CHAPTER-III SECTION-I

Synthesis and Characterization of $\text{CoFe}_2\text{O}_4$ Magnetic Nanoparticles
3.1.1 Introduction

Magnetic nanoparticles (MNPs) have a diverse range of applications in material science. For designing MNPs for specific applications, it is essential to understand the atomic structure of the particles, surface features and their magnetic properties [1]. However, the extent of stability of these magnetic particles under different conditions determines the successful application in different fields.

Cobalt ferrite (CoFe$_2$O$_4$) nanoparticle has high coercivity (~5.4 kOe) and moderate saturation magnetization (~80 emu$^\text{g}^{-1}$), remarkable chemical stability and mechanical hardness, which make it a possible material for several applications [2]. One of the most advantages of using CoFe$_2$O$_4$ is that, magnetic properties can finely be tuned and tailored, according to the requirement by selecting different divalent cations in them [3]. However, in many cases, the nanoparticles obtained were severely aggregated with non-uniform shape which is disadvantageous for their application. For many applications it is thus crucial to develop protection strategies to chemically stabilize the naked MNPs against degradation during or post-synthesis by coating with organic or inorganic species. In general, the MNPs can be stabilized by addition of carboxylate or phosphate functionalities [4-7], coating with silica [2, 8, 13] and coating with organic materials such as surfactants and polymers [14-19].
3.1.2 Review of Literature

In the recent past, nano-sized magnetic powders of CoFe$_2$O$_4$ are occupying an important place in the realm of synthetic and biological chemistry for their unusual properties such as multiferroic materials [20], doping or strain enhanced coercivity [21], photoinduced magnetic effects [22] and magnetic labeling of biological systems [23]. Much effort has therefore been undertaken to synthesize cobalt ferrite with well-defined properties which include important examples such as mechanochemical method [24], sonochemical reactions [25], co-precipitation [26-33], micro-emulsion procedure [34, 35], and others [36-40]. However, in many cases, the nanoparticles cannot be stored for a long period due to agglomeration, which is a serious disadvantage in their applications especially in ferrofluids and magnetic fluids [41, 42]. Sometimes, the particles formed are of poorly crystalline and milling or high temperature annealing is required to obtain highly crystalline structure. Also, the magnetic hardening occurs only after high temperature annealing. Microemulsion methods are very effective for synthesizing nanoparticles with well-defined size and narrow size distribution, but these methods are not suitable to produce in large quantities. The most advantageous method for production of nanoparticles is the coprecipitation method where the particles were prepared by coprecipitating a mixture of cobalt (II) and iron (II) salts with hydroxide ions using potassium nitrate [26] or air [43] as oxidizing agent. Even though the aqueous co-precipitation is an economic and a versatile technique, it gives nanoparticles with a relatively broad size distribution. Salazar-Alvarez, et al. reported a convenient
method for the synthesis of cobalt ferrite by aqueous co-precipitation method [29]. This method uses KNO₃ as oxidizing agent and mechanical milling is necessary in the final stage to obtain cobalt ferrite nanoparticle of desired size and shape. Moreover, the coercivity of the particle obtained by this procedure is not very high. Very recently, Kulkarni and his coworkers reported a co-precipitation method for oleic acid capped CoFe₂O₄ nanoparticles [33]. They found that, the coercivity of the CoFe₂O₄ nanoparticles is dependent on the amount of the capping agent as well as the annealing temperature. Although several reports are available in the literature for the synthesis of cobalt ferrite, most of them did not focus on the stability of the colloidal dispersions during storage. An organic capping agent such as oleic acid is necessary to make a stable colloidal dispersion of the nanoparticles.

The use of nanoparticles as catalysts in organic transformations has attracted considerable interest in the recent past, as nanoparticles provide a larger number of active sites per unit area [44, 45]. Although activity of a catalyst can be enhanced very significantly by synthesizing them in nanometer dimensions, recovery of the catalyst from the reaction mixture is a problem as they cannot be efficiently filtered out of the reaction medium. In this respect, magnetic nanoparticles hold out significant potential as a reusable catalyst as they can be recovered simply by magnetic separation which in tern prevents loss of catalyst and increases reusability.

There are few reports in the literature for utilization of CoFe₂O₄ nanoparticles as heterogeneous catalyst or support for organic transformations. Diaminosilane-functionalized CoFe₂O₄ MNPs (Fig. 3.1.1) were used as efficient heterogeneous base
catalysts for the Knoevenagel condensation of benzaldehyde with malononitrile to produce 2-benzylidenemalononitrile [46].

![Fig. 3.1.1](image)

The sulphonic acid group immobilized on CoFe$_2$O$_4$ MNPs (a and b in Fig. 3.1.2) was found to be active catalyst for the deprotection of benzaldehyde dimethylacetal with water to produce benzaldehyde. Although the catalyst showed very high activity compared to homogenous catalyst triflic acid, the catalyst could not be used as a true heterogeneous catalyst [47].

![Fig. 3.1.2](image)

Recently, nanocomposites of CoFe$_2$O$_4$ with ZnO and TiO$_2$ semiconductors were synthesized and used as heterogenous catalyst for photodegradation of dye in water [48, 49].
3.1.3 Present Work

Objective

Among various reported methods of CoFe$_2$O$_4$ synthesis, the aqueous co-precipitation method is simple and cost-effective and suitable to synthesize nanoparticles in large batches; however, the particles generally existed in agglomeration which is a serious drawback of this method. Moreover, the particles synthesized by this method are not stable in dispersed solution for longer periods. It is also noteworthy that in most of the synthetic reports, the stability of the colloidal dispersions of CoFe$_2$O$_4$ MNPs during storage was not focused which is important for catalytic use. In general, magnetic nanoparticles tend to agglomerate to form thermodynamically more favored bulk material which in turn decrease the surface area dramatically and hence reduce catalytic activity. To prevent this unwanted agglomeration, magnetic core are surrounded by functional ligands containing phosphoric acid, thiol or carboxylic acid group that are either immobilized on the surface or dispersed in solution. However, the coating may affect the catalytic activity of the magnetic nanoparticles [50].

We wish to develop a simple technique for synthesis of highly stable, high dispersive CoFe$_2$O$_4$ MNPs in aqueous medium without any surfactant or organic capping agents. The catalytic efficiency of the as-synthesized MNPs would be examined for important organic transformations such as Knoevenagel reaction, Aldol type reactions, protection of alcohols and amines, etc. To the best of our knowledge this is the first report of synthesis of highly stable dispersion of nanoparticles without any stabilizing agent and direct use of MNPs for catalytic applications.
3.1.4 Result and Discussion

Cobalt ferrite nanoparticles were synthesized by a combined sonochemical and co-precipitation technique in aqueous medium without any surfactant or organic capping agents. The synthesis was carried out in an alkaline pH under repeated ultrasonic irradiation.

At the initial stage of the synthesis, formation of a dark brown precipitate was observed which on ultrasonication, transforms into black particles. Interestingly, the resulting black nanomaterials exhibit excellent stability. The solid nanoparticles can be easily dispersed in aqueous or alcoholic medium to form colloidal solution. Aqueous dispersion of the cobalt ferrite particles can be stored without any stabilizer for 2 months in a refrigerator. Agglomeration of the nanoparticles was not observed during storage. The morphology and properties remain unaltered during storage which is evident from electron microscopic analysis. EDX analysis confirms the desired composition of the CoFe$_2$O$_4$ nanoparticles. Formation of stable nanoparticle could be due to repetitive ultrasonic treatment during synthesis [51, 52]. Cavitation effect during ultrasonic treatment might be responsible for generation of tremendous pressure and temperature [51]. This effect creates some short lived localized hot-spots which induce in situ calcinations to obtain directly cobalt ferrite particles. Hence, extra high temperature is not necessary in this method to get crystalline nanoparticles. We observed that it is not possible to produce stable nanoparticles if the synthesis is carried out without repetitive ultrasonic treatment.
Further we observed that, nanoparticle dispersions cannot be made in aprotic solvent such as DCM and agglomeration takes place in such solvents. The excessive hydroxyl ions entrapped in the surface of the cobalt ferrite nanocrystals during sonication [51] may be a reason of high stability in polar solvent and instability in less polar or non-polar solvent.

Due to repetitive sonication during synthesis of the catalyst, basic surface sites are formed which was further corroborated by comparing the FT-IR spectra of the as-synthesized cobalt ferrite particles and with those prepared by normal co-precipitation method [53] (Fig. 3.1.3). The intense peak at 593 cm\(^{-1}\) in the FT-IR spectrum is attributed to M-O tetrahedral site in the spinel structure which is more exposed in the as-synthesized sample. This may be one of the reasons for basic nature of the as synthesized nanoparticle [54]. Moreover, the stretching frequencies for the surface adsorbed -OH group are around 3400 cm\(^{-1}\) and 1620 cm\(^{-1}\) are more intense for the as-synthesized sample which indicates more polar character of the surface.
Fig. 3.1.3 FT-IR spectra of (a) as-synthesized CoFe$_2$O$_4$ and (b) CoFe$_2$O$_4$

synthesized by normal co-precipitation method.

A study on the colloidal stability of as-synthesized MNPs was carried out by optical absorbance (or turbidity) measurement according to González-Caballero et al. [55]. Absorbance decay against time measured at $\lambda_{\text{max}}$ of 550 nm for a period of two month at 10 days intervals revealed the stability of the nanoparticle in aqueous medium.

a. immediately after synthesis
b. after one month
Optical measurement of the colloidal suspension in water was carried out as a function of time in the range of wavelength from 200 nm to 800 nm. All suspensions contained 0.1g/L of cobalt ferrite particles in water. The absorption spectrum of the nanoparticles immediately after the synthesis is shown in Fig. 3.1.4.a. The absorbance measurements were done at an interval of 1 h upto 24 h. From the spectra it was evident that there is no characteristic change in absorbance with time which revealed the stability of the suspension of the ferrite particles. Fig.3.1.4.b shows the absorption spectra taken after one month of the suspension at 1 h intervals up to 11 h. In this case, though the absorbance of the parent suspension was decreased approximately 3\% over a period of a month, there is no characteristic change of absorbance of suspension at an hour intervals. However, after 2 months of storage, substantial decrease of absorbance
with time was observed, when the experiment was conducted for 10 h with 1 h interval of time (Fig. 3.1.4.c). The absorbance decay against time measured at $\lambda_{\text{max}}$ of 550 nm for first 10 days for each consecutive month (Fig. 3.1.4.d) revealed the stability of the nanoparticles up to two months. However, dispersion is not stable thereafter. The observed absorption spectrum of the CoFe$_2$O$_4$ is arised from Co$^{2+}$ d to d on-site transitions.

The quasi homogeneous nanoparticle dispersion can be compartmented by using an external magnet (Fig.3.1.5).

![Fig. 3.1.5](image)

**Fig. 3.1.5** (a) Dispersion in aq. Ethanol (1:3) and (b) magnetic separation of CoFe$_2$O$_4$ MNPs
**Effect of Ultrasonic treatment**

The Co(OH)$_2$ and Fe(OH)$_3$ nanoparticles are first obtained from metallic salts and sodium hydroxides. Because they have a smaller diameter and higher reaction activity, and the freshly produced Co(OH)$_2$ and Fe(OH)$_3$ decompose immediately to produce CoO and Fe$_2$O$_3$ nanoparticles with a strong heat of reaction from ultrasonic treatment at room temperature, the CoFe$_2$O$_4$ is easily formed when the further irradiation is carried out at elevated temperature. Thus it can be seen the ultrasonic treatment induces easy formation of CoFe$_2$O$_4$ particle from its precursors upon vigorous heat and tremendous pressure generated in ultrasonication process.

\[
\text{CoCl}_2.6\text{H}_2\text{O} + 2 \text{NaOH} \rightarrow \text{Co(OH)}_2 + 2 \text{NaCl} + 6\text{H}_2\text{O} \\
\rightarrow \text{CoO} + 2 \text{NaCl} + 7\text{H}_2\text{O (room temperature)} \quad (1)
\]

\[
\text{2FeCl}_3.6\text{H}_2\text{O} + 6 \text{NaOH} \rightarrow 2\text{Fe(OH)}_3 + 6 \text{NaCl} + 12 \text{H}_2\text{O} \\
\rightarrow \text{Fe}_2\text{O}_3 + 6 \text{NaCl} + 15 \text{H}_2\text{O (room temperature)} \quad (2)
\]

\[
\text{CoO} + \text{Fe}_2\text{O}_3 \xrightarrow{\text{Ultrasonication}} \text{CoFe}_2\text{O}_4
\]

**Structural analysis**

Fig. 3.1.6 shows the XRD pattern of the CoFe$_2$O$_4$ nanoparticles which indicates the presence of all the characteristic signals which are present in spinel cobalt ferrite (JCPDS—International center diffraction data, PDF cards 3-864 and 22-1086) [31, 40] were appeared in the XRD measurement. The crystallite size calculated according to
Scherrer's equation [56] was found to be 41 nm. This confirms that the synthesis method is feasible and complete.

