-1}): 3426, 3368, 3209, 2930, 2245, 1655, 1606, 1510, 1395, 1362, 1213, 870. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.88 (s,2H), 2.2(brs,2H) 2.86(s,2H), 3.73(s,3H), 4.0(brs,1H), 4.43(s,1H), 6.65 (d, J=8 Hz, 2H), 6.95(d, J=8 Hz, 1H); ESI-MS: 324 (M+1) m/z.
 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4p)	White solid: IR (KBr, cm^{-1}): 3395, 3310, 3198, 2984, 2285, 1675, 1634, 1495, 1365, 1310, 860, 760. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.88 (s,2H), 2.2(brs,2H) 2.86(s,2H), 4.0(brs,1H), 4.43(s,1H), 7.00 (d, J=8 Hz, 2H), 7.15(d, J=8 Hz, 1H). ESI-MS: 328 (M+1) m/z.
 2-amino-4-(3-hydroxy-4-methoxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4q)	White solid: IR (KBr, cm^{-1}): 3550, 3431, 3312, 3184, 2958, 2290, 1685, 1599, 1511, 1372, 1365, 1270, 1219, 867, 761. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.88 (s,2H), 2.2(brs,2H) 2.86(s,2H), 3.73(s, 3H), 4.0(brs,1H), 4.43(s,1H), 5.0(s, 1H), 6.42 (s, 1H), 6.48 (d, J=8 Hz, 1H), 6.51 (d, J=8 Hz, 1H). ESI-MS: 340 (M+1) m/z.
 2-amino-4-(3-ethoxy-4-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (4r)	White solid: IR (KBr, cm^{-1}): 3495, 3450, 3329, 3150, 2950, 2245, 1682, 1600, 1516, 1385, 1352, 1277, 1213, 850, 740. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.33(t,3H), 1.88 (s,2H), 2.2(brs,2H) 2.86(s,2H), 3.9(q,2H), 4.0(brs,1H), 4.43(s,1H), 5.0(s, 1H), 6.4 (s, 1H), 6.45 (d, J=8 Hz, 1H), 6.5 (d, J=8 Hz, 1H). ESI-MS: 354 (M+1) m/z.

 ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4s)	White solid: IR (KBr, cm^{-1}): 3380, 3289, 2980, 2950, 1691, 1655, 1524, 1372, 1361, 786, 760. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.3(t,3H), 1.88 (s,2H), 2.0(brs,2H) 2.86(s,2H), 3.9(q,2H), 4.0(brs,1H), 4.19(q,3H), 4.43(s,1H), 7.06-7.17(m, Ar, 5H); ESI-MS: 341 (M+1) m/z.
 ethyl 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate 4t)	White solid: IR (KBr, cm^{-1}): 3480, 3328, 2976, 2869, 2360, 1688, 1622, 1525, 1371, 1359, 858, 775, 640. ^1H NMR ($CDCl_3$, 400 MHz)(ppm in δ): 1.11(s,6H), 1.3(t,3H), 1.88 (s,2H), 2.0(brs,2H) 2.86(s,2H), 3.9(q,2H), 4.0(brs,1H), 4.19(q,3H), 4.43(s,1H), 7.00 (d, J=8 Hz, 2H), 7.15(d, J=8 Hz, 1H); ESI-MS: 375 (M+1) m/z.

3. RESULTS AND DISCUSSION

3.1 Proposed reaction mechanism for formation of products:



Scheme 3: Plausible reaction path way for the formation of products.

According to the literature survey[16,17,23,48] the plausible reaction path way has been proposed in Scheme 3. The above interpretations permit us to conclude that in Step1 Knoevenagel type adduct (E) was formed by the condensation between 1,3-di ketone (A) and aromatic aldehyde (B). Enamine type of intermediate (F) was formed in Step 2 by the condensation between active methylene compound (C) and ammonium acetate (D). Step 3 involves the Michael type of reaction between (E) and (F) leads to the formation of substituted polyhydro quinoline derivative (G). The role of the catalyst comes in step 1 and 3, where Copper ferrite particles catalyses the Knoevenagel condensation between 1,3-di ketone and aromatic aldehyde. Then Micheal type of reaction takes place between Knoevenagel type of adduct and enamine intermediate. The role of catalyst in the activation of reactants was shown in Scheme 4. The mechanism follows same pathway with all active methylene compounds.

