Novel Ceric Ammonium Nitrate-Stabilized Maghemite Nanoparticles (CAN-\(\gamma\)-Fe2O3) for Ultrasound Assisted Synthesis of \(\beta\)-Amino Derivatives

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Abstract

Owing to their inherent features like smaller size and higher surface area exposed to reactants, nanoparticles have gained enormous interest and are extensively used as magnetically recyclable catalysts for various organic reactions. Herein, we report highly hydrophilic, non-aggregated, and strongly positively charged ($\zeta$ potential: +45.7 mV) ultra-small cerium cations/complexes-stabilized maghemite nanoparticles in water as an efficient and reusable nanoscaled magnetically active catalyst for the nucleophilic addition reaction of various amines with $\alpha,\beta$-unsaturated carbonyl compounds to give corresponding $\beta$-amino derivatives under ultrasonic irradiation. The developed protocol provides several merits such as high product yields, mild reaction conditions, reusable catalyst and easy workup.

Introduction

Nanoscience and nanomaterial have become an area of tremendous importance in the field of catalysis because of the extremely smaller particle size and higher surface area available for the reaction [1-4]. During the recent years, several kinds of nanomaterials, their synthetic approaches and advanced characterization tools are being developed all over the globe. Within the known materials, magnetic iron oxide (Fe$_3$O$_4$ and Fe$_2$O$_3$) nanoparticles have been acknowledged as eco-materials and have been successfully used as a magnetically recyclable catalyst for various organic transformations including degradation of organic compounds [5-7]. Surface modification/functionalization of these magnetic nanoparticles plays an important role in the field of catalysis as it prevents the oxidation and agglomeration of the nanoparticles to make them compatible for organic reactions [8-9]. Although a vast number of surface functionalized magnetically recoverable catalysts based on iron oxide supports have been known [10-12], but lanthanide cerium cations/complexes immobilized nanoparticles have never been realized in the literature.

Magnetically responsive maghemite (Fe$_2$O$_3$, $\gamma$-Fe$_2$O$_3$), also known as Fe(II) deficient magnetite nanoparticles with similar spinel ferrite structure, has gained considerable attention mainly due to their efficient and economical synthesis, scalability and nontoxic nature [13-14]. These nanoparticles can readily be synthesized by the oxidation of magnetite nanoparticles, using a co-precipitation method followed by heat treatment at different temperatures ranging from 200 to 300 °C [15-16]. Maghemite nanoparticles because of their low cost, biocompatibility and higher chemical stability have been widely explored in pharmaceutical and nano-medicines related applications [17]. However, a few reports are known related to their uses as support matrix in the area of heterogeneous catalysis for organic transformations [18-19]. Importantly, Rathi et al. [20-21] reported maghemite decorated with ultra-small palladium nanoparticles ($\gamma$-Fe$_2$O$_3$-Pd) for Heck-Mizoroki olefination, Suzuki reaction and allylic oxidation of alkenes. In a subsequent report, this similar group described the hydrogenation of nitroarenes, azides and alkenes using maghemite-Pd nanocomposites in a continuous flow reactor system. However, the Rathi’s nanoparticles involve nanofabricated catalytic Pd-surface engineered maghemite nanoparticles, which were synthesized by following a simple two-step co-precipitation method. Further, the Rathi’s
catalytic double phase iron oxide nanoparticles have not been analyzed via surface charge (zeta potential values), which is very important to study and check the aggregation behavior of the nanoparticles before and after any involved catalytic reaction. In contrast, herein we report a quite innovative Lewis acid-based chemical activity of novel highly positively charged ($\zeta$ potential: $+45.7$ mV), non-aggregated ultra-small ($6.61\pm2.04$ nm-sized) super-paramagnetic $\text{Ce}^{3/4+}$-cation/complex-doped maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanoparticles, which are synthesized by an innovative high-power ultrasonication methodology [22-23]. Global Design Of Experiment (DoE, MINITAB®16 DoE software) optimization provided quite innovative surface engineering of maghemite nanoparticles doped with Lewis acid $\text{Ce}^{3/4+}$ cations/complexes based on the well-known coordinative/ligand exchange chemistry. Indeed, both inductive coupled plasma-atomic emission spectroscopy (ICP-AES) and transmission electron microscopy-energy dispersive X-ray spectroscopy (TEM-EDAX) analyses demonstrated the presence of various exchangeable $\text{Ce}^{3/4+}$ cations/ligands ($\text{NO}_3^-$ anions, $\text{H}_2\text{O}$ & $\text{OH}$ species) onto the maghemite nanoparticles surface that might be effectively exchanged by any organic species containing Lewis base N/S/O-relating groups [22-23] (Israel et al. 2014; Lellouche et al. 2014). These $\text{Ce}^{3/4+}$ cations/complexes-doped maghemite ($\gamma\text{-Fe}_2\text{O}_3$) nanoparticles have never been realized as reusable catalyst in organic synthesis.