![XRD pattern of as-synthesized CoFe$_2$O$_4$ MNPs](image)

Fig. 3.1.6 XRD pattern of as-synthesized CoFe$_2$O$_4$ MNPs

The structural composition and crystallinity of the cobalt ferrite nanoparticles was further examined by using SEM and TEM. The EDX analysis (Fig. 3.1.7) showed that the distribution of the elements (atomic percent) in the product was Co=12.31%, Fe=24.93%, and O=62.76%. Thus the iron/cobalt ratio in the nanocrystals by EDX was found to be 2.02 which is very much close to the atomic ratio in the formula CoFe$_2$O$_4$. The mapping (line scanning) analysis by EDX on as-synthesized cobalt ferrite sample (Fig. 3.1.8) revealed the uniform distribution of CoFe$_2$O$_4$ particles in the sample.

The particle sizes were also measured in SEM micrograph (Fig. 3.1.9) and were found to be in the range of 40-50 nm.
Fig. 3.1.7 EDX analysis of CoFe$_2$O$_4$

Fig. 3.1.8 Mapping analysis of CoFe$_2$O$_4$ MNPs

Fig. 3.1.9 SEM micrograph of CoFe$_2$O$_4$ MNPs

Fig. 3.1.10 shows the TEM image of the CoFe$_2$O$_4$ nanocrystals deposited on a carbon coated copper grid. The average size of the nanoparticles from the TEM analysis was found to be 40-50 nm (a and b in Fig. 3.1.10) which is consistent with the particle size obtained from XRD analysis. The diffraction pattern (SAED) obtained from the TEM (c in Fig. 3.1.10) showed spinel phase CoFe$_2$O$_4$, with the rings corresponding to
reflections from the (220), (311), (422), (440) and (642) planes. The interplanar distance of the (111) reflections observed in HRTEM image (d in Fig. 3.1.10) is 0.45 nm corresponds to the spinel phase crystalline nanoparticle [27].

Fig.3.1.10 TEM micrographs of the synthesized nanosized CoFe$_2$O$_4$: (a) Bright Field TEM(300KX), (b) Bright Field TEM (20KX), (c) SAED pattern and (d) HRTEM

Fig.3.1.11 shows the N$_2$ adsorption-desorption isotherms of the CoFe$_2$O$_4$ MNPs. The BET surface area of the particles was found to be 48.14 m$^2$g$^{-1}$ as calculated by linear part of the BET plot, which is much higher than nanoparticles prepared by conventional co-precipitation method [53]. The total pore volume at P/Po = 0.98 is 0.20 cm$^3$g$^{-1}$. The BET isotherm is of type II and H3 hysteresis loop (BDDT/IUPAC classification), characteristic of mesoporous adsorbents [57].
Magnetic properties of the cobalt ferrite nanocrystals

The magnetic properties of the as-prepared CoFe$_2$O$_4$ crystals were investigated using ESR and VSM measurement. The ESR spectra were recorded in the temperature range from 300K to 100K (Fig. 3.1.12). The value of g-factor (= 2.01) determined from EPR measurement is in good agreement with that reported in the literature for nanostructured CoFe$_2$O$_4$ particles [25]. When the spectra was recorded by varying the temperarute, line broadening of the EPR signal was observed with decreasing temperature with no significant shift in resonance magnetic field, which can be attributed to strong magnetocryllinie anisotropy in the synthesized sample.
In the VSM measurement, M-H loop was taken at room temperature with a maximum applied field of ± 2 T. From the hysteresis loop both saturation magnetization (Ms) and coercivity values (Hc) were extracted. Coercivity of 2100 Oe was obtained from the extracted data where as saturation magnetization, Ms was found to be 43 emug$^{-1}$. In order to understand the coercivity behavior of the cobalt ferrite nanoparticles hysteresis loops were taken at different temperatures starting from the room temperature to 80 K. Fig. 3.1.13 shows the hysteresis loops taken at three different temperatures i.e.300K, 200K and 80K. As the temperature decreased, the coercivity increased with a shoulder like feature in the M-H loop at 80K was observed. Also the magnetization curves showed non saturation with the applied field as the temperature decreased from the room temperature. This indicates the effect of uniaxial anisotropy present in the system which causes magnetic hardening at lower temperature. The coercivity of the
nanoparticles at 80K was found to be 8.6 KOE (2.1 kOe at 300 K) with a squareness ratio (Mr/Ms) of 0.73 (0.55 at 300K).

![Graph showing field dependence coercivity at T= 80, 200, and 300 K at ±2T field](image)

Fig. 3.1.13 Field dependence coercivity at T= 80, 200, and 300 K at ±2T field

### 3.1.4 Conclusion

In conclusion, a new type of CoFe$_2$O$_4$ magnetic nanocatalyst has been developed with average sizes in the range 40-50 nm using a combined sonochemical and co-precipitation process. The resulting nanocrystals, as well as its dispersion exhibit excellent stability in ethanol or aqueous solvent and can be stored without any stabilizer for months. Agglomeration of the uncapped nanoparticles was not observed during storage. The as-synthesized nanoparticles showed high values of coercivity, saturation magnetization and squareness ratio.
3.1.5 Experimental Section

*Synthesis of cobalt ferrite MNPs*

Cobalt-ferrite nanocrystals have been synthesized by a combined sonochemical and co-precipitation technique. Two aqueous solutions of FeCl₃ (1.5 g, 9.3 mmol, 50 mL) and CoCl₂·6H₂O (1 g, 4.2 mmol, 50 mL) were mixed in a 200 mL flat bottom flask and placed in an ultrasonic bath. An aqueous KOH solution (3M, 25 mL) was added dropwise under argon atmosphere with continuous ultrasonic irradiation (frequency 40 KHz and power of 40 KW). Prior to mixing, all these three solutions were sonicated for 30 min to remove dissolved oxygen. The temperature of the sonicator bath was raised up to 60 °C and the mixture was further sonicated for 30 minutes in air atmosphere. The black precipitate formation was observed during that time. Energy dispersive X-ray spectroscopy (EDX) analysis at this point confirms the formation of cobalt ferrite. The reaction mixture was centrifuged (14000 rpm) at ambient temperature for 15 minutes. The mixture was further subjected to successive sonication (30 min) and centrifugation (15 min) for five times. The black precipitate was then separated, washed with copious amount of distilled water, ethanol and kept overnight in an incubator at 60 °C for ageing. The precipitate was further dried in oven at 100 °C for one hour and subsequently kept under high vacuum (10⁻² bar) for one hour. Finally, the black particles were taken in 50 mL of dry ethanol and subjected to successive sonication (30 min) and centrifugation (15 min) repeatedly till a brown colored solution appears. The precipitate was separated, dried and used for further analysis. The whole procedure was repeated twice to check the reproducibility.
CoFe$_2$O$_4$ nanocrystals as quasi-homogenous catalyst for Knoevenagel condensation
3.2.1 Introduction

Nanoparticles of magnetic oxides, including most representative ferrites, have been studied for last few decades for their application as magnetic storage media and as ferro fluids. However, their catalytic application has gain considerable interest in recent years. These are foreseen as an active area of research in the future because of their potent catalytic activity, possible processability, easy preparation, high stability, ease of recyclability as well as greener compared to other nanoparticles. Magnetic iron oxide-based nanoparticles, such as magnetite (Fe₃O₄), maghemite (γ-Fe₂O₃) and cobalt ferrite (CoFe₂O₄) are the commonly used ferrite materials in various applications including catalysis and biomedical applications [58].

Although the homogenous catalysts have many advantages over heterogenous counterparts, they suffer the serious disadvantage of separation from products and reaction solvents. Moreover, some heterogeneous catalysts are expensive, especially for noble and/or toxic metal complexes are used [59, 60]. The classical bulk heterogenous catalysts are widely used in industry [61, 62], although they have lower activities or selectivities compared to their homogenous counterparts. The nanoparticle catalysts have improved activity and selectivity [44, 63, 64], which is due to small particle size and high surface area and easy dispensability in solution to form a quasi-homogenous
emulsion [44, 45, 62, 64]. However, recovery and recycling of these nano-catalysts is difficult as they cannot be efficiently filtered out of the reaction medium. Therefore, an efficient technique for facile separation of the catalyst is desired and hence magnetic separation was introduced.

Amongst the various MNPs, CoFe$_2$O$_4$ has received much attention in recent years because of their easy preparation method, tunable size, chemical and thermal stability. Moreover, the Fe$_3$O$_4$ or γ-Fe$_2$O$_3$ is not chemically or thermally stable [65, 66] compared to CoFe$_2$O$_4$ MNPs.

The Knoevenagel condensation reaction is a popular and widely used reaction in organic chemistry for the synthesis of α,β-unsaturated carbonyl compounds from active methylene and carbonyl compounds [67, 68]. Traditionally, this reaction is catalysed by organic bases such as aliphatic amines, urea, ethylenediamine and piperidine or their ammonium salts, and amino acids glycine or β-alanine under homogenous conditions [69, 70].

3.2.2 Review of Literature

Over last decades, there are various homogenous as well as heterogeneous catalysts have been addressed to the Knoevenagel reaction. The Lewis acids and bases including TiCl$_4$ [71], AlPO$_4$-Al$_2$O$_3$ [72], ZnCl$_2$ [73], CdI$_2$ [74], Na$_2$CaP$_2$O$_7$ [75], Ca$_2$P$_2$O$_7$ [76] K$_2$NiP$_2$O$_7$ [77] KF-Al$_2$O$_3$ [78], Ni-SiO$_2$ [79], MgO and ZnO [80] have been employed to catalyze this reaction, each affording variable yields of α,β-unsaturated carbonyl compounds. In most of these cases, benzene, ethanol and DMF
were used as solvent. However, these methods are not very suitable for large scale production due to waste products or toxic solvents. In recent past, there are many catalyst have been introduced for the Knoevenagel reaction such as inorganic solids [81-83], resins [84], phase-transfer agents [85], ionic liquid [86, 87], LDH-F hydrotalcite [88], cation-exchanged zeolites [81], or mesoporous materials [89], and MCM-41 [90]. There are also reports on electrochemical, microwave, ultrasound activation methods for the Knoevenagel reaction [91-96].

Nevertheless, many of these known methods suffer from significant limitations, which include toxic reagents, harsh reaction conditions, low yields or long reaction times. Only a few sustainable procedures and particularly with basic heterogeneous catalyst were reported [97-100].

There were many efforts to avoid these disadvantages such as the use of inorganic solid supports as catalyst [74, 101, 102], and new methods exploiting solvent free microwave assisted conditions [93, 103, 104, 105]. Although these routes decrease reaction time, they produce the desired alkenes in poor yield. The use of ionic liquids (ILs) has also been emerged as green solvent of choice and being used as environmentally benign media for many important organic reactions [106-109]. Although, ionic liquids such as [6-mim][PF6](1-hexyl-3-methylimidazolium hexafluorophosphate), [bmim]Cl·XAlCl3, [bpy]Cl·XAlCl3 etc. have been used for Knoevenagel reactions, there are also drawbacks of reaction times, yield, moisture sensitivity and competing side reactions [110, 111]. Y. Wang et al. effectively used proline in
imidazolium-based ILs ([emim][BF4], bmim][BF4], [bmim][PF6]) for the Knoevenagel condensation in moderate to high yield along with its regenerability [112].

Very recently, S. Mallouk et al. has reported a sustainable Knoevenagel condensation protocol using a cooperative effect of microwave activation and natural hydroxyapatite catalysis [Ca10(PO4)6(OH)2](p-HAP) under solvent-free conditions [113]. The products are obtained in high yield in short reaction times. There are also few reports on the use of magnetic nanoparticles such as Ni supported on SiO2 catalyzed Knoevenagel reaction [114-116]. However, some of these methods have drawbacks associated with longer reaction time, excessive solvent, lower yield etc.

Nam T. S. Phan et al. studied the catalytic use of organosilane-functionalized CoFe2O4 MNPs in Knoevenagel reaction [47]. Though the reaction produced good yield, it was performed in benzene and THF solvent both of which are highly toxic.

### 3.2.3 Present Work

**Objective**

During past few years, various reactions systems have been developed for the Knoevenagel reactions. Many of these methods have one or more disadvantages such as hazardous or carcinogenic solvents, high temperature, longer reaction times, use of expensive and non-recovery of the catalysts. In case of using the Lewis acidic catalysts, TiCl4 and ZnCl2, the reaction cannot be performed in aqueous solvent and the catalysts are not stable and cannot be reused because of the water made from the reaction itself. These disadvantages make the limit of the use of these reactions in industry [117].
Therefore, a new approach for the Knoevenagel reaction is needed so as to perform the reaction under mild conditions using catalysts with the advantages of easy recovery and recyclability.

Environmentally benign, economical, practical, and efficient processes for catalyst separation and reuse have been increasingly important goals in the chemical community from economic, safety, and environmental points of view [118]. The strategy of magnetic separation, taking advantage of magnetic nanoparticles, is typically more effective than filtration or centrifugation as it prevents loss of the catalyst [119]. Magnetic separation of the magnetic nanoparticles is simple, economical and promising for industrial applications [120-122].