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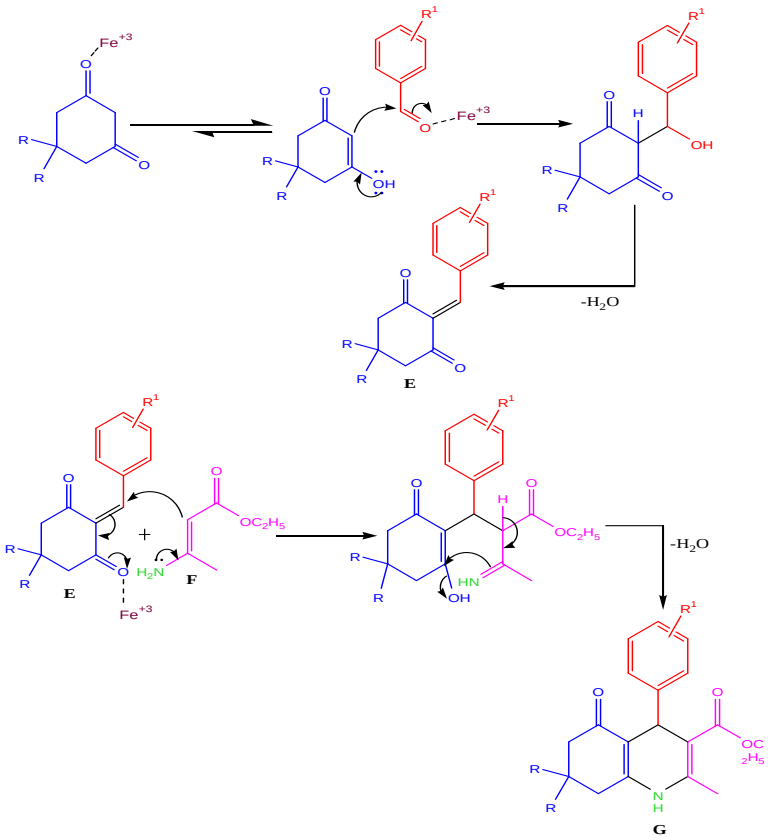

Scheme 4: Catalytic reaction path way of formation of products.

3.2 Optimization of Reaction Conditions:

3.2.1: Comparison of the effect of the current catalyst on the synthesis of substituted polyhydro quinoline derivatives with other catalysts:

Several catalytic methods for the synthesis of polyhydro quinoline derivatives via Hantzsch reaction have been reported earlier as described in the introduction section. The efficacy of Copper ferrite nano particles has been compared with some other recorded catalysts in this study. For this reason, the model reaction (Scheme 1) was chosen as a mixture of 4-hydroxy benzaldehyde, 5,5-di-methyl, cyclohexane 1,3-dione, ethyl acetoacetate and ammonium acetate to evaluate the use of nano-copper ferrite and to investigate optimised reaction conditions. The observations have been summarised in Table 1.

Table 1: Nano copper ferrite's comparative catalytic study with other earlier reported catalysts

S.No.	Catalyst	Time	Temp (^{0}C)	Yield (%)	Ref.
1.	Baker's yeast	24hrs	R.T.	81	15
2.	$Hf(NPf_2)_4$ in $C_{10}F_{18}$	4hrs	60	87	26
3.	$Yb(OTf)_3$	8hrs	R.T.	90	13
4.	PEG-DAIL	40min	80	86	22
5.	Montmorillonite K10 Clay	30min	80	91	30
6.	nano-γ-Fe_2O_3-SO_3H	50min	60	93	25
7.	Nano $CuFe_2O_4$	14min	60	90	Present work

$Hf(NPf_2)_4$ in $C_{10}F_{18}$ = Hafnium (IV) bis (perfluoro octanesulfonyl) imide complex, PEG-DAIL= poly(ethylene glycol)-linked dicationic acidic ionic liquid, MontmorilloniteK10 Clay= $(Na,Ca)_{0.33}(Al,Mg)_2(Si_4O_{10})(OH)_2{\cdot}nH_2O$,.

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3.2.2 Effect of catalyst loading on the formation of products.

The present reaction was also investigated under different catalytic amounts. The result shows that 0.5 g of catalyst is adequate to achieve reasonable product yields. Increasing the catalyst quantity further would not lead to a major change in the product yield. Therefore, 0.5g of catalyst was taken for the reaction to perform. The condensation of 4-bromo benzaldehyde, 5,5-dimethyl, cyclohexane1,3-dione, ethylacetoacetate and ammonium acetate in ethanol was selected as the model reaction for this analysis (Scheme 1). In table 2, the results are tabulated.

Table 2: Catalyst loading on product formation.

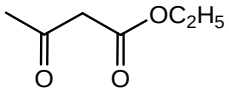
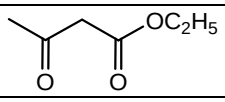
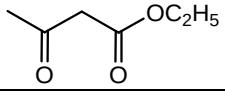
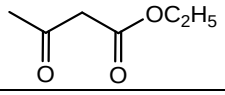
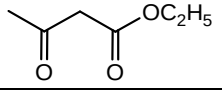
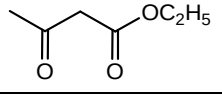
S.No.	Catalytic loading in (grams)	Time (min)	Yield (%)*
1.	0.2	12	42
2.	0.3	12	66
3.	0.4	12	78
4.	0.5	12	90
5.	0.6	12	92
6.	0.7	12	92

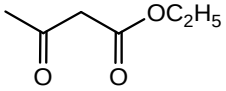
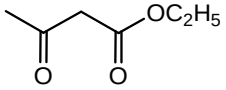
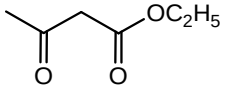
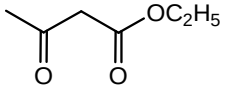
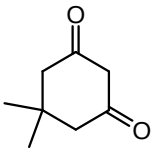
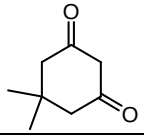
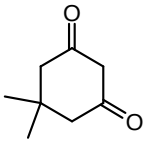
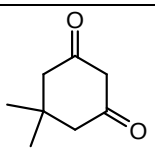
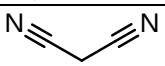
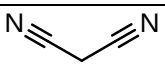
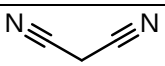
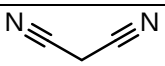
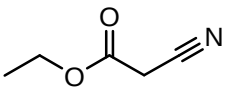
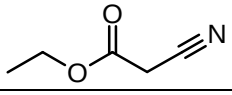
*Reaction conditions: 4-bromo benzaldehyde (10mmol), 5,5-dimethyl,cyclohexane1,3-dione (10mmol), ethylacetoacetate (10mmol) and ammonium acetate (10mmol) in ethanol (5mL), reflux at 60^0C