The aza-Michael addition of amines with $\alpha,\beta$-unsaturated carbonyl compounds, nitriles to provide $\beta$-amino derivatives is one of the important reactions for the formation of carbon-nitrogen bond in organic chemistry [24-25]. These $\beta$-amino derivatives have found wide spread applications as synthetic intermediates in the preparation of numerous pharmaceuticals, natural products and medicinally important precursors [26-27]. The diversified applications of these $\beta$-amino compounds have led to the development of several unique and novel synthetic approaches for aza-Michael addition in recent decades. Conventionally, these addition reactions are carried out in the presence of strong base or/and acid. However these methods are associated with the drawbacks such as harsh reaction conditions and formation of by-products [28]. In order to overcome these limitations, subsequently a number of milder approaches utilizing Lewis acid catalysts such as $\text{PtCl}_4\cdot5\text{H}_2\text{O}$, $\text{Cu(OTf)}_2$, $\text{InCl}_3$, $\text{Yb(OTf)}_3$, $\text{LiClO}_4$, $\text{Bi(NO}_3)_3\cdot5\text{H}_2\text{O}$, $\text{FeCl}_3$, $\text{6H}_2\text{O}$, $\text{CeCl}_3$, $\text{7H}_2\text{O}$, $\text{ZnO}$, $\text{MgO}$, silica-supported perchloric acid and sulfated zirconia have been reported in the literature [29-36]. In addition, some metal-free catalysts for example, cyclodextrin in water [37], polyethylene glycol [38] and boric acid in water [39] have been developed. Furthermore, heterogeneous catalysts such as graphene oxide, Amberlyst-15, modified mesoporous SBA-15, copper nanoparticles, silica gel, KF/Al$_2$O$_3$ have been explored for this important transformation [40-42]. However, most of the catalytic methods are associated with the drawbacks, such as requirement of excessive amount of acidic reagents that causes serious environmental hazard, use of volatile and toxic organic solvents, inefficient recovery of the catalyst by conventional filtration and prolonged reaction times. Moreover, most of the methods were found to be ineffective for the aromatic amines owing to their less reactivity as compared to the aliphatic ones. Ceric ammonium nitrate (CAN), a well-known one electron transfer reagent has been used as a promoter in various C-C and C-N bond forming reactions [43-44]. The main advantages of using CAN include its lower toxicity, inexpensiveness, easy handling, and solubility in most of the organic solvents. Duan et al. [45] reported the use of CAN (ceric ammonium
nitrate) as an efficient promoter for aza-Michael addition of aromatic and aliphatic amines with α,β-
unsaturated carbonyl compounds using ultrasound irradiation under solventless condition. However,
ineffective mixing of the reagents during the reaction along with the poor recovery of CAN after the
reaction, leaves a scope for the further development of a novel catalytic methodology for this
transformation.

Accordingly, we herein report the use of highly hydrophilic, non-aggregated and strongly positively
charged ceric ammonium nitrate-stabilized maghemite (CAN-γ-Fe$_2$O$_3$) nanoparticles (Ce$_{3/4}^+$
cations/complexes doping) in water as an efficient and reusable nanoscaled catalyst for the addition of
various amines with α,β-unsaturated carbonyl and nitrile compounds to give corresponding β-amino
compounds under ultrasonic irradiation (Scheme 1).

All the substrates and solvents were commercially available and used as received without further
purification. Hydrophilic CAN-stabilized maghemite (γ-Fe$_2$O$_3$) Nanoparticles were synthesized by
following the procedure reported in the previous literature [22].