In the previous section, we have developed a new synthetic strategy for the synthesis of CoFe$_2$O$_4$ MNPs which shows good dispersibility and stability in aqueous solution. Herein, we wish to employ the as-synthesized CoFe$_2$O$_4$ MNPs in Knoevenagel reaction of aldehydes with ethylcyanoacetate in aqueous ethanol solvent (Scheme 3.2.1).

Scheme 3.2.1 Knoevenagel condensation reaction
3.2.4 Result and Discussion

We examined the catalytic activity of the synthesized CoFe$_2$O$_4$ MNPs for Knoevenagel condensation reaction. Very recently, magnetic nanoparticle supported basic catalyst have been developed for Knoevenagel condensation reaction [123-125]. However, prior functionalization of nanoparticles for introduction of basic site is necessary for catalytic applications. Our method has the advantage that no further modification of the magnetic particles is necessary for utilization as catalyst. We observed that the pH of the 0.02 molar solution of the as-synthesized CoFe$_2$O$_4$ MNPs is 8.98 at 25 °C (Fig. 3.2.1). Hence, we presumed that these cobalt ferrite nanoparticles can directly be used as catalyst for Knoevenagel condensation between different aromatic aldehydes and ethylcyanoacetate (Scheme 3.2.1).

![Temperature dependent pH curve of 0.02 molar aq. dispersion of CoFe$_2$O$_4$ MNPs](image)

**Fig. 3.2.1** Temperature dependent pH curve of 0.02 molar aq. dispersion of CoFe$_2$O$_4$ MNPs

Since, water is the most desired solvent from the point of green chemistry and the catalyst forms a homogeneous aqueous dispersions, we initially, carried out the reaction in water as solvent at room temperature. The test reaction was carried out by
taking 4-chlorobenzaldehyde and ethylcyanoacetate as the model substrate and the progress of the reaction was monitored by TLC. In all cases, the product was isolated for determination of actual product yield. Initial reaction at room temperature produced low yield of the product after 3 h of reaction. However, at 50 °C, the reaction produced 72% of isolated product yield after 1 h of reaction. Thereafter, we have examined the reaction using different solvent to find out the optimum reaction condition. The influence of solvent on the Knoevenagel reaction between p-chloro benzaldehyde and ethylcyanoacetate was investigated at 50 °C and the products were isolated after 1 h of reaction. Results were presented in Fig. 3.2.2.

![Fig. 3.2.2 Solvent effect on Knoevenagel condensation using 5 mol% of cobaltferrite nanocrystals at 50 °C ( *water, at 25 °C).](image)

We observed that a polar protic solvent such as ethanol is very effective to achieve good product yield. However, in water the yield is lower than in ethanol due to low solubility of the reagents. It is well known that, if the charge species are involved as in case of Knoevenagel reaction, the transition-state is better solvated by polar solvents.
in homogeneous phase, decreasing the activation free enthalpy and enhancing rate and hence increase the product yield. In heterogeneous catalysis, the reaction occurs on the surface and if polar reagents are involved, the transition-state is stabilized by polar surfaces which increase the reaction rate and hence the product yield. When the reaction was carried out in 1:3 water-ethanol mixture, we obtained 95% yield of the corresponding product. Repetition of the reaction revealed that the reaction is very fast in aqueous ethanol and it takes only 25 min. for completion of reaction. However use of other solvents such as DMF, THF, DCM, MeCN and toluene did not produce good results. Low yield in polar aprotic solvent may be due to low stability of the colloidal dispersion of the MNPs in these solvents. High dispersability of the MNPs in water and ethanol makes the system a quasi-homogenous phase which facilitate a better interaction of the nanoparticle with the reactants and hence a faster reaction rate. This is in good agreement with previous observations in the homogenous phase [126] for high reaction rate and high product yield. In non polar solvent such as toluene, the product yield is very much low which is in accordance with the polar mechanism involved in the reaction as well as non-dispersibility of the magnetic nano catalyst in this solvent. Finally aqueous ethanol (1:3) was found to be the solvent of choice for the reaction. The quasi homogeneous nanoparticle dispersion can be compartmented by using an external magnet.

The reaction was further examined in presence of different amount of catalyst. The yield generally increased with the increasing concentration of the catalyst from 2 mol% to 5 mol%. However, further increase of the molar concentration of the catalyst
from 5 to 15 mol% did not significantly increase the yield of the product (Fig. 3.2.3). Hence, a concentration of 5 mol% of the MNPs was chosen for the optimum yield of Knoevenagel products.

![Fig. 3.3.3 Effect of CoFe$_2$O$_4$ MNPs concentration on the Knoevenagel reaction](image)

*aq. Ethanol (1:3) solvent*

After optimizing the reaction conditions we extended the procedure using different aldehydes, the results are summarized in Table 3.2.1.
Table 3.2.1 Knoevenagel condensation with different aldehydes catalyzed by CoFe$_2$O$_4$ magnetic nanocatalyst*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>Product</th>
<th>t (min)</th>
<th>Yield (%)$^b$</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>$\text{C}_6\text{H}_5\text{CHO}$</td>
<td>$\text{C}_6\text{H}_5\text{C}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>20</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>$\text{C}_6\text{H}_4\text{CHClO}$</td>
<td>$\text{C}_6\text{H}_4\text{CHClC}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>$\text{C}_6\text{H}_4\text{BrCHO}$</td>
<td>$\text{C}_6\text{H}_4\text{BrC}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>15</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>$\text{C}_6\text{H}_4\text{CHO}$</td>
<td>$\text{C}_6\text{H}_4\text{C}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>$\text{C}_6\text{H}_4\text{CHO}$</td>
<td>$\text{C}_6\text{H}_4\text{F}C=\text{C}(\text{COOEt})\text{CN}$</td>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>$\text{C}_6\text{H}_4\text{ClC}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>$\text{C}_6\text{H}_4\text{ClC}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>$\text{C}_6\text{H}_4\text{CHO}$</td>
<td>$\text{C}_6\text{H}_4\text{OC}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>10</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>$\text{C}_6\text{H}_4\text{N}=\text{NO}_2\text{CHO}$</td>
<td>$\text{C}_6\text{H}_4\text{N}=\text{NO}_2\text{C}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>$\text{C}_6\text{H}_4\text{CHO}$</td>
<td>$\text{C}_6\text{H}<em>4\text{CH}</em>{\text{5}}\text{C}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>$\text{C}_6\text{H}_4\text{CHO}$</td>
<td>$\text{C}_6\text{H}<em>4\text{CH}</em>{\text{5}}\text{C}=\text{C}(\text{COOEt})\text{CN}$</td>
<td>30</td>
<td>68</td>
</tr>
</tbody>
</table>
Reactions were carried out using 1 mmol of aldehyde, 1 mmol of ethylcyanoacetate and 0.05 mmol of cobalt ferrite in a 3 ml mixture (1:3) of water and ethanol. The reaction mixture was stirred using a magnetic stirring bar at 50°C for the appropriate time as indicated by TLC. After completion of the reaction, MNPs were separated by an external magnet and after usual work up the crude product was purified either by recrystallization or column chromatography. The products were characterized by comparing the IR and NMR spectroscopic data which revealed the excellent purity. High catalytic activity of the un-capped cobalt ferrite nanocrystals for Knoevenagel reaction may be primarily due to surface basicity of the MNPs.

As expected for nucleophilic addition reactions, aromatic aldehydes with electron-withdrawing group such as nitro (-NO₂) moiety were more reactive, with 96%
yield being achieved (entry 8), while much lower isolated yield was obtained for the reaction of aldehydes containing an electron-donating group such as hydroxyl (-OH) (entry 7). This trend in product yield is consistent with the fact that in case of electron withdrawing groups the possibility of attack of the carbanion at the carbonyl carbon is enhanced compared to that of the electron withdrawing groups. The heterocyclic aldehydes (entry 11 to 14) also afforded good to excellent yield. For the reaction of aliphatic aldehyde, the short chain aldehyde was found to be slightly more reactive than long chain aldehyde (entries 9 and 10).

Recyclability of the catalyst

The recyclability of the catalyst was checked by carrying out repeated runs on the same batch of the used 5 mol% cobalt ferrite magnetic catalyst in Knoevenagel condensation of 4-chlorobezaldehyde and ethylcyanoacetate (Fig. 3.3.4). Catalytic activity of the cobalt ferrite did not decrease significantly even after four catalytic cycles. The SEM and XRD analysis of the nanoparticle revealed that the morphology of the recovered MNPs remains unaltered during the recycling process which indicates that the catalyst is stable towards oxidation during the reaction.
Fig. 3.3.4 Recyclability for Knoevenagel reaction of 4-chlorobenzaldehyde and Ethylcyanoacetate

Fig. 3.3.5 $^1$H NMR of Ethyl(E)-3-(4-Chlorophenyl)-2-Cyano-2-propeonate (entry 2)
Fig. 3.3.6 $^1$H NMR of Ethyl (E)-3-(4-Methyl)-2-Cyano-2-propeonate (entry 4)

Fig. 3.3.7 $^1$H NMR of Ethyl (E)-2-Cyano-2-decenoate (entry 10)
3.2.5 Conclusion

CoFe$_2$O$_4$ MNPs were used as efficient quasi-homogenous catalyst for Knoevenagel condensation reaction of several aldehydes with ethylcyanoacetate in mild conditions. The catalyst could be recovered very easily from the reaction mixture by compartmentation with the aid of an external magnet and could be reused four times without significant loss in activity.
3.2.6 Experimental Section

**Typical procedure for the CoFe$_2$O$_4$ MNPs catalysed Knoevenagel reaction**

To a mixture of aldehydes (1 mmol), ethylcyanoacetate (1 mmol, 0.12 g) in 3 mL aqueous ethanol (1:3 ratio) in a round-bottom flask, CoFe$_2$O$_4$ MNPs were added as catalyst (0.05 mmol, 0.01 g). The resulting reaction mixture was stirred at 50 °C for a specified period (Table 3.2.1). The progress of the reaction was monitored by thin layer chromatography (TLC). After complete conversion, as indicated by TLC; the catalyst was separated by magnetic decantation. The reaction mixture was diluted by adding Ethyl acetate (10 ml) and washed with water thrice followed by brine. The organic layer was dried over anhydrous sodium sulphate (Na$_2$SO$_4$) followed by evaporation of solvent using a rotary evaporator under reduced pressure and concentrated to dryness gave the desired product. The crude products upon re-crystallisation (solid products) or column chromatography using ethyl acetate-petroleum ether as eluent (liquid products) afforded the pure Knoevenagel products (Table 3.2.1). The analysis of complete spectral and compositional data (FT-IR and $^1$HNMR) revealed the formation of Knoevenagel products with excellent purity.

**Typical procedure for the recycling of the CoFe$_2$O$_4$ MNPs (catalyst)**

After completion of the reaction (as confirmed by TLC), an external magnet was applied to concentrate the catalyst on the side of the round-bottom flask. The reaction mixture was decanted holding the magnet on outside of the flask. The magnetic
nanoparticles were washed with ethanol 4-5 times to confirm the complete removal of any residual material. The particles were then dried in an oven at 120 °C for 6 h and preserved for further catalytic reaction cycles. The same process was repeated after each reaction cycle to isolate and reuse the CoFe$_2$O$_4$ MNPs as catalyst.

**Experimental Data:**

**Entry 1 (Ethyl (E)-2-Cyano-3-phenyl-2-proponate)**

\[ \text{\includegraphics[height=1.5cm]{co2h}} \]

Colorless crystalline solid

IR (cm$^{-1}$): v 3020, 2400, 2225, 1727, 1268, 1215, 1188, 1104, 1100, 750, 688

$^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 1.31 (t, $J = 7.0$ Hz, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 7.39-7.61 (m, 4H), 7.98 (dd, $J = 7.4$ Hz, 1H), 8.25 (s, 1H).