3.2.3 Effect of reaction conditions on synthesis of various polyhydro quinoline derivatives.

The reaction was performed with diffrent substituted aromatic aldehydes and active methylene compounds in presence of catalyst. When ethylacetoacetate, 5,5-di-methyl,1,3-cyclohexane dione were taken as active methylene compounds in the model reaction, the reflux reaction is carried out at 60^0 C and 50^0 C respectively. But interesting results were obtained when malononitrile and ethyl 2-cyano acetate were taken as active methylene compounds. While using malononitrile and ethyl 2-cyanoacetate as active metylene compounds, the products were formed at room temperature on occasional stirring for prescribed time. The observations are tabulated in table 3.

Table 3: Optimization of reaction conditions for the synthesis of different derivatives of polyhydro quinolines.

S.No.	R^1 in Aromatic aldehyde	R in 1,3-di keto compound	Active methylene molecule	Temp (^{0}C)	Time (min)	Yield (%)	Product
1.	H	H		60	18	94	(4a)
2.	4-OCH_3	H		60	20	92	(4b)
3.	4-F	H		60	16	88	(4c)
4.	4-CH_3	H		60	20	90	(4d)
5.	4-NO_2	H		60	35	84	(4e)
6.	4-Br	CH_3		60	12	90	(4f)

7.	3-OC_2H_5, 4-OH	CH_3		60	20	88	(4g)
8.	4-OH	CH_3		60	14	90	(4h)
9.	3-OH,4-OCH_3	CH_3		60	25	86	(4i)
10.	3,4 di-OCH_3	CH_3		60	28	88	(4j)
11.	H	CH_3		50	20	90	(4k)
12.	2-OCH_3	CH_3		50	30	82	(4l)
13.	3-OC_2H_5, 4-OH	CH_3		50	35	80	(4m)
14.	3,4 di-OCH_3	CH_3		50	40	84	(4n)
15.	4-OCH_3	CH_3		R.T.	45	86	(4o)
16.	4-Cl	CH_3		R.T.	40	82	(4p)
17.	3-OH,4-OCH_3	CH_3		R.T.	50	84	(4q)
18.	3-OC_2H_5, 4-OH	CH_3		R.T.	50	88	(4r)
19.	H	CH_3		R.T.	45	94	(4s)
20.	4-Cl	CH_3		R.T.	55	90	(4t)

After observation of the results experimentally, we conclude that the formation of products from (4o) to (4t) at room temperature is due to liberation of heat during the addition of activemethylene compound to the contents, which leads to activate the catalyst, which promote the reaction towards the formation of products. In absence of catalyst the formation of products was not possible at room temperature, because the heat liberated during the addition will not sufficient to lead the reaction alone.

3.2.4 Effect of solvent on the synthesis of polyhydro quinoline derivatives:

In the presence of polar solvents rather than non-polar solvents, the Hantzsch reaction is favourable, according to the literature survey[19,24,26]. With different classical solvents selected as the medium for the comparison, the present reaction was investigated. For this analysis, the mixture of 4-bromo benzaldehyde, 5,5-dimethyl,cyclohexane1,3-dione, ethylacetoacetate, ammonium acetate, nano Copper ferrite (500mg) was taken as the model reaction in the investigated solvent (Scheme 1). The findings were contrasted with literature showing that polar solvents like ethyl alcohol and ethyl acetate were better than non-polar solvents. Bad yields are obtained in the presence of non-polar solvents including toluene and cyclohexane. The findings could be interpreted as the stronger solubility of the reactants in polar solvents. Based on the findings ethyl alcohol was chosen as a suitable solvent for this transformation. Even though water is polar solvent, trace amounts of yields were obtained due to aggregation of the hydrophobic catalyst. The results are presented in table 4.

Table 4: Effect of solvent on the synthesis of polyhydro quinoline derivatives.

S.No.	Solvent	Yield (%)*
1.	Ethyl alcohol	90
2.	Ethyl acetate	70
3.	Acetonitrile	58
4.	Water	trace
5.	Toluene	30
6.	Cyclohexane	25

*Reaction conditions: Mixture of 5,5-dimethyl,cyclohexane 1,3-dione (10mmol), p-bromo benzaldehyde (10mmol), ethylacetoacetate (10mmol), ammonium acetate (10mmol), nano Copper ferrite (500mg) in the investigated solvent (5mL) was refluxed at 60^0 C for 12min.