Typical experimental procedure for the aza-Michael addition

A reaction mixture containing amine (2 mmol) and Michael acceptor compound, i.e. methyl acrylate (2.5
mmol) into a round bottom flask was added aqueous solution of CAN-γ-Fe$_2$O$_3$ nanoparticles (0.5 ml; [Ce]
0.0075 mmol). The resulting mixture was sonicated at room temperature for 2 h. The progress of the
reaction was monitored by thin-layered chromatography (TLC). After 2 hrs of sonication, the mixture was
diluted with dichloromethane followed by isolation of the product simply by liquid-liquid extraction. The
obtained crude product was purified by column chromatography using EtOAc/hexane (6:4) as eluent.
Conversion of the products was analyzed by GC-FID model-Varian CP3800 (Column specification:
Stabilwax® w/Integra-Guard®, length-30 m, 0.25 ID) at the flow rate 0.5 mL min$^{-1}$, injector temp 250 °C,
FID detector temperature 275 °C. The structural identity of the products was established by comparing
their spectral data, i.e. both $^1$H and $^{13}$C nuclear magnetic resonance ($^1$H & $^{13}$C NMR) with those of
authentic compounds.

3-(Butylamino)propanenitrile [46]: $^1$H NMR (CDCl$_3$, 500 MHz) δ 2.92 (2H, t), 2.58 (2H, t), 2.48 (2H, t), 2.34
(1H, s, -NH), 1.72 -1.48 (2H, m), 1.21-1.12 (2H, m), 0.88 (3H, t); $^{13}$C NMR: δ 112, 61, 53, 47, 36, 29, 20, 15;
ESIMS (m/z) = 127 (M+1).

Results And Discussion

The desired nanocatalyst (CAN-γ-Fe$_2$O$_3$) was obtained via simultaneous oxidation of starting MASSART
magnetite (Fe$_3$O$_4$) to maghemite (γ-Fe$_2$O$_3$) Nanoparticles and surface modification by using a strong
mono-electronic ceric ammonium nitrate oxidant (CAN) as Ce-donor using high power ultrasonic
irradiation. The detailed synthetic procedure and characterization of the obtained CAN-γ-Fe$_2$O$_3$
nanoparticles are reported in previous literature reports [22]. The Fe and Ce contents in the prepared
nanocatalyst were found to be 2.71 and 0.22 mg/ml (Ce/Fe w/w ration 0.077), respectively as determined by ICP-AES analysis. The CAN-mediated modification of the nanoparticles surface provided extremely stable colloidal water dispersion containing non-aggregated, strongly positively charged Ce$^{3+4}$ cations-doped maghemite nanoparticles. The obtained colloidal water suspension of nanoparticles has been used as Lewis acid catalyst for aza-Michael addition reactions during the present study. Initially, the catalytic activity of the water suspension containing CAN-$\gamma$-Fe$_2$O$_3$ nanoparticles was tested for the Michael addition of diethylamine and methyl acrylate at room temperature under sonication. The reaction progress was monitored by thin-layer chromatography (TLC) by withdrawing the samples from the reaction mixture at a regular time interval. After completion of the reaction, the product was recovered by simple extraction of the reaction mixture with dichloromethane followed by usual work-up to obtain pure product.

It is worthy to mention that no reaction was observed by using bare $\gamma$-Fe$_2$O$_3$ nanoparticles, mainly due to the severe aggregation of the Nanoparticles in the absence of CAN-based doping step. Furthermore, the use of cerium oxide (CeO$_2$) in water provided only 30% conversion under otherwise identical reaction conditions. It is important to mention that the use of cerium oxide (CeO$_2$) for the surface modification of maghemite ($\gamma$-Fe$_2$O$_3$) nanoparticles produced aggregated and non-reactive nanoparticles, which did not exhibit any catalytic activity under the described conditions. Furthermore in the absence of catalyst, the reaction was found to be very slow and afforded only 20% conversion in 4h under ultrasonic irradiation. Hence, it was confirmed that strongly positively charged Ce$^{3+4}$ cations-doped CAN-stabilized $\gamma$-Fe$_2$O$_3$ nanoparticles were only capable to act as a potential catalyst for the present transformation. Ultrasonic irradiation played a key role and enhanced the reaction rates significantly; whereas under conventional stirring, the reaction afforded only 25% conversion in 2h. The addition of organic solvents such as acetonitrile and dichloroethane affected the reaction adversely, which might be due to the observed phase separation and inefficient mixing of the catalyst with the substrates. Hence, aqueous colloidal suspension of nanoparticles has been used without additional solvent under ultrasonic irradiation for the efficient conversion of the reactants to the desired products. Furthermore, a minute quantity of catalytic aqueous suspension (0.5 ml; [Ce]=0.0075 mmol) was found to be sufficient for the efficient conversion under the described experimental conditions. Further enhancement in the catalyst solution from 0.5 to 1.0 ml did not improve the results to any significant scale.