**Entry 2 (Ethyl(E)-3-(4-Chlorophenyl)-2-Cyano-2-proponate)**

\[ \text{\includegraphics[height=1.5cm]{co2h}} \]

White crystalline solid

IR (cm$^{-1}$): v 3100, 2990, 2223, 1723, 1612, 1492, 1263, 832, 762

$^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 1.38 (t, $J = 7.0$ Hz, 3H), 4.35 (q, $J = 7.0$ Hz, 2H), 7.46 (d, $J = 7.8$ Hz, 2H), 7.92 (d, $J = 7.2$ Hz, 2H), 8.18 (s, 1H)
**Entry 3** (Ethyl (E)-3-(4-Bromophenyl)-2-Cyano-2-propeionate)

![Chemical Structure of Entry 3](image)

White crystalline solid

IR (cm\(^{-1}\)): \(\nu\) 2992, 2890, 2224, 1721, 1611, 1498, 1264, 838, 764

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.39 (t, \(J = 7.0\) Hz, 3H), 4.38 (q, \(J = 7.0\) Hz, 2H), 7.64 (d, \(J = 7.8\) Hz, 2H), 7.85 (d, \(J = 7.8\) Hz, 2H), 8.18 (s, 1H)

**Entry 4** (Ethyl (E)-3-(4-Methyl)-2-Cyano-2-propeionate)

![Chemical Structure of Entry 4](image)

White crystalline solid

IR (cm\(^{-1}\)): \(\nu\) 2994, 2906, 2216, 1726, 1596, 1366, 1272, 816, 761

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.38 (t, \(J = 7.0\) Hz, 3H), 2.42 (s, 3H), 4.36 (q, \(J = 7.0\) Hz, 2H), 7.29 (d, \(J = 7.2\) Hz, 2H), 7.89 (d, \(J = 7.2\) Hz, 2H), 8.20 (s, 1H)

**Entry 5** (Ethyl (E)-3-(4-Fluoro)-2-Cyano-2-propeionate)

![Chemical Structure of Entry 5](image)

White crystalline solid

IR (cm\(^{-1}\)): \(\nu\) 2989, 2850, 2226, 1718, 1610, 1510, 1268, 842, 764

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.39 (t, \(J = 7.0\) Hz, 3H), 4.37 (q, \(J = 7.0\) Hz, 2H), 7.11-7.23 (m, 2H), 7.97-8.07 (m, 2H), 8.20 (s, 1H)
Entry 6 (Ethyl (E)-3-(2,4-Dichloro)-2-Cyano-2-propeionate)

White crystalline solid

IR (cm\(^{-1}\)): \(2970, 2854, 2220, 1711, 1590, 1491, 1248, 835, 755\)

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.30 (t, \(J = 7.0\) Hz, 3H), 4.39 (q, \(J = 7.2\) Hz, 2H), 7.35-6.43 (m, 1H), 7.53 (s, 1H), 8.19 (d, \(J = 8.6\) Hz 1H), 8.60 (s, 1H)

Entry 7 (Ethyl (E)-3-(4-Hydroxy)-2-Cyano-2-propeionate)

Pale yellowish solid

IR (cm\(^{-1}\)): \(3215, 2961, 2879, 2225, 1671, 1604, 1291, 1164, 834, 710\)

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.39 (t, \(J = 7.0\) Hz, 3H), 4.37 (q, \(J = 7.0\) Hz, 2H), 6.97 (d, \(J = 6.6\) Hz, 2H), 7.81 (d, \(J = 6.2\) Hz, 2H), 8.17 (s, 1H)

Entry 8 (Ethyl (E)-3-(4-Nitro)-2-Cyano-2-propeionate)

Pale yellowish solid

IR (cm\(^{-1}\)): \(2928, 2846, 2230, 1721, 1514, 1348, 859, 765\)

\(^1\)HNMR (400MHz, CDCl\(_3\)): \(\delta\) 1.41 (t, \(J = 7.0\) Hz, 3H), 4.41 (q, \(J = 7.0\) Hz, 2H), 8.12 (d, \(J = 8.6\) Hz, 2H), 8.29 (s, 1H), 8.34 (d, \(J = 8.9\) Hz, 2H)
Entry 9 (Ethyl (E)-5-(phenyl)-2-Cyano-2-pentenoate)

Light yellow liquid

IR (cm\(^{-1}\)): \( \nu \) 3029, 2985, 2945, 2252, 1747, 1455, 1371, 1248, 1027, 854, 751

\(^1\)HNMR (400MHz, CDCl\(_3\)): \( \delta \) 1.34 (t, \( J = 7.0 \) Hz, 3H), 2.55-3.05 (m, 4H), 4.30 (q, \( J = 7.0 \) Hz, 2H), 7.10-7.40 (m, 6H).

Entry 10 (Ethyl (E)-2-Cyano-2-decenoate)

Colorless liquid

IR (cm\(^{-1}\)): \( \nu \) 2929, 2858, 2251, 1748, 1466, 1370, 1253, 1025, 854, 764

\(^1\)HNMR (400MHz, CDCl\(_3\)): \( \delta \) 0.86 (t, \( J = 6.24 \) Hz, 3H), 1.10-1.61 (m, 13H), 2.31-2.5 (m, 2H), 4.29 (q, \( J = 7.4 \) Hz, 2H), 7.64 (t, \( J = 7.8 \) Hz, 1H)

Entry 11 (Ethyl (E)-2-Cyano-3-(2-naphthyl)-2-propeonate)

White crystalline solid

IR (cm\(^{-1}\)): \( \nu \) 2987, 2906, 2219, 1725, 1599, 1365, 1249, 817,754,713

\(^1\)HNMR (400MHz, CDCl\(_3\)): \( \delta \) 1.39 (t, \( J = 7.0 \) Hz, 3H), 4.38 (q, \( J = 7.0 \) Hz, 2H), 7.45-7.65 (m, 2H), 7.78 – 8.00 (m, 3H), 8.17 (d, \( J = 8.9 \) Hz, 1H), 8.36 (s, 1H), 8.38 (s, 1H).
Entry 12 (Ethyl (E) - 2-Cyano-3-(2-furyl)-2-propeionate)

\[ \text{CN} \quad \text{COOEt} \quad \text{O} \]

Colorless solid

IR (cm\(^{-1}\)): \(v = 3030, 2215, 1760, 1530, 1460, 1380, 1215, 1091, 756\)

\(^1^H\)NMR (400MHz, CDCl₃) \(\delta = 1.37 (t, J = 7.0 \text{ Hz}, 3\text{H}), 4.34 (q, J = 7.0 \text{ Hz}, 2\text{H}), 6.65 (t, J = 3.9 \text{ Hz}, 1\text{H}), 7.37 (d, J = 3.9 \text{ Hz}, 1\text{H}), 7.74 (d, J = 1.6 \text{ Hz}, 1\text{H}), 8.0 (s, 1\text{H})\)

Entry 13 (Ethyl (E) - 2-Cyano-3-(3-pyridyl)-2-propeionate)

\[ \text{CN} \quad \text{COOEt} \quad \text{N} \]

Pale-yellow solid

IR (cm\(^{-1}\)): \(v = 2999, 2220, 1721, 1611, 1420, 1279, 1093, 1016, 820, 762, 704\)

\(^1^H\)NMR (400MHz, CDCl₃) \(\delta = 1.40 (t, J = 7.0 \text{ Hz}, 3\text{H}), 4.39 (q, J = 7.0 \text{ Hz}, 2\text{H}), 7.47 (t, J = 6.6 \text{ Hz}, 1\text{H}), 8.25 (s, 1\text{H}), 8.57 (d, J = 7.8 \text{ Hz}, 1\text{H}), 8.74 (d, J = 2.74 \text{ Hz}, 1\text{H}), 8.91 (s, 1\text{H}).\)

Entry 14 (Ethyl (E) - 2-Cyano-3-(4-pyridyl)-2-propeionate)

\[ \text{CN} \quad \text{COOEt} \quad \text{N} \]

Colourless solid

IR (cm\(^{-1}\)): \(v = 2994, 2223, 1723, 1618, 1417, 1275, 830, 764\)

\(^1^H\)NMR (400MHz, CDCl₃) \(\delta = 1.41 (t, J = 7.0 \text{ Hz}, 3\text{H}), 4.41 (q, J = 7.0 \text{ Hz}, 2\text{H}), 7.75 (d, J = 5.1 \text{ Hz}, 2\text{H}), 8.19 (s, 1\text{H}), 8.65-8.92 (m, 2\text{H}).\)
3.2.7 References

[1] M. A. Willard, L. K. Kurihara, E. E. Carpenter, S. Calvin, V. G. Harris,


Use of CoFe$_2$O$_4$ magnetic nanoparticles (MNPs) as catalyst for Aldol type reactions
CHAPTER-III: SECTION-III

Use of $\text{CoFe}_2\text{O}_4$ magnetic nanoparticles (MNPs) as catalyst for

Aldol type reactions

3.3.0 General Introduction

Aldol type reactions such as Aldol and Nitroaldol condensations are very important class of C-C bond forming reaction in organic chemistry [1, 2]. These kinds of reactions can be carried out in presence of a base or acid catalyst in liquid phase. Base catalyzed reactions such as aldol [3, 4], Knoevenagel [5-7], Henry [8, 9] and Michael [10-12] reactions are widely employed in bulk and fine chemical industries. The use of environmentally benign catalyst and design of new synthetic methods which reduce the amount of toxic waste and by-products arising from chemical processes has been more emphasized in recent decades. In this context, design and development of environmentally safe catalyst for C-C bond formation reactions in organic transformation is highly desirable. The development of magnetic nanoparticles in these types of reactions is the consequence of such necessity.

In this section, we account for two important aldol type reactions catalyzed by CoFe$_2$O$_4$ MNPs viz. cross-aldol condensation of aromatic aldehydes with aromatic ketones and Nitroaldol condensations in aqueous ethanol medium. Section III- Part A deals with the aldol condensation and nitroaldol condensation is discussed in Section III-Part B.
CHAPTER-III: SECTION-III, Part-A

Aldol condensation by $\text{CoFe}_2\text{O}_4$ Magnetic Nanoparticles

3.3.1.1 Introduction

Aldol condensation is one of the most widely used reactions having diverse applications in different industrially important processes for manufacturing pharmaceuticals, agrochemicals etc. This is a coupling reaction in which an enol or an enolate ion reacts with a carbonyl compound to form a $\beta$-hydroxyaldehyde or $\beta$-hydroxyketone, followed by a dehydration to give a conjugated enone. A simple case is addition of an enolate to an aldehyde to afford an alcohol, thus the name aldol.

The Aldol condensations are classically carried out in presence of strong acids and bases [13, 14]. The cross aldol condensation between two different aldehydes with no $\alpha$-hydrogen in one aldehyde or between a ketone and aldehyde with no $\alpha$-hydrogen which gives $\alpha, \beta$-unsaturated ketones called chalcones is often called Claisen-Schmidt reaction. The chalcones are very important class of compounds which have been used as pesticides, photoreceptors in plastic, solar creams, food additives, antimalaria [15], antiinflammatory [16], cytotoxicity [17-19], anticancer [20, 21], diuretic, and choleretic [22].
3.3.1.2 Review of Literature

Normally, the aldol condensation is carried out using various base catalysts such as aq NaOH, KOH, Ba(OH)₂, hydrotalcites etc. and acid catalyst such as AlCl₃, dry HCl, TiCl₄, Zeolites etc. [13, 14]. Other catalysts like bis (p-ethoxyphenyl) telluroxide (BOMPTO) [23], Cp₂ZrH₂ [24], Cp₂TiPh₂ [25], TiCl₃(SO₃CF₃) [26], KF-Al₂O₃ [27], FeCl₃ [27] also catalyze this reaction. The reaction can be performed under mild reaction conditions by using various divalent metal complexes such as Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) with different ligands [28]. In most of these reactions high temperature is required for better product yield and work-up and purification steps are tedious [29]. The use of acid catalyst such as anhydrous ruthenium chloride [30], indium trichloride [31], silica sulfuric acid [32] and lanthanum triflates [33] has been reported with good yields. The acid catalyzed processes have the advantages of avoiding competitive Cannizzaro reaction of the aldehyde and also other unwanted side reactions when base-sensitive groups are present. However, these reactions also suffer the complicacy that the reactions have to be carried out in sealed tubes at high temperatures.

Several of metal oxide catalyst i.e CaO, La₂O₃, ZrO₂, A1₂O₃ Sn/SiO₂ etc. [34-37] can also be used for aldol condensations. Recently, a new kind of Lewis acids of rare earth (III) perfluoroctane sulfonates (RE(OSO₂C₈F₁₇)₃, RE(OPf)₃, RE = Sc, Y, La-Lu) has been used for aldol condensation of aldehydes and ketones [38-45]. The catalyst has the advantage of low hygroscopicity, ease of handling, robustness for the recycling and high solubility in fluorous solvent [46, 47]. There are many reports during
the last decade on direct synthesis of α, β-unsaturated carbonyl compounds by Claisen-Schmidt condensations where under strong basic conditions [48-56]. However, most of these suffer from several side reactions and narrow substrate diversity. Mild Lewis acid catalyzed tandem Mukaiyama aldol-dehydration reaction has been described where preformation of enolates from ketones is required [57-61]. But, the reaction always produces mixed products. Wang and co-workers have reported a novel pyrrolidine imide-catalyzed aldol condensation from ketones and aldehydes, with moderate to good yields in DMSO (41–95%) [62]. However, the ketone substrates are limited to acetone and cyclopentanone, and reactions with other ketone substrates proceed very slowly, with low yields. Recently, Wang has reported a method of direct aldol condensation between various ketones and aldehydes affording the corresponding (E)-α, β-unsaturated ketones in presence of catalytic amount of L-proline-TEA (triethylamine) [63]. The reaction is mild and can be applied to synthesize complicated (E)-α, β-unsaturated ketone C-glycosides from unmodified ketone C-glycosides and aldehydes. It is particularly efficient for the preparation of (E)-α, β-unsaturated ketone C-glycosides from unmodified ketone C-glycosides.
3.3.1.3 Present Work

Objective

The normal acid or base catalyzed aldol condensation process suffers from side reactions such as self condensation, thus resulting in low yield of the desired product such as unsatisfactory yield, high temperature, longer reaction times, competing side reaction and tedious purification processes. Moreover, the reusing of catalysts requires tedious work up procedures such as filtration, purification and drying.