3.2.5 Recycling of the Catalyst:

In heterogeneous catalysis, catalyst recyclability and reusability are of considerable concern. Recycling of the catalyst was accomplished by magnetically fixing the catalyst with a heavy Neodymium35 magnet at the bottom of the flask, after which the solution was extracted with a pipette, the solid washed twice with acetone, and the fresh substrate dissolved in the same solvent, enabling the reaction to begin for the next run. Without any apparent loss of its catalytic activity, the catalyst was successively reused five times. These catalysts are highly magnetic and it is found that their magnetization saturation values are 32.45 emu/g, which is much higher than other magnetic catalysts recorded. Therefore an external strong Neodymium35 magnet used for complete isolation of heterogeneous catalyst conveniently.

4. Conclusion:

We have reported an effective, inexpensive and modified process for the synthesis of polyhydro quinoline derivatives using nano copper ferrite as a heterogeneous reusable catalyst. Low catalyst loading, shorter reaction times and simple work-up procedures are found to be involved in the process. All these features make it an environmentally benign approach for this method

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

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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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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 ac-

count [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

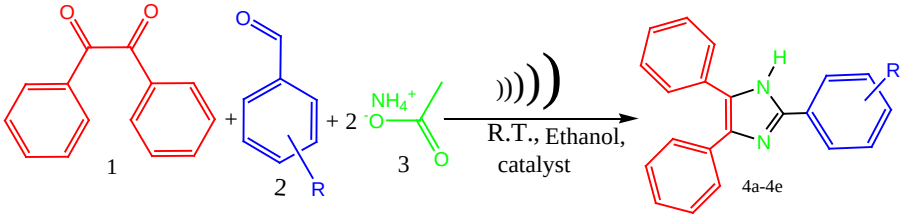
The catalyst has been characterized using FTIR, SEM, TEM, XRD and particle size analyzer as reported earlier [46].

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.

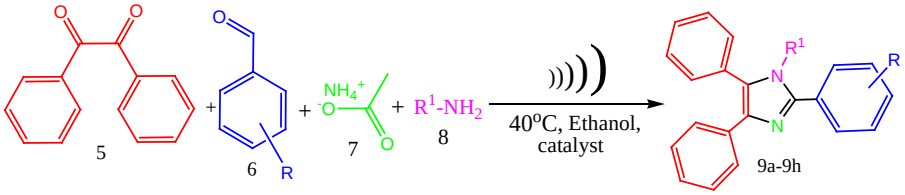
2.5. General Procedure for the Synthesis of 1,2,4,5-Tetra Substituted Imidazoles

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.

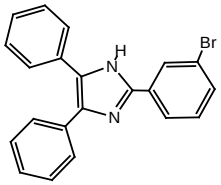
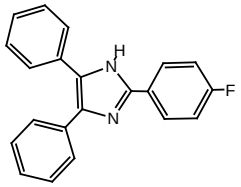
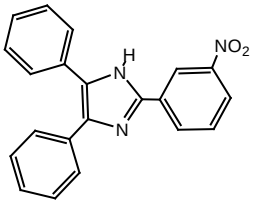


a) R= H, R^1= C_6H_5 b) R= p-OCH_3, R^1= C_6H_5, c) R= H, R^1= C_6H_5-CH_2
d) R= p-OCH_3, R^1= C_6H_5-CH_2 e) R= p-CH_3, R^1= C_6H_5-CH_2 f) R=p-Cl, R^1=C_6H_5-CH_2
g) R=p-Cl, R^1=cyclohexyl h) R=p-CH_3, R^1=cyclohexyl

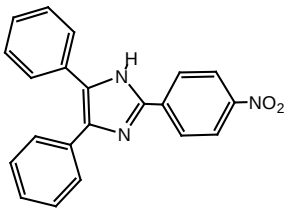
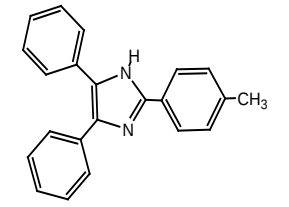
Scheme 2. A generalized scheme for synthesis of 1,2,4,5-tetra substituted imidazoles in presence of catalyst by cyclo condensation of benzil, aromatic aldehyde, ammonium acetate and substituted amine under ultra sonic irradiation.

2.6. Spectra Data

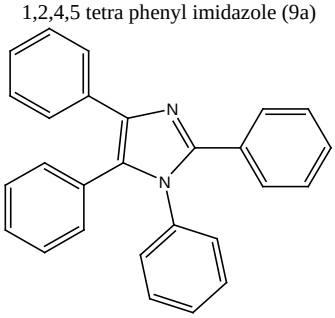
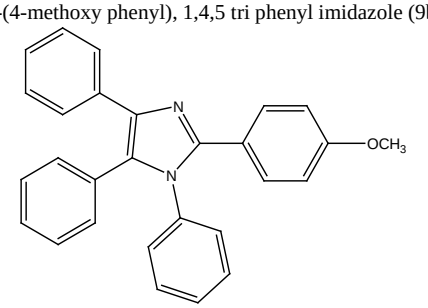
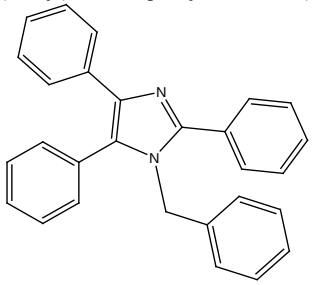
2.6.1. Spectral Data for 2,4,5-Tri Substituted Imidazoles