Therefore, in further study, the reaction was generalized by using a variety of primary and secondary aliphatic as well as aromatic amines with various $\alpha,\beta$-unsaturated carbonyl compounds and acrylonitrile under the described experimental conditions. All the results of these experiments are summarized in Table 1. All the reactants were smoothly converted to the corresponding $\beta$-amino compounds in excellent yields within 1-2 h without observing any by-product during the reaction. Among the various aliphatic and aromatic amines tested, in general more basic aliphatic amines (Table 1, entries 1-3) afforded better results as compared to the aromatic ones (Table 1, entries 4-8). The nature of the substituent on the phenyl ring had significant effect on the reactivity. The substrate having electron donating group was found to be more reactive as compared to that containing electron withdrawing group (Table 1, entries 6-
Importantly, 4-nitroaniline did not produce any addition product under the described reaction conditions (Table 1, entry 8). Furthermore, the position of the substituent had marginal effect on the reactivity and afforded almost similar product yield (Table 1, entry 7). Among the primary and secondary aliphatic amines studied, secondary amines showed better activity than primary ones. Importantly, in primary amines the selective formation of mono-addition product was obtained without formation of bis-products as mentioned in several existing procedures. Cyclic amines such as pyrrolidine, piperidine and morpholine underwent facile addition with Michael acceptors such as acrylic ester, acrylonitrile and afforded excellent yield of the corresponding products (Table 1, entries 9-12). Similarly the reaction of 2-aminopyridine with methyl acrylate, acrylonitrile under the described conditions provided excellent yields of the corresponding β-amino adducts (Table 1, entry 13). The reaction of olefins containing substituents at double bond, like ethyl crotonate and methyl methacrylate underwent facile addition with pyrrolidone to give excellent product yields (Table 1, entries 14-15). The conversion of the products was confirmed by GC-FID analysis; whereas, the structural identity of the products was established by comparing their physical and spectral data (FTIR & NMR) with the authentic compounds.

Further, the recycling ability of the recovered aqueous layer containing CAN-γ-Fe$_2$O$_3$ nanoparticles was evaluated by selecting the reaction of diethylamine with methyl acrylate under described condition as a representative example. After completion of the reaction, the product was isolated by extraction with dichloromethane and the recovered aqueous solution containing catalyst nanoparticles was thus utilized for the subsequent run by adding fresh substrates. The recovered aqueous solution was tested for three consecutive runs using fresh substrates under the described experimental conditions. Almost similar conversions (95-96%) were obtained during the recyclability experiments, which further confirmed the highly stable and non-aggregated nature of Ce$^{3+/4}$-doped maghemite nanoparticles. Furthermore, the Ce/Fe ratio in recovered nanoparticles aqueous suspension after third cycle remained almost similar (0.076) as the fresh one (0.077) which was as ascertained by ICP-AES analysis. These results indicated that the developed nanocatalyst is highly stable that can be reused for several runs without leaching during the catalytic reactions.

In conclusion, we have demonstrated the first successful application of highly hydrophilic, non-aggregated, strongly positively charged Ce$^{3+/4}$-doped maghemite (CAN-γ-Fe$_2$O$_3$) nanoparticles as highly efficient with high turnover number (TON) and reusable nanocatalyst for the aza-Michael reaction of various amines with α,β-unsaturated carbonyl compounds, acrylonitrile under ultrasound irradiation to give corresponding β-amino derivatives in excellent yields. The developed nanocatalyst showed efficient recycling ability without any detectable leaching during the reaction. Furthermore, the use of an aqueous solution of CAN-γ-Fe$_2$O$_3$ nanoparticles provided a facile separation of the products by simple liquid-liquid extraction.

Declarations

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**Tables**

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.