In recent years there are many reports in the literature on the use of magnetic nanoparticles as catalyst for various organic transformations with their notable advantages of easy separation and recovery by magnetic filed and hence reusability [64]. CoFe$_2$O$_4$ was also found to be a good catalyst for a variety of organic transformations which has mild Lewis acid and basic character. In the previous section, we have developed a new synthetic strategy for the synthesis of CoFe$_2$O$_4$ MNPs which shows good dispersibility and stability in aqueous solution and employed as catalyst in Knoevenagel reaction under mild reaction condition. So, we want to explore the possibility of its use in the cross-aldol condensation of aldehydes and ketones under mild reaction conditions (Scheme 3.3.1.1).

Scheme 3.3.1.1 Knoevenagel condensation catalyzed by CoFe$_2$O$_4$ MNPs
3.3.1.4 Result and Discussion

Herein, we describe the cross-aldol condensation reaction of aromatic aldehydes and ketones catalyzed by CoFe₂O₄ MNPs in aqueous ethanol medium (Scheme 3.3.1.1) at the temperature of 50-60 °C. The aldol condensation was carried out in order to improve the reaction conditions and to extend the scope and applicability of this type of reaction. Treatment of aldehydes (1 mmol) with ketones (1 mmol) in the presence of CoFe₂O₄-MNPs catalyst (40 mol%) in 5 mL aqueous ethanol at 50-60 °C gave the corresponding α,β-unsaturated ketones in moderate to good yields. We examined the scope of the reaction by using various aryl aldehydes such as benzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-methyl-benzaldehyde, 4-methoxybenzaldehyde etc. and ketones such as acetophenone, 4-hydroxy acetophenone, 4-methoxyacotophenone etc., the results are summarized in Table 3.3.1.1.

Table 3.3.1.1 Aldol condensation of aromatic aldehydes and ketones by CoFe₂O₄ MNPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reactant</th>
<th>Product (b)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="benzaldehyde" /></td>
<td><img src="image2.png" alt="acetophenone" /></td>
<td><img src="image3.png" alt="a,b-unsaturated ketone" /></td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="4-chlorobenzaldehyde" /></td>
<td><img src="image2.png" alt="acetophenone" /></td>
<td><img src="image5.png" alt="4-chloro-a,b-unsaturated ketone" /></td>
<td>1.5</td>
<td>70</td>
</tr>
</tbody>
</table>
The reactions were completed within 3 h and the aldol products were obtained in moderate to good yields (60-76%) and most importantly no self-condensation was observed. Moreover, the chalcones formed were stable under the reaction conditions.
and no reversibility was observed. Also, the operational simplicity of this protocol and mild reaction conditions, are the advantages of this method to the other methods used for the reaction of aryl ketones and aldehydes.

Investigations using benzaldehyde and acetophenone as model substrates showed that the recovered $\text{CoFe}_2\text{O}_4$ could be successfully reused. The recovered $\text{CoFe}_2\text{O}_4$ could be used three times and similar yields were obtained in all runs.

The products were characterized by analyzing NMR and IR spectroscopic data.

Fig. 3.3.1.1 $^1\text{H}$ NMR of Chalcone (entry 1)

Fig. 3.3.1.2 $^1\text{H}$ NMR of (E)-3(4-methoxyphenyl)-1-phenylprop-2-en-1-one (entry 4)
It is well known that the recovery and reuse of the catalyst is an important feature for a process to be environmentally benign. The CoFe$_2$O$_4$ MNPs forms a quasi-homogenous dispersion in the reaction medium and can be separated by an external magnetic field after the reaction is completed. Therefore, the reaction not only allows the reduction of waste but also results in the reduction of costs.
3.3.1.5 Conclusion

In conclusion, we have demonstrated that the CoFe₂O₄ MNPs is an efficient catalyst for the reaction between aldehydes and carbon nucleophiles, such as acetophenone. The use of CoFe₂O₄ MNPs simplifies the workup of the reaction, as the catalyst can be removed by simple magnetic decantation, thereby minimizing the need of solvent for extractions. Since, the quasi-heterogeneous nature of the MNPs in ethanol has the advantage of high reactivity and easier separation of the catalyst from the reaction medium, catalyst regeneration, and reuse; it would be a good replacement of other homogenous or heterogeneous catalyst.

3.3.1.6 Experimental Section

General procedure for Aldol condensation

To a 5 mL aqueous ethanol in a round bottom flask, was added ketone (1 mmol), aldehyde (1 mmol) and CoFe₂O₄ MNPs (0.4 mmol) and the mixture was heated at 50-60 °C for 1-3 h. The catalyst was then separated from the reaction mixture by simple magnetic decantation keeping an external magnet at the side of the round bottom flask and given washings with ethanol for complete separation of the product. The product was purified by recrystallizing from ethanol. The catalyst can be reused after drying in an oven at 200 °C for 6 h.
Experimental Data:

Entry 1 (Chalcone)

White solid

IR (KBr, cm\(^{-1}\)): 2928, 1660, 1602, 1446, 1335, 1210, 1079, 992, 750

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 7.39-7.41 \text{ (m, 3H)}, 7.51-7.63 \text{ (m, 4H)}, 7.64 \text{ (dd, } J = 6 \text{ Hz } 2\text{H)}, 7.82 \text{ (d, } J = 15.6 \text{ Hz, 1H)}, 8.01 \text{ (dd, } J = 8.4 \text{ Hz, 2H)}.

MS (ESI): \(m/z\) 209.2 (M+H\(^+\)).

Entry 2 ((E)-3(4-chlorophenyl)-1-phenylprop-2-en-1-one)

White solid

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 8.0 \text{ (dd, } J = 7.2 \text{ Hz, 2H)}, 7.75 \text{ (d, } J = 16 \text{ Hz, 1H)}, 7.38-7.60 \text{ (m, 6H)}, 6.93 \text{ (dd, } J = 8.4 \text{, 2H)}.

- 111 -
Entry 4 ((E)-3(4-methoxyphenyl)-1-phenylprop-2-en-1-one)

Pale yellow solid

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.0 (dd, $J$ = 7.2 Hz, 2H), 7.75 (d, $J$ = 15.6 Hz, 1H), 7.38-7.60 (m, 6H), 6.93 (dd, $J$ = 8.4, 2H), 3.84 (s, 3H)

Entry 7 ((E)-3(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1-one)

Yellow solid

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.9 (dd, $J$ = 12 Hz, 2H), 7.74 (d, $J$ = 15.6 Hz, 1H), 7.45-7.53 (m, 5H), 7.32 (d, $J$ = 15.2 Hz, 1H), (dd, $J$ = 8.8, 2H), 3.0 (s, 6H)

Entry 8: ((E)-1-phenyl-3-p-tolylprop-2-en-1-one)

White solid

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.0 (dd, $J$ = 6.9 Hz, 2H), 7.77 (d, $J$ = 15.6 Hz, 1H), 7.47-7.58 (m, 6H), 7.21 (dd, $J$ = 7.8, 2H), 2.4 (s, 3H)
3.3.2.1 Introduction

The Henry reaction i.e. nitroaldol reaction is a coupling reaction between a carbonyl compound and an alkyl nitro compound bearing α-hydrogens with generation of a C-C bond with concomitant formation of difunctionalities i.e β-nitroalcohol function [65-70]. Conventionally, the Henry reaction is catalyzed by strong bases such as sodium methoxide, sodium hydroxide, LDA, butyl lithium, barium hydroxide or sodium carbonate and the reaction is carried out in organic solvents (Scheme 3.3.2.1).

\[
\text{Scheme 3.3.2.1}
\]

Due to the versatile chemistry of nitro group, this reaction provides access to valuable structural motifs, such as β-amino alcohols, α-hydroxycarboxylic acids, 2-nitroketones or nitroalkenes [10, 71]. Generally the reaction suffers the difficulty of poor selectivity and thus waste includes nitroalkene and its possible subsequent reaction and Cannizzaro reaction of the aldehydic component.
3.3.2.2 Review of Literature

There are many reports on nitroaldol reactions under various sets of conditions under the influence of a homogenous or a heterogenous catalyst or promoter. Nitroaldol reaction using strong bases such as alkoxide or hydroxide has a limited substrate scope in many cases. Amines such as triethyl amine or diisopropylethylamine were reported to catalyze Henry reaction in alcoholic solvent [72-74]. Guanidine (TMG) (Fig. 3.3.2.1a) and its cyclic analogs, the bicyclic guanidines (Fig. 3.3.2.1b) and including the polymer linked (Fig. 3.3.2.1c) were found to efficiently catalyze the reaction in solvents such as diethyl ether or THF [72-75].

![Chemical structures](image)

**Fig. 3.3.2.1**

Proazaphosphatranes [76, 77] such as those of type (d and e in Fig. 3.3.3.1) have also been used as catalyst for the nitroaldol reaction of both ketones and aldehydes [78]. However, it is necessary to add Lewis-acid type activator such as magnesium sulphate to achieve better yield.
Y. H. Kim and his co-worker used Lithium aluminum hydride (LiAlH₄) catalyst for the Henry reaction. They efficiently performed the reaction between a wide variety of aromatic and aliphatic aldehydes and simple nitroalkenes such as nitromethane, nitroethane or nitropropane in tetrahydrofuran (THF) solvent under dried condition with a good to excellent yield [79]. The mechanistic pathway of this reaction is depicted as below (Scheme 3.3.2.2).

In recent years, different research groups found that the nitroaldol reaction can be performed efficiently in aqueous media or under free solvent conditions. Very recently, T. Punniamurthy and his co-workers carried out the reaction using a new copper(II) open cubane as catalyst in water [80]. DNA has also been investigated as catalyst for the Henry reaction in aqueous medium recently [81]. The Henry reaction was also reported under solventless condition for a variety of aldehydes and 4-nitro-2-butanol using Amberlyst A-21 catalyst [82]. The reaction can also be carried out under
microwave irradiation using ammonium acetate [83] or potassium hydroxide [84] without using any solvent. The La\textsuperscript{3+} coordination polymer or La host ‘network’ formed from the admixture of lanthanum trisisopropoxide (La(O-i-Pr)\textsubscript{3}) and the anthracene bisresorcinol was also found to catalyze the condensation of hydrocinnamaldehyde and nitromethylene in benzene [85]. The nitroaldol reaction under heterogeneous conditions gained significant interest which has the easy separation and purification steps after completion of the reaction. For example, using Sm(HMDS)\textsubscript{3} the nitroaldol reaction between nitromethane and aldehydes such as hydrocinnamaldehyde, benzaldehyde and cyclohexylcarboxaldehyde can be easily carried out [86].

The selectivity is a major aspect in nitroaldol reactions and many researchers attempted to improve selectivity by using catalysts such as basic alumina [87], alumina-KF [88], amberlyst [89] and phase transfer catalyst with surfactants [90]. However, these approaches also have the drawbacks of longer reaction times and formation of alkenes. Chaudhury et al. have successfully carried out the reaction with modified Mg-Al hydrotalcite as a catalyst [91]. The reaction is highly selective and the reaction can be stopped at nitroaldol stage as shown in the following scheme.

\[
\begin{align*}
\text{R} + \text{CH} &+ \text{CH}_3\text{NO}_2 &\xrightarrow{\text{Catalyst}} & \text{RCH(OH)CH}_2\text{NO}_2 \\
\text{RCH} &\text{CHNO}_2 &\xrightarrow{\text{Dehydrated product}} & \\
\end{align*}
\]

Scheme 3.3.2.3
The most important advantages of this catalyst system are easy separation, excellent yield and selectivity (100%) and environmental friendly.

There are many advancements have been going on asymmetric aldol condensation reactions for enantio- and diastereoselective products by a set of chiral catalysts [10, 67, 70, 71, 92-110, 113]. While some of these methods require the use of activated silyl nitronates and tetrabutylammonium triphenylsilyldifluorosilicate (TBAT) [102, 114], others provide excellent results with aromatic aldehydes. But most importantly, the yields and ee values typically decrease when aliphatic or sterically hindered aldehydes are used. [70, 92, 114, 115]. Though many improvements in this field have attained, the limitations such as long reaction times, use of expensive catalysts, use of additives e.g. molecular sieves etc. are still observed in many catalytic nitroaldol reactions.

3.3.2.3 Present Work

Objective

Chemoselectivity is an important parameter to determine the quality of any reaction. In case of the Henry reaction the possibility to occur various side reactions lowers the chemoselectivity of the reaction. During nitroaldol condensation, in presence of a base, the aldehyde substrates may undergo aldol condensation and cannizaro reaction, however if nitroaldol is formed then base catalyzed elimination of water gives nitroalkenes which can readily polymerize. This elimination is difficult to avoid if aryl aldehydes are employed. Further to better the yield, the reaction has been carried out
under various conditions such as volatile organic solvents, homogeneous catalyst which make the process more environmental unsafe.