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

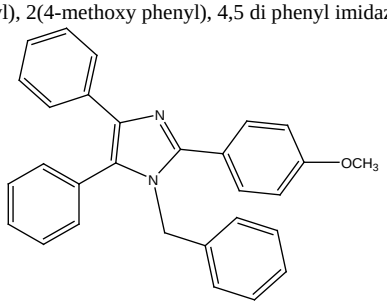
2-(4-Nitro phenyl)-4,5,diphenyl-1-H Imidazole: (4d) 	M.P: 199˚C - 201˚C. FTIR (KBr, cm^{-1}): 3402, 2928, 1598, 1519, 1346, 856; ^{1}H NMR (Bruker) (400 MHz, $CDCl_3$/DMSO-d_6): δ = 12.81 (s, 1H), 8.01 - 7.42 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ = 148.9, 143.7, 131.6, 130.6, 129.7, 128.4, 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);

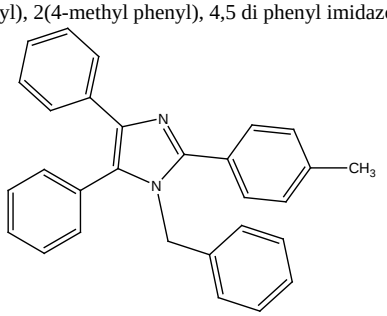
Continued

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



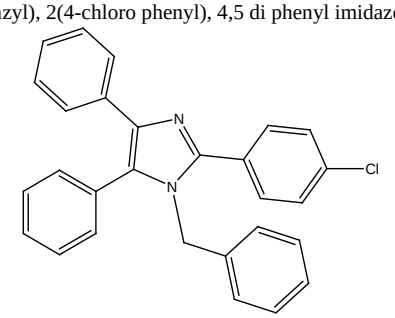
M.P: 158˚C - 160˚C: FTIR (KBr, (cm^{-1}) : 3047 (C-H aromatic), 1604 (C=C aromatic); ^{1}HNMR (400 MHz, $CDCl_3$/DMSO-d_6): d 7.58 (d, J1/4 7.8 Hz, 4H), 7.31 - 7.12 (m, 11H), 6.92 - 6.80 (m, 4H), 5.08 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ = 159.9, 147.9, 137.6, 134.5, 131.0, 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)



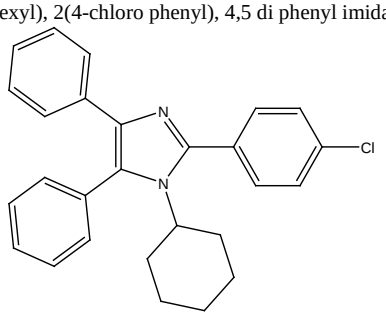
M.P: 168˚C - 170˚C: FTIR (KBr) (cm^{-1}): 3020 (C-H aromatic), 1600 (C=C aromatic), 1484 (C=N), 1448.
^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 6.80 - 7.59 (m, 19H, Ar-H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6):
δ = 159.9, 147.9, 137.6, 134.5, 131.0, 130.9, 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)



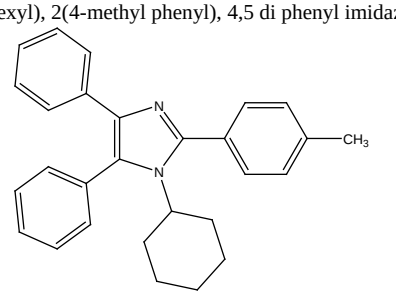
M.P: 162˚C - 164˚C: FTIR (KBr) (cm^{-1}): 1600, 1477, 1447, 1414.
^{1}HNMR (400 MHz, $CDCl_3$/DMSO-d_6): δ = 5.08 (s, 2H, CH_2), 6.81 - 7.60 (m, 19H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ = 48.3, 125.9, 126.5, 126.8, 127.5, 128.1, 128.7, 128.75, 128.8, 128.85, 129.5, 130.2, 130.4, 130.8, 131.0, 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