The Henry reaction continues to attract interest in broad areas of synthetic organic chemistry. In developing a new synthetic strategy, chemists are more concerned to environmental friendly processes where the toxic waste or byproducts can be minimized or eliminated. In this context, the use of recyclable heterogeneous catalysts with minimized use of toxic solvents is utmost necessary. In recent years, there has been increasing recognition of magnetic nanoparticle catalyst in various organic transformations.

In continuation our earlier use of CoFe$_2$O$_4$ MNPs as mild basic catalyst in Knoevenagel and Aldol condensation reaction, we intend to employ the CoFe$_2$O$_4$ MNPs as catalyst to the nitroaldol condensation. We wish to investigate the possibility to achieve the reaction in aqueous medium. To the best of our knowledge, the magnetic nanoparticle catalyzed Henry reaction in aqueous medium has not been addressed yet.

### 3.3.2.4 Result and Discussion

Initial reaction for Henry reaction was carried out between $p$-nitrobenzaldehyde and nitromethane at room temperature in three sets of reaction in water, ethanol and 1:1 water ethanol mixture using 20 mol% CoFe$_2$O$_4$ MNPs. Product formations was observed in all case. However, the yield in ethanol and 1:1 water ethanol (85%, entry 2)
was much better than in water. To optimize the reaction conditions, we performed a set of experiment in different mmol concentrations of benzaldehydes and nitromethane. Next we examined the influence of catalyst concentration (5, 10 and 20 mmol%) on the reaction time and yield. The optimal reaction conditions to be used for various aldehydes and nitromethane were found to be 1 mmol of benzaldehyde, 2 mmol of nitromethane, 3 mL of 1:1 ethanol water mixture, 20 mmol% of CoFe$_2$O$_4$ MNPs catalyst and ambient temperature which generated the nitroaldol products with good to excellent yields (Table 3.3.2.1, entries 1-10).

\[
\begin{align*}
R^+ \text{CHO} + \text{CH}_3\text{NO}_2 & \xrightarrow{\text{CoFe}_2\text{O}_4 \text{ MNPs}} \text{H}_2\text{O, r.t, 1-4 h}} \xrightarrow{COFe_2O_4 MNPs} \text{OH} \text{NO}_2 \\
\end{align*}
\]

Scheme 3.3.2.4 Henry reactions between nitromethane and various substituted aromatic and aliphatic aldehydes.

Table 3.3.2.1. Henry reactions of various aldehydes with nitromethane catalyzed by CoFe$_2$O$_4$ MNPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction time (h)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>0.5</td>
<td>85 (81)$^b$</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>1</td>
<td>70</td>
</tr>
</tbody>
</table>
The benzaldehyde produced a yield of 65% in a 3 h reaction. The aromatic aldehydes bearing strong electron-withdrawing substituents (entry 2) had better reactivities and gave better yields than those bearing weak electron-withdrawing substituents (entries 3-6). In these cases, the para-substituted reactant had a greater activity on the reaction than that having ortho-substitution (entries 2-6). In contrast, the aromatic aldehydes with electron-donating substituents produced slightly lower yields.
than benzaldehyde (entries 7-8). Notably, excellent yields were found for 4-nitrobenzaldehyde and 4-fluoro benzaldehyde within 1 h of reaction time (entries 2 and 4). Aliphatic aldehydes, such as octanal also generated the nitroaldol product with good yields (60 %, entry 10). It is important to note that without the catalyst, all the substrates produced no (or trace amounts of) nitroaldol product.

The CoFe$_2$O$_4$ MNP catalyst is a recyclable one and found to be quite effective as reusable up to several times. We tested the recyclability of the catalyst in the Henry reaction by using p-nitrobenzaldehyde and nitromethane under the optimized reaction conditions in three consecutive cycles. No significant decrease in catalytic activity was observed in the third round of catalytic cycle and is depicted in Fig. 3.3.2.2

![Graph](image.png)

**Fig. 3.3.2.2** Recycling experiments for the Henry reaction.

It may be inferred that there are many advantages of using this heterogeneous CoFe$_2$O$_4$ MNPs in Henry reactions. Apart from easy separation of the catalys form the reaction mixture, this catalyst is selective in producing only the nitroaldol product.
Other competing reactions such as aldol condensation and cannizaro reaction were not observed in this case.

**Fig. 3.3.2.3** $^1$H NMR of 1-Phenyl-2-nitroethan-1-ol (entry 1)

**Fig. 3.3.2.4** $^1$H NMR of 2-nitro-1-(4-nitrophenoxy)ethanol (entry 2)
3.3.2.5 Conclusion

We have shown that the CoFe$_2$O$_4$ MNPs can be used as a heterogenous catalyst to facilitate the nitroaldol reaction in aqueous ethanolic solution under mild reaction conditions. Most of the substrates resulted in good to excellent yields of the expected reaction products. More interestingly, the catalyst could be separated using an external magnet and recycled three times without any loss of activity.
3.3.2.6 Experimental Section

Typical Procedure for the Nitroaldol (Henry) Reaction

To a mixture of nitroalkane (1.5 mmol) and aldehyde (1 mmol), in 1:1 aqueous ethanol (5 mL) in a 25 mL round-bottom flask was added CoFe$_2$O$_4$ MNPs (0.2 mmol, 20 mmol%) at room temperature. The mixture was stirred at room temperature using a magnetic stirrer for the appropriate time as monitored the progress of the reaction by TLC from time to time till completion. After completion of the reaction as monitored by TLC, the catalyst was removed by using an external magnet and washed several times with ethanol, dried and kept under vacuum till further use. Dichloromethane was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic extract was washed with brine solution. The organic layer thus obtained was dried over anhydrous Na$_2$SO$_4$, concentrated under reduced pressure. The dried crude product was purified by column chromatography of silica gel (60-120 mesh size) column using ethylacetate-petroleum ether as eluting solvent. All the products were characterized by IR, $^1$H NMR, and mass spectroscopic methods and also by comparison with the reported values.
**Experimental Data:**

**Entry 1 (1-Phenyl-2-nitroethan-1-ol)**

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & \nu 3400, 1553. \\
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } & \delta 2.68-2.95 \text{ (br, 1H)}, 4.45-4.60 \text{ (m, 2H)}, 5.35-5.50 \text{ (m, 1H)}, 7.20-7.55 \text{ (m, 5H)}. \\
\text{MS: } & m/z 149 (M-H}_2\text{O).}
\end{align*}
\]

**Entry 2 (2-nitro-1-(4-nitrophenyl)ethanol)**

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & \nu 3431, 1597, 1556. \\
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } & \delta 3.17-3.22 \text{ (br, 1H)}, 4.44-4.49 \text{ (m, 1H)}, 4.51-4.58 \text{ (m, 1H)}, 5.37-5.42 \text{ (m, 1H)}, 7.31 \text{ (d, 2H, J=8.40Hz)}, 7.35 \text{ (d, 2H, J=8.40 Hz)}. \\
\text{MS: } & m/z 184 (M-H}_2\text{O).}
\end{align*}
\]
Entry 3 (1-(4-bromophenyl)-2-nitroethanol)

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & \text{v 3431, 1597, 1556.} \\
{^1}\text{H NMR (400 MHz, CDCl}_3\text{): } & \delta 3.17-3.22 \text{ (br, 1H), 4.44-4.49 (m, 1H),} \\
& 4.51-4.58 \text{ (m, 1H), 5.37-5.42 (m, 1H), 7.31 (d, 2H, J=8.40Hz), 7.35 (d, 2H, J=8.40 Hz).}
\end{align*}
\]

Entry 4 (1-(4-fluorophenyl)-2-nitroethanol)

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & \text{v 3430, 1595, 1554.} \\
{^1}\text{H NMR (400 MHz, CDCl}_3\text{): } & \delta 3.17-3.22 \text{ (br, 1H), 4.44-4.49 (m, 1H),} \\
& 4.48-4.61 \text{ (m, 1H), 5.44-5.52 (m, 1H), 7.21 (d, 2H, J=8.40Hz), 7.35 (d, 2H, J=8.40 Hz).}
\end{align*}
\]

Entry 5 (1-(4-chlorophenyl)-2-nitroethanol)

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & \text{v 3441, 1597, 1553.} \\
{^1}\text{H NMR (400 MHz, CDCl}_3\text{): } & \delta 2.67-2.94 \text{ (br, 1H), 3.79 (s,3H), 4.46-4.50 (m, 1H),} \\
& 4.58-4.63 \text{ (m, 1H), 5.40-5.43 (m, 1H), 7.14 (d, 2H, J=8.40 Hz), 7.33(d, 2H, J=8.40Hz).} \\
\text{MS: m/z 179 (M-H}_2\text{O).}
\end{align*}
\]
Entry 6 (1-(3-chlorophenyl)-2-nitroethanol)

\[
\text{IR (film, cm}^{-1}\text{): } \nu 3563, 1597, 1557.
\]

\[
^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.42 (s, 1 H), 7.34-7.33 (m, 2 H), 7.29-7.25 (m, 1 H), 5.46-5.43 (m, 1 H), 4.57-4.52 (m, 2 H), 2.30 (s, 1 H).
\]

MS: \text{m/z 201}

Entry 7 (2-nitro-1-p-tolylethanol)

\[
\text{IR (film, cm}^{-1}\text{): } \nu 3548, 1555, 1516.
\]

\[
^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.27 (d, J = 7.8 \text{ Hz, 2 H}), 7.20 (d, J = 7.8 \text{ Hz, 2 H}), 5.43-5.39 (m, 1 H), 4.59 (dd, J = 9.9, 3.6 \text{ Hz, 1 H}), 4.46 (dd, J = 9.9, 3.3 \text{ Hz, 1 H}), 2.70 (\text{br, 1 H}), 2.35 (s, 3 H).
\]

MS: \text{m/z 181}
Entry 8 (1-(4-methoxyphenyl)-2-nitroethanol)

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & n 3464, 1553, 1514. \\
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } & \delta \text{ 7.31 (d, } J = 8.7 \text{ Hz, 2 H), 6.91 (d, } J = 8.7 \text{ Hz, 2 H), 5.41-5.38 (m, 1 H), 4.58 (dd, } J = 12.9, 9.6 \text{ Hz, 1 H), 4.46 (dd, } J = 12.9, 3.0 \text{ Hz, 1 H), 3.80 (s, 3 H), 2.69 (br, 1 H).} \\
\text{MS: } & m/z 197
\end{align*}
\]

Entry 9 (1-(Naphthalen-2-yl)-2-nitroethanol)

\[
\begin{align*}
\text{IR (film, cm}^{-1}\text{): } & 3416, 1552, 1515. \\
\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } & \delta 2.94-3.23 (br, 1H), 4.56-4.60 (m, 1H), 4.46-4.71(m, 1H), 5.59-5.62 (m, 1H), 7.45-7.47 (m, 1H), 7.54-7.56 (m, 2H), 7.85-7.89 (m, 4H). \\
\text{MS: } & m/z 199 (M-H}_2\text{O).}
\end{align*}
\]
3.3.2.7 References


Catalytic use of CoFe$_2$O$_4$ MNPs for acetylation of alcohols and amines Boc-protection of amines
3.4.1 Introduction

Acylation of alcohols and amines is one of the most fundamental transformations in organic chemistry [1]. Conversion of hydroxyl or amino group into the corresponding acetate or acetamide is essential because some of the acetylated compounds have medicinal value, e.g. the preparation of paracetamol from 4-aminophenol. Moreover, presence of hydroxyl or amino group in a compound can also be ascertained using this method. In addition, the protection of hydroxyl or amino functionality as acetate is preferred due to its ease of introduction, stability under mild acidic reaction conditions and ease of removal by mild alkaline hydrolysis. Usually acetylation is performed using acetic anhydride, acetyl chloride or acetic acid in presence of a base catalyst such as such as triethylamine, pyridine, 4-(dimethylamino)pyridine (DMAP), 4- pyrrolidinopyridine and tributylphosphine [2].

The N-tert-butoxycarbonyl (N-Boc) group is one of the most frequently used protecting groups for amines and amine derivatives in synthetic organic chemistry [3]. This group is stable towards catalytic hydrogenolysis and extreme resistance to basic and nucleophilic conditions [2, 3] and hence mostly used as efficient protecting group for amines. Moreover, the amine can be readily generated by removing the Boc-
protecting group by reagents such as CF$_3$COOH, formic acid, 3N HCl in ethyl acetate or 10% H$_2$SO$_4$ in dioxane within a short time.

There are many reagents available for N-Boc protection such as Boc$_2$O, BocONH$_2$, BocN$_3$, BocON=N(CN)Ph, 1-(tert-butoxycarbonyl)benzotriazole, and di-tert-butoxypyrocarbonate. Out of these the (Boc)$_2$O is widely used and the di-tert-butoxypyrocarbonate is also becoming popular due to its low cost, availability and stability for protection of amines. Normally, Boc protection of amines is performed by basic catalyst. Recently, some Lewis acids have also been applied as catalysts for this purpose.

### 3.4.2 Review of Literature

*Acetylation of alcohols and amines*

The acetylation of alcohols and amines is an important reaction in organic synthesis and is catalyzed by a variety of acidic or basic homogenous or heterogenous catalysts.