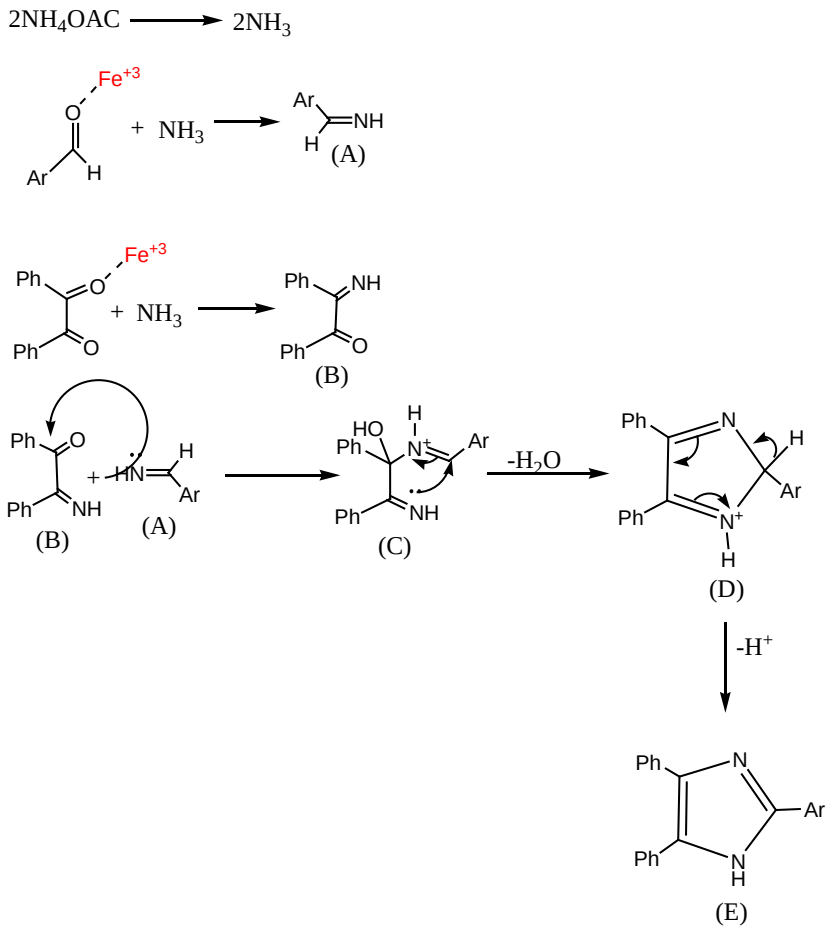
3.1. Plausible Mechanism for the Formation of Products under Nano Copper Ferrite

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

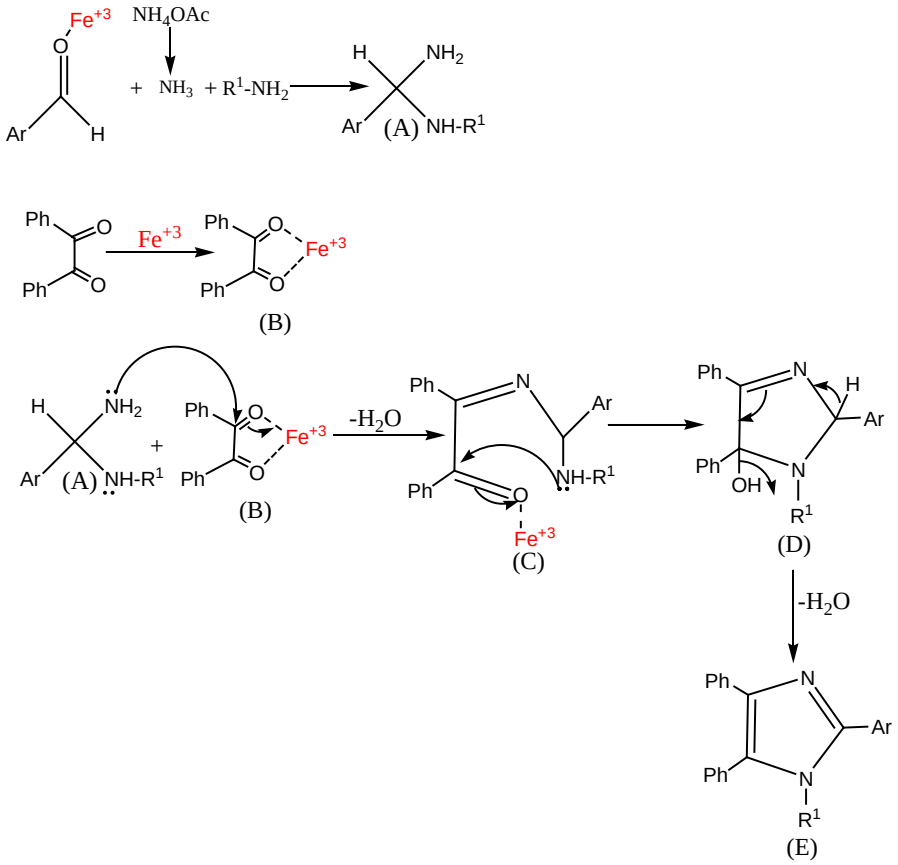


Scheme 3. Plausible mechanism for the formation of 2,4,5-tri substituted Imidazoles.

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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One-Pot Synthesis of Substituted Pyridine

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Abstract

The studies on application of magnetically separable substituted nano ferrites towards the multicomponent one-pot synthesis of heterocyclic compounds were thoroughly investigated. The present study gives an efficient method for the one-pot three-component synthesis of poly substituted pyridine derivatives by the cyclo-condensation of aromaticaldehyde, malononitrile and substituted phenols in the presence of magnetically recoverable nano copper ferrite catalyst. This method involve simproved advantages like low percentage of catalyst used, lesser reaction times, higher yields ,magnetic recoverability and reuse of the catalyst, which makes it an environmentally benign process.

Keywords: Nano copper-ferrite, Magnetically separable catalyst, One-pot multi-component synthesis, Poly substituted pyridines.

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I.INTRODUCTION

Multi-component reactions play a significant role in the organic synthesis particularly in the synthesis of medicinally potent heterocyclic compounds. It involves a simple workup procedure for the synthesis of medicinally privileged scaffolds by the combination of two or more components in a single step process. Thereby it offers a great advantage over convergent, combinatorial and multistep synthesis. [1]

The poly substituted pyridine moiety has been identified as key constituent in many naturally occurring and synthetic biological active pharmaceuticals. Among these pyridine derivatives of 2-amino-pyridine-3,5-dicarbonitrile skeleton have great importance as medicinally active compounds like antiprion, antibacterial, anti-biofilm, anti-infective, anticancer and anti-hepatitis-B. Penta-substituted pyridine moiety is a medicinally privileged scaffold useful in the potassium channel opening for the treatment of urinary incontinence and the treatment for Creutzfeldt-Jakob disease, Parkinson disease, Hypoxia, Asthma, kidney disease and Epilepsy. The importance of this class of compounds can be understood by the number of patents filed in recent years. [2,3,4]

Due to vast range of biologically active poly substituted pyridine frameworks, they attract much attention in their synthesis. A number of procedures were carried out for the synthesis of poly-substituted pyridine derivatives using various synthetic procedures such as Diels-Alder reaction of 3-siloxy-1-aza-1,3-butadiene with 6-alkyl-3,5-dichloro-2H-1,4-oxazin-2-one with different types of acetylenic compounds, [4+2] cycloaddition of oximinosulphonates,Vilsmeier-Haackreaction α-hydroxy ketene dithioacetals, Ruthenium-catalysed cyclo-isomerisation of 3-azadienynes and 6 π-azaelectrocyclization of azatrienes which limit with conventional multi-step process, low yield and challenging work up procedures. [5,6,7]

Afterward a first convenient and interesting synthetic methodology reported for the one- pot synthesis of poly-substituted pyridine derivatives by the cyclocondensation of aromatic aldehyde, malononitrile and thiophenol using Et3N or 1, 4-diazabicyclo[2,2,2]-octane [DABCO] as catalyst. Then a few MCR methods have been reported for the one-pot synthesis of poly substituted pyridine derivatives by the three component condensation of aromatic aldehyde, malononitrile and thiophenol in presence of various catalysts like K2CO3 under reflux, Ionic liquid 1-n-butyl-3-methylimidazolium hydroxide, Nano crystalline MgO, Ammonium hydroxide, TBAH [tetra butyl ammonium hydroxide] and Piperdine. The above reported methods have their own importance and merits. But these methods limit in their longer reaction times, low yields, use of toxic chemicals and non- recoverability of the catalyst. Hence there is a necessity to develop newer, greener, effective and environmental friendly methods of synthesis of poly substituted pyridine derivatives. It is further observed that in the above reported methods thiophenol has been used as a reactant but substituted phenolic derivatives such as 2-amino-6-phenoxy-pyridine-3, 5- dicarbonitrile derivatives have not been reported. [8,9,10]

Nano copper ferrite has earlier been used as magnetically separable catalyst for several organic synthetic reactions such as asymmetric hydrosilylation of ketones, synthesis of diaryl or aryl alkyl sulfides via cross coupling process under ligand free conditions, synthesis of substituted benzoxazoles

via Ullmann-type coupling under ligand free conditions, cross- coupling of aryl halides with diphenyl diselenide, green one-pot three component synthesis of spirooxindoles, multicomponent synthesis of 1,4-di substituted 1,2,3-triazoles in tap water and synthesis 1,4 dihydro pyridines involving aromatic aldehyde, ethylacetoacetate and ammonium acetate. [11,12,13,14]

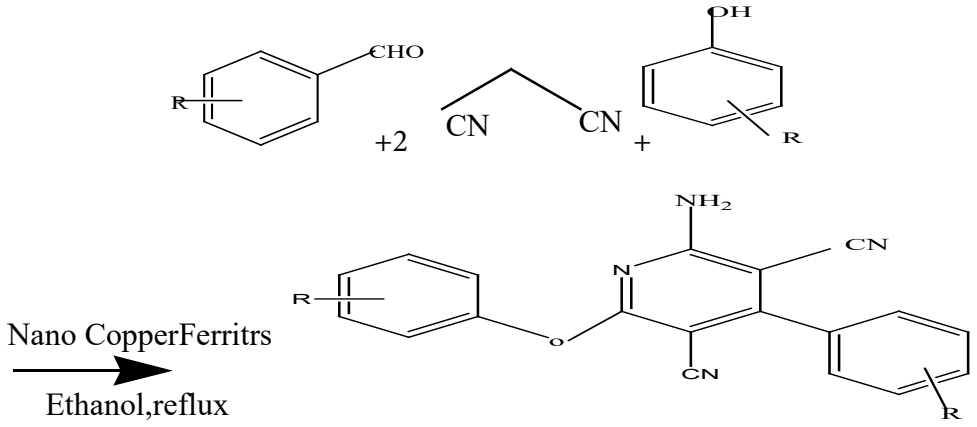
As a part of our ongoing research towards the synthesis of biologically active heterocyclic compounds using magnetically separable nano catalysts, keeping environmental friendly methods in mind, here we are reporting an efficient improved procedure for one-pot multi- component synthesis of some new poly substituted pyridine derivatives by condensation of aromatic aldehyde, malononitrile and substituted phenols using nano copper ferrite as a catalyst. This methodology involves high catalytic activity of the catalyst, its magnetic recoverability and reuse for five cycles without any noticeable loss of its catalytic activity.