During last few decades, various metal salts such as CoCl$_2$ [4], ZnCl$_2$ [5], TiCl$_4$-AgClO$_4$ [6] Me$_3$SiCl [7], LiClO$_4$ [8] and MgClO$_4$ [9] as well as metal triflates e.g. Sc(OTf)$_3$ [10] Me$_3$SiOTf [11], Cu(OTf)$_2$ [12, 13] have been investigated to meet the demand for more efficient and selective methods. In most of these cases the catalyst is either less or not effective for secondary or tertiary alcohols or longer reaction times are necessary in order to achieve good yields. These limitations are eliminated by the use of
Lewis acids but many of these are moisture sensitive and expensive. In recent past, perchlorates [14, 15] were reported to catalyze the acetylation of alcohols, however, perchlorates, particularly of lithium, are explosive and moisture sensitive. An efficient method of acetylation of a wide variety of alcohols was achieved by P. Phukan using molecular iodine as catalyst under solvent-free conditions at room temperature [16]. 3-Nitrobenzoic acid has also been reported as benign catalyst for acetylation of alcohols [17].

Apart from these homogenous catalysts few heterogeneous catalysts have also been developed for acetylation of alcohols and amines. The catalysts such as yttria-zirconia-based catalysts [18-20], metal oxides such as ZnO, CuO, NiO, CoO, Mn2O3, Cr2O3 [21-23], montmorillonites [24], HClO4-SiO2 [25], H2SO4-SiO2 [26], AlPW12O40 [27, 28], zeolites [29], Nafion-H [30], HBF4-SiO2 [31], KF-Al2O3 [32], silica embedded-triflate catalysts [33], Cp2ZrCl2 [34], H14NaP5W30O110 [35], MoO3-Al2O3 [36], NaHSO4-SiO2 [37], Sn(TPP)(BF4)2 [38], sulphated zirconia [39] and H3PV2Mo10O40 [40] have been employed to achieve the acetylation of a wide variety of alcohols, phenols, thiols, and amines.

**Boc-Protection of amines**

Besides numerous applications for protection of amines in intermediate steps in organic reactions, N-tert-butoxycarbonyl (N-Boc) protection has been widely used for the amino acids during peptide synthesis [41-43]. There is a variety of base catalyzed Boc-protection reactions reaction in the literature [44-47]. Recently, some Lewis acids
such as Zn(ClO₄)₂·6H₂O, yttria-zirconia, LiClO₄, β-cyclodextrin, and ZrCl₄ have also been applied as catalysts for this purpose [48-52]. However, there is some limitations of using Lewis acids for Boc-protection. Due to the strong affinity of several Lewis acids towards amino groups, the regeneration of these catalysts is not possible in the reaction. Also they are deactivated or decomposed by the amines/their derivatives with the use of more than stoichiometric amounts [53, 54].

Recently, S. R. Adapa and his co-workers has reported a facile procedure for protection of various aryl and aliphatic amines using (Boc)₂O in the presence of a catalytic amount of iodine under solvent-free conditions (Scheme 3.4.1). The reaction produces high to excellent yield of products (up to 98%) at ambient temperature [55].

\[
\begin{align*}
& R' N^+ H + \text{Boc}_2O \\& \xrightarrow{1 \text{ eq. (Boc)}_2O, 0.1 \text{ eq. } I_2} \text{solvent- free, r.t., 0.1-12 h} \\
& \xrightarrow{} R' N_{\text{Boc}}
\end{align*}
\]

Scheme 3.4.1

Heydari et al. reported the use of 1, 1, 1, 3, 3, 3-hexafluoroisopropanol (HFIP) as solvent and catalyst for a simple and efficient chemoselective mono-N-Boc protection of various structurally diverse amines with di-tert-butyl dicarbonate (Scheme 3.4.2) [56].

\[
\begin{align*}
& R' N^+ H + \text{Boc}_2O \\& \xrightarrow{(CF_3)_2CHOH (HFIP) \text{ r.t., 5-30 min}} R' N_{\text{Boc}}
\end{align*}
\]

Scheme 3.4.2
Perchloric acid adsorbed on silica-gel (HClO₄-SiO₂) was found to be a new, highly efficient, inexpensive and reusable catalyst for chemoselective \(N\text{-}\text{tert-}
\text{butoxycarbonylation of various aromatic and aliphatic amines at room temperature and under solvent-free conditions [57].}

A simple and efficient regioselective preparation of mono-N-Boc protected aromatic amines in high yield was reported by V. Perron et al. using (Boc)₂O without affecting aliphatic amino groups and other functionalities [58].

A stereoconservative protection and deprotection method of amino and carboxyl groups is reported (Scheme 3.4.3) [59].

![Scheme 3.4.3](image)

3.4.3 Present Work

Objective

Although a large number of methods for acetylation and Boc-protection are available, there are several drawbacks behind these classical protection techniques such as the use of expensive, moisture sensitive and toxic catalysts, long reaction times, intolerance of other functional groups, tedious preparation of catalysts, harsh reaction
conditions, utilization of halogenated volatile organic solvents and poor yields of the desired products. Moreover, most of the catalysts reported in literature for these transformations are homogenous. It is well known that heterogeneous catalysts are more advantageous over homogeneous catalysts as they can be easily recovered from reaction mixture by simple filtration and can be reused several times, making the process more economically and environmentally viable.

\[
\begin{align*}
R\text{OH} & \xrightarrow{\text{Ac}_2\text{O}} \text{CoFe}_2\text{O}_4 \text{ MNPs} \rightarrow R\text{OAc} \\
R\text{NH}_2 & \xrightarrow{\text{Ac}_2\text{O}} \text{CoFe}_2\text{O}_4 \text{ MNPs} \rightarrow R\text{NHAc} \\
R\text{NH}_2 & \xrightarrow{\text{Boc}_2\text{O}} \text{CoFe}_2\text{O}_4 \text{ MNPs} \rightarrow R\text{NHBoc}
\end{align*}
\]

Scheme 3.4.4

In order to overcome the above problems and owing to the growing environmental considerations, development of green processes using heterogeneous catalysts under solvent-free conditions has aroused great interest in recent years. However, there is always the need for better methodology for this type of widely used reaction. In the previous sections, we have evaluated the catalytic potential of CoFe$_2$O$_4$ MNPs for Aldol condensation, Henry reaction and Knoevenagel reactions. So, we thought that the catalyst might also activate acid anhydrides and Boc-anhydride for acetylation of alcohols and amines and Boc-protection of amines (Scheme 3.4.4).
3.4.4 Result and Discussion

*Acetylation of alcohols and amines*

At first, we intended to evaluate the catalytic property of CoFe$_2$O$_4$ MNP for acetylation under solvent-free conditions. For this purpose, initial experiments were carried out for acetylation of benzyl alcohol with acetic anhydride. The reaction under solvent-free condition is fast and corresponding benzyl acetate forms in 86% yield after 30 minutes of reaction in presence of 10 mol% of the catalyst. Similarly, for acetylation of aniline takes 5 minutes for completion with 85% yield.

Several examples illustrating this convenient heterogeneous catalysis for acetylation of alcohols and amines are presented in Table 3.4.1. In a short reaction time, the desired esters were obtained in good to excellent yields from the reaction of a variety of benzylic, primary and secondary alcohols (1 mmol) with Ac$_2$O (2 mmol) in the presence of catalytic amount of CoFe$_2$O$_4$ MNPs (10 mol%).

To explore the applicability of CoFe$_2$O$_4$ MNPs as an acetylation catalyst, we studied the acetylation of various amines containing various electron-donating and withdrawing groups with Ac$_2$O under solvent-free conditions (Table 3.4.1). Good to excellent results were obtained in each case affording the corresponding acetylated derivatives in 77-88% yields in 5-30 min at room temperature. The excellent activity of CoFe$_2$O$_4$ MNPs was demonstrated by the high yields obtained for anilines having electron-withdrawing groups (Table 3.4.1, entry 12).
Table 3.4.1 Acetylation of alcohols and amines by CoFe\textsubscript{2}O\textsubscript{4} MNPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>10</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>20</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>24 h</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>(\text{[Structure]})</td>
<td>(\text{[Structure]})</td>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>
Fig. 3.4.1 $^1$H NMR of Benzyl acetate (entry 1, Table 3.4.1)
Fig. 3.4.3 $^1$H NMR of Octyl acetate (entry 4, Table 3.4.1)
Fig. 3.4.5 $^{13}$C NMR of Cyclohexyl acetate (entry 6, Table 3.4.1)

Fig. 3.4.6 $^1$H NMR of N-phenylacetamide (entry 9, Table 3.4.1)
Fig. 3.4.7 $^1$H NMR of N-benzylacetamide (entry 10, Table 3.4.1)

Fig. 3.4.8 $^1$H NMR of N-(4-nitrophenyl)acetamide (entry 12, Table 3.4.1)
**Boc-protection of amines**

To study the Boc-protection reactions, we have first chosen aniline as the model substrate in presence of catalytic amount CoFe₂O₄ MNPs under solvent-free condition (Scheme 3.4.5).

![Reaction Scheme](image)

**Scheme 3.4.5** Protection of amines as N-tert-butylcarbamate

When benzyl amine (Table 3.4.2, entry 1) was treated with (Boc)₂O in presence of 10 mol% CoFe₂O₄ MNPs at room temperature, the reaction afforded the corresponding product in 90% yield in 5 min. The same reaction took long reaction time (50 h) in absence of the catalyst with poor yield.

**Table 3.4.2** Boc protection of amines by CoFe₂O₄ MNPs

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\text{NH}_2
\] \[\text{NH}_2\] | \[
\text{NH}_2
\] \[\text{NH}_2\] | 5 | 90 |
| 2     | \[
\text{NH}_2
\] \[\text{NH}_2\] | \[
\text{NH}_2
\] \[\text{NH}_2\] | 10 | 85 |
| 3     | \[
\text{NH}_2
\] \[\text{NH}_2\] | \[
\text{NH}_2
\] \[\text{NH}_2\] | 20 | 84 |
This interesting result prompted us to explore the catalytic activity of the CoFe$_2$O$_4$ MNPs with a variety of amines with (Boc)$_2$O. Accordingly, aryl, heteroaryl, alkyl, benzyl, allyl amines and secondary amine (entry, 4) underwent smooth Boc protection to furnish the corresponding products (Boc protected amines) in good to excellent yields (Table 3.4.2) in 5-60 min. It is worth mentioning that 1, 2-
Diaminobenzene (entry 11) on treatment with (Boc)\textsubscript{2}O at room temperature chemoselectively gave mono-protected product in high yield. Thus this procedure could be conveniently be applied to variety of amines.

![Diaminobenzene Structure](image)

**Fig. 3.4.9** \( ^1\text{H} \) NMR of (tert-butyl N-benzylcarbamate) (entry 1, Table 3.4.2)

![NMR Spectrum](image)
3.4.5 Conclusion

Cobalt ferrite nano magnetic catalyst has been found to be an efficient catalyst for acetylation of alcohols and amine and Boc-protecton of amines. The reactions were very fast under solvent-free condition to produce the corresponding products within a short period.
3.4.6 Experimental procedure

**Acetylation of alcohols and amines by CoFe$_2$O$_4$ MNPs**

To a mixture of CoFe$_2$O$_4$ MNPs (0.02 g) and acetic anhydride or acetyl chloride (2 mmol), amine or alcohol (1 mmol) was added. The reaction mixture was stirred for the required period of time at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the product was extracted with CH$_2$Cl$_2$ and removed the catalyst by magnetic decantation. The organic phase was treated with saturated bicarbonate solution and dried over anhydrous sodium sulphate. The solvent was removed under vacuum to afford the pure product.