2.Plausible mechanism for the scheme of the reaction:

A plausible mechanism had been proposed for the catalytic activity of the reaction. It can be predicted from the mechanism that it follows a base catalyzed pathway. The reaction is initiated by ferrite-mediated Knovenagel condensation of aldehyde and malononitrile, generating cinnamonitrile(1), which reacts with another molecule of malononitrile producing dihydropyridine intermediate (2). Then there are two possibilities to oxidize dihydropyridine to pyridines (3), one is aerobic oxidation of dihydropyridine, which plays a minor role limited by the solubility of oxygen in reaction solvent [ethanol] and the other is an efficient path,which involves hydrogen transfer from the dihydropyridine intermediate (2) to the Knovenagel intermediate (1). This step causes the involvement of an extra equivalent of aldehyde and malononitrile to get quick good yield of the product.

3.Experimental:

All chemicals were purchased from the commercial sources and liquid aromatic aldehydes and liquid aromatic phenols are purified by distillation prior to use. XRD spectra were recorded on PANalytical-XPert pro diffractometer and the average crystallite size was determined from the corresponding XRD data. The microstructural morphology was studied with a Scanning Electron Microscope (SEM) model JEOL–JSM 6610 LV. FTIR spectra were recorded on BRUKER ALPHA FT-IR with Opus 6.1 version. Magnetization M [H] measurements were made using a commercial vibrating sample magnetometer (VSM) model BHV-50 of Riken Denshi Co. Ltd. Japan. Specific surface area (SBET) of samples was determined by BET surface area analyzer (Nova 2000 series, Quanta chrome Instruments, UK). 1H NMR spectra were recorded on the Bruker-Avance 300-MHz spectrometer in CDCl3. The chemical shift values were reported on the δ scale in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. 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. Silica gel used for column chromatography was purchased from ACME Chemical Company. All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F254 (Merck) and spots were visualized with UV light.



2-Amino-6-phenoxy-4-phenylpyridine- 3,5-dicarbonitrile

4.General procedure for the synthesis of poly substituted pyridine derivatives:

The one-pot synthesis of poly substituted pyridine derivatives was carried out in a 250 mL round bottomed flask and fixed with a reflux condenser in an oil bath with temperature control and refluxed. About 500 mg of the catalyst was taken and activated at 500 °C for 2 h and cooled to room temperature before the experiment. Aromatic aldehyde (5 mmol) and malononitrile (10 mmol) were mixed together along with the catalyst and 5 mL of ethanol then the contents are stirred for 15 min at 50 °C. Afterwards the substituted phenol (5 mmol) was added to the reaction mixture and refluxed. The completion of the reaction was monitored by TLC (n-hexane: ethyl acetate 2:1) and the products were isolated by removing the catalyst magnetically from the reaction mixture. All the products were identified by FTIR, 1H NMR and mass spectra of representative compounds and compared.

5.Results and Discussion:

5.1 Effect of catalysts on the synthesis of pyridine derivatives:

As mentioned in introduction part, several catalysts have

been reported for the synthesis of poly substituted pyridine derivatives by the cyclocondensation of aromatic aldehyde, malononitrile and thiophenol in presence of various catalysts have been presented. The reaction time, temperature of the reaction and yield of the corresponding product in presence of nano copper ferrite catalyst has been presented. It is observed fromthe literature that the synthesis of substituted pyridines with substituted phenols in presence of nano copper ferrite has not been reported earlier.

5.2 Effect of solvent on the synthesis of poly substituted pyridine derivatives:

Investigation of the reaction medium for the process revealed that solvents played an important role in the reaction under investigation. The results are summarized. It was found that polar solvents such as CH_3OH, CH_3CN and C_2H_5OH were much better than non-polar solvents. Trace amounts of yield observed when H_2O was used as solvent, presumably due to the aggregation of the hydrophobic catalyst. Although methanol was effective, low yield was obtained when the catalyst was reused. We therefore selected ethanol as solvent. The effect of solvent was checked by the system

5.3 Effect of temperature on the synthesis of poly substituted pyridine derivatives:

The reaction temperature has a notable effect on the proposed reaction. The reaction was examined for temperature effect in presence of ethanol as solvent at different temperatures ranging from r.t. to 50 °C. The results are reported in Table. It is clear that at lower temperatures, even if the time was increased, only low percentage of yields were obtained. Hence, consequently we chose 50 °C as the optimal temperature for the reaction.

Table:Effect of temperature on the synthesis of poly substituted pyridine derivatives

S.No.	Time, min	Temp, °C	Product	Yield, %
1	120	R.T.	(4a)	30
2	75	40	(4a)	65
3	45	50	(4a)	95

5.4 Recycling of the catalyst:

Catalyst reusability is of major concern in heterogeneous catalysis. 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, the solid washed thrice with ethyl acetate and 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. The catalyst is highly magnetic and the saturation magnetization value is found to be 35.56 emu/g, which is much higher than other reported magnetic catalysts. Therefore, it could be easily and almost completely separated by an external magnet which is of a great advantage for a heterogeneous catalyst.

6.Conclusion:

We have reported an efficient and environmentally benign method for the synthesis of poly substituted pyridine derivatives using nano copper ferrite as catalyst. This method offers several advantages including high yield, short reaction times and ease of separation and recyclability of the catalyst.

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