**Boc-protection of amines by CoFe$_2$O$_4$ MNPs**

To a mixture of amine (1 mmol) and (Boc)$_2$O (1.5 mmol), was added CoFe$_2$O$_4$ MNPs (10 mol%) at room temperature. After stirring the reaction mixture for the specified time (*Tables 3.4.2*), the product was extracted with CH$_2$Cl$_2$ and the catalyst was separated by magnetic decantation. The organic layer was washed with water (10 mL), brine (10 mL), dried (Na$_2$SO$_4$), evaporated under reduced pressure and purified the residue by column chromatography (silica gel, 60-120 mesh) using petroleum ether-EtOAc as eluent to furnish the pure product.
**Experimental Data:**

**Table 3.4.1**

**Entry 1 (Benzyl acetate)**

![Chemical structure of Benzyl acetate]

White solid

IR (Nujol, cm⁻¹): ν 2955, 1741, 1457, 1360, 1232, 1028

¹H NMR (400 MHz, CDCl₃): δ 2.09 (s, 3H), 5.09 (s, 2H), 7.30-7.38 9m, 5H

¹³C NMR (400 MHz, CDCl₃): δ 20.8, 66.4, 127.8, 128.5, 137.1, 171.3

**Entry 2 (1-Acetoxy-2-(4-hydroxyphenyl)-ethane)**

![Chemical structure of 1-Acetoxy-2-(4-hydroxyphenyl)-ethane]

Colourless sticky liquid

IR (cm⁻¹): ν 3421, 3021, 2960, 1721, 1516, 1449, 1372, 1254, 1034

¹H NMR (400 MHz, CDCl₃): δ 2.05 (s, 3H), 2.86 (t, J=6.80Hz, 2H), 4.23(t, J=6.80Hz, 2H), 5.14 (s, br, 1H), 6.76 (d, J=8.00Hz, 2H), 7.07 (d, J=8.80Hz, 2H);

**Entry 3 (4-Methoxybenzyl acetate)**

![Chemical structure of 4-Methoxybenzyl acetate]

Colourless sticky liquid
IR (Nujol, cm⁻¹): ν 2953, 1764, 1597, 1460, 1365, 1235, 1028

¹H NMR (400 MHz, CDCl₃): δ 2.09 (s, 3H), 3.80 (s, 3H), 5.04 (s, 2H), 6.87 (d, J= 8.6 Hz), 7.27 (d, J= 8.6Hz, 2H)

¹³C NMR (400 MHz, CDCl₃): δ 21.8, 66.4, 114.8, 126.5, 130.6, 171.3

Entry 4 (Octyl acetate)

\[ \text{\text{OAc}} \]

Colourless sticky liquid

IR (Nujol, cm⁻¹): ν 2920, 2851, 1730, 1463, 1377, 1240

¹H NMR (400 MHz, CDCl₃): δ 0.8 (t, J=6.5 Hz, 3H), 1.30-1.33 (m, 10H), 1.38-1.50 (m, 2H), 2.1 (s, 3H), 3.58 (t, J=6.6 Hz, 2H)

¹³C NMR (400 MHz, CDCl₃): δ 14.3, 21.2, 27.1, 29.1, 19.8, 32.1, 63.3, 171.5

Entry 5 (1-methylhexyl acetate)

\[ \text{\text{OAc}} \]

Colourless sticky liquid

IR (Nujol, cm⁻¹): ν 3075, 2954, 2859, 1740, 1464, 993.

¹H NMR (400 MHz, CDCl₃): δ 0.85 (t, J=7.1 Hz, 3H), 1.15 (d, J= 6.4 Hz, 3H), 1.24-1.34 (m, 6H), 1.35-1.46 (m, 1H), 1.5-1.6 (m, 1H), 2.1 (s, 1H), 4.8-4.9 9m, 1H)

¹³C NMR (400 MHz, CDCl₃): δ 14.1, 20.0, 21.1, 22.4, 25.0, 32.0, 35.8, 71.2, 170.8.
Entry 6 (Cyclohexyl acetate)

\[
\text{\includegraphics[width=0.2\textwidth]{cyclohexyl_acetate}}
\]

Colourless sticky liquid

IR (Nujol, cm\(^{-1}\)): \(\nu \) 2921, 2845, 1725, 1446, 1365, 1246, 1060, 1025.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 1.04-1.41 (m, 6H), 1.51-1.76 (m, 4H), 2.09 (s, 3H), 4.56-4.76 (m, 1H)

Entry 7 (2-isopropyl-5-methylcyclohexyl acetate)

\[
\text{\includegraphics[width=0.2\textwidth]{2-isopropyl_5-methylcyclohexyl_acetate}}
\]

Colourless sticky liquid

IR (Nujol, cm\(^{-1}\)): \(\nu \) 2955, 2871, 1735, 1600, 1454, 1371, 1242, 1024.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta \) 0.74 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 2.4 Hz, 3H), 0.9 (J = 2.1 Hz, 3H), 0.9-1.2 (m, 2H), 1.26-1.44 (m, 1H), 1.4-1.5 (m, 1H), 1.56-1.68 (m, 2H), 1.8-2 (m, 2H), 2-2.19 (m, 1H), 2.03 (s, 3H), 4.6-4.8 (m, 1H)

\(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta \) 16.5, 20.4, 21.3, 22.1, 24.0, 26.2, 31.2, 34.2, 41.0, 47.2, 74.2, 171.0

Entry 9 (N-phenylacetamide)

\[
\text{\includegraphics[width=0.2\textwidth]{N-phenylacetamide}}
\]
White crystalline solid

\[ ^{1}H\text{ NMR (400 MHz, CDCl}_{3}): \delta 2.12 (s, 3H), 7.20 (t, J= 8.8, 2H), 7.26 (t, J= 8.7, 1H), 7.61 (d, J= 8.4, 2H) \]

\[ ^{13}C\text{ NMR (400 MHz, CDCl}_{3}): 22.0, 121.4, 124.2, 131.1, 139.5, 171.0 \]

**Entry 10 (N-benzylacetamide)**

\[
\begin{align*}
\text{NHAc} \\
\text{Ph}
\end{align*}
\]

White solid

\[ ^{1}H\text{ NMR (400 MHz, CDCl}_{3}): \delta 1.96 (s, 3H), 4.37 (d, 2H), 6.1 (b, 1H), 7.25-7.31 (m, 5H) \]

\[ ^{13}C\text{ NMR (400 MHz, CDCl}_{3}): 169.1, 138.1, 128.3, 126.9, 126, 43.7, 23.1 \]

**Entry 11 (N-(4-chlorophenyl) acetamide)**

\[
\begin{align*}
\text{NHAc} \\
\text{Cl}
\end{align*}
\]

White crystalline solid

\[ ^{1}H\text{ NMR (400 MHz, CDCl}_{3}): \delta 2.17 (s, 3H), 7.26 (dd, J= 9.2, 2H), 7.46 (dd, J= 8.4, 2H) \]

\[ ^{13}C\text{ NMR (400 MHz, CDCl}_{3}): 168.7, 136.5, 130.1, 128.9, 121.2, 22.9 \]

**Entry 12 (N-(4-nitrophenyl) acetamide)**

\[
\begin{align*}
\text{NHAC} \\
\text{O}_{2}N
\end{align*}
\]

- 158 -
Light yellow crystalline solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.23 (s, 3H), 7.44 (dd, $J$= 9.2, 2H), 8.18 (dd, $J$= 9.2, 2H)

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 168.7, 145.1, 144.1, 122.3, 121.2, 22.8

**Entry 13** (N-(3-chlorophenyl) acetamide)

\[
\begin{array}{c}
\text{Cl} \\
\text{NHAC}
\end{array}
\]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.20 (s, 3H), 7.02 (d, $J$= 8.8, 1H), 7.18 (t, $J$= 8, 1H), 7.3 (d, $J$= 9.2, 1H), 7.6 (s, 1H), 7.82 (b, 1H)

$^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 168.8, 138.7, 134.6, 131.1, 124.4, 122.1, 118.6, 21.9

**Table 3.4.2**

**Entry 1** (tert-butyl N-benzylcarbamate)

\[
\begin{array}{c}
\text{NHBOc}
\end{array}
\]

White solid

IR (neat, cm$^{-1}$): v 3335, 2975, 2927, 1690, 1440, 1234, 1159, 874.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.46 (s, 9H), 4.24 (d, $J$= 5.2 Hz, 2H), 4.85 (br s, 1H), 7.26-7.33 (m, 5H)

$^{13}$C NMR (400 MHz, CDCl$_3$): 28.1, 44.2, 127.1, 127.1, 128.5, 138.6, 155.5

**Entry 2** (tert-butyl phenylcarbamate)

\[
\begin{array}{c}
\text{NHBOc}
\end{array}
\]
White solid

IR (neat, cm\(^{-1}\)): \(\nu\) 3331, 2972, 2920, 1680, 1436, 1211, 1140, 865.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.40 (s, 9H), 4.81 (br s, 1H), 7.25-7.32 (m, 5H)

\(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 22.0, 121.4, 124.2, 131.1, 139.5, 171.

**Entry 3** (tert-butyl N-(2-pyridyl) carbamate)

\[ \text{NHBoc} \]

IR (neat, cm\(^{-1}\)): \(\nu\) 3215, 2981, 1713, 1580, 1538, 1471, 1435, 1307, 1231, 1150, 773.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.51 (s, 9H), 6.94 (m, 1H), 7.64 (dd, \(J=7.88, 8.59\) Hz, 1H), 7.93 (d, \(J=8.59\) Hz, 2H), 8.33 (d, \(J=4.68\) Hz, 1H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 28.5, 80.8, 112.6, 118.1, 138.7, 147.7, 152.9, 153.2

**Entry 4** (tert-butyl benzylmethylcarbamate)

\[ \text{NHBoc} \]

IR (neat, cm\(^{-1}\)): \(\nu\) 3331, 2980, 2922, 1680, 1445, 1228, 1156, 868.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.40 (s, 9H), 3 (s, 3H), 4.23 (d, \(J=5.2\) Hz, 2H), 7.24-7.30 (m, 5H)

\(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta\) 28.5, 35.1, 50.2, 127.1, 128.1, 136.6, 154.8

**Entry 6** (tert-butyl N-(4-nitrophenyl)carbamate)

\[ \text{O}_2\text{N} \]

IR (neat, cm\(^{-1}\)): \(\nu\) 3380, 2990, 2965, 1718, 1588, 1522, 1492, 1461, 1365, 1305, 1281, 1220, 1106, 840
$^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 1.53 (s, 9H), 4.29 (br s, 1H), 6.63 (d, $J$=9.36 Hz, 2H), 8.05 (d, $J$=8.57 Hz, 2H); $^{13}$CNMR (400MHz, CDCl$_3$): $\delta$ 29.1, 51.5, 113.0, 125.3, 126.3, 137.6, 152.7;

**Entry 7 (tert-butyl N-(2-hydroxyphenyl)carbamate)**

![NHBOC](image)

IR (neat, cm$^{-1}$): $\nu$ 3423, 3286, 3300, 2982, 2926, 1689, 1622, 1612, 1523, 1455, 1444, 1325, 1151, 1054, 749
$^1$HNMR (400 MHz, CDCl$_3$): $\delta$ 1.52 (s, 9H), 6.71-7.42 (m, 4H), 6.58 (br s, 1H), 8.00 (br s, 1H)
$^{13}$CNMR (400 MHz, CDCl$_3$): $\delta$ 28.5, 82.0, 118.5, 120.7, 121.2, 125.4, 147.3, 154.9

**Entry 8 (tert-butyl N-(1-naphthyl)carbamate )**

![NHBOC](image)

Dark brown solid
IR (neat, cm$^{-1}$): $\nu$ 3262, 2974, 2928, 1692, 16292, 1536, 1513, 1498, 1449, 1365, 1240, 1248, 1157, 996, 765
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.55 (s, 9H), 6.81 (br s, 1H, NH), 7.41-7.89 (m, 7H); $^{13}$CNMR (400 MHz, CDCl$_3$): $\delta$ 28.3, 80.7, 118.7, 120.5, 124.5, 126.0, 128.7, 133.0, 134.1, 153.6.
Entry 9 (tert-butyl N-undecylcarbamate)

\[
\begin{align*}
\text{NHB} & \quad \text{oc} \\
\end{align*}
\]

IR (neat, cm\(^{-1}\)): \(\nu 3378, 2919, 2851, 1688, 1522, 1474, 1364, 1174, 868, 761, 583\)

\(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta 0.88 (t, J= 6.79 \text{ Hz}, 3H), 1.27-1.43 (m, 18H), 1.53 (s, 9H), 3.09 (q, J=6.79 \text{ Hz}, 2H), 4.38 (\text{br s}, 1H, \text{ NH}); \)

\(^13\)CNMR (400 MHz, CDCl\(_3\)): \(\delta 14.0, 22.6, 26.8, 27.4, 28.4, 29.3, 29.5, 29.6, 29.8, 30.1, 31.8, 53.6, 78.9, 156.0; \)

Entry 10 (tert-butyl N-allyl carbamate)

\[
\begin{align*}
\end{align*}
\]

IR (neat, cm\(^{-1}\)): \(\nu 3415, 2923, 2853, 2361, 1750, 1435, 1369, 1246, 1170, 1074, 761\)

\(^1\)HNMR (400 MHz, CDCl\(_3\)): \(\delta 1.42 (s, 9H), 3.69-3.73 (m, 2H), 4.49 (\text{br s}, 1H), 5.07 (d, J=11.71 \text{ Hz}, 2H), 5.74-5.87 (m, 1H); \)

\(^13\)CNMR (400 MHz, CDCl\(_3\)): \(\delta 28.3, 43.1, 79.4, 115.6, 134.9, 155.7\)

Entry 11 (tert-butyl N-(2-aminophenyl)carbamate)

\[
\begin{align*}
\end{align*}
\]

Gray crystalline solid

IR (neat, cm\(^{-1}\)): \(\nu 3445, 3350, 3300, 3120, 2975, 1677, 1622, 1587, 1513, 1484, 1444, 1365, 1294, 1248, 1159, 1049, 740\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 1.51 (s, 9H), 3.28 (\text{br s}, 2H), 6.24 (\text{br s}, 1H), 6.61-6.73 (m, 2H), 7.19-7.30 (m, 2H)\)

\(^13\)C NMR (400 MHz, CDCl\(_3\)): \(\delta 28.0, 80.4, 117.8, 119.8, 124.9, 125.0, 126.0, 139.7, 154.2\)
3.4.7 References


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