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Efficient synthesis of clopidogrel using magnetically recoverable Fe_3O_4 nanoparticles via strecker reaction

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Abstract
The significance of magnetic nanoparticles, particularly magnetite (Fe_3O_4) nanoparticles, in various applications such as medicine and catalysis. The unique magnetic properties of these nanoparticles allow for their efficient immobilization and separation using external magnets, eliminating the need for traditional separation techniques like filtration or centrifugation. Magnetite nanoparticles are explored extensively due to their properties within the inverse spinel structure. The potential applications of Fe_3O_4 nanoparticles include their role as carriers for targeted drug delivery and contrast agents in magnetic resonance imaging (MRI) due to their biocompatibility, low toxicity, and high saturation magnetization. Additionally, these nanoparticles serve as effective catalysts and catalyst supports. The abstract highlights their magnetic separability in catalytic reactions, enhancing reaction efficiency. The synthesis of α-aminonitriles through the Strecker reaction, a valuable pathway for α-amino acid and heterocyclic compound synthesis. The use of alternative cyanide sources, such as trimethylsilyl cyanide (TMSCN), is emphasized for its practicality and environmental benefits compared to traditional toxic cyanide sources synthesis of clopidogrel (Plavix), a platelet aggregation inhibitor used in the treatment of various cardiovascular conditions.

Keywords: Magnetic nanoparticles, immobilization, biocompatibility, clopidogrel, cardiovascular

Introduction
Magnetic nanoparticles a group of nanostructure material having magnetic properties are current interest having applications in technical and medical areas, among different nanomaterials iron oxide (ferric oxide) having a peculiar position in the magnetic behavior and activity for immobilization magnetic nanomaterials, catalysts easily removed from the reaction mass by applying external magnet, without using any filtration or centrifugation. Having advantages in the field of Medical [1-3] and organometallic chemistry, among various magnetic nanoparticles under study, magnetite (iron oxide) nanoparticles are extensively studied [4-6]. Magnetite (ferric oxide) (Fe_3O_4) is one of the inverse spinel group members with the common formula A $(B)_2O_4$. In Fe_3O_4, the A metal is Fe^{2+} and the B metal is Fe^{3+}. The structure of magnetite consists of a FCC closed-packed oxygen arrangement with the divalent Fe^{2+} ion in tetrahedral sites and the trivalent Fe^{3+} ions in octahedral sites.
Fe_3O_4 nanoparticles can potentially be used as magnetic targeted drug delivery carriers and magnetic resonance imaging (MRI) contrast agents due to their high saturation magnetization, low toxicity, and biocompatibility [7]. Furthermore, recent reports show that Fe_3O_4 nanoparticles are act as both catalysts and efficient supports for catalysts. Fe_3O_4 nanoparticles can facilitate their separation effectively from the reaction mass by magnetization with a permanent magnetic field [8].
α-Aminonitriles are essential synthetic intermediates for synthesis of α-amino acids and nitrogen-containing heterocyclic compounds [9]. The Strecker reaction, is the cyanide ion (nucleophile) addition to the imines, is of very significant in modern organic chemistry as it offers one of the easy method for the preparation of α-amino nitriles [10-11]. A number of the Strecker methods are on the use of toxic cyanide analogues relating harsh reaction conditions. In order to avoid incompletely this problem, trimethylsilyl cyanide (TMSCN), diethyl aluminium cyanide, acetone cyanohydrin, etc. have been introduced as cyanide sources in the Strecker reaction. TMSCN is known to be simple to handle and more efficient cyanide ion resource for the nucleophilic addition under simple conditions as compared to KCN, NaCN or HCN. In contrast, a lot of these reported methods involve the use of costly reagents, dangerous solvents, longer reaction times and tedious workup procedure. Thus, it is desirable to synthesize a capable and practical method for the Strecker reaction under eco-

friendly conditions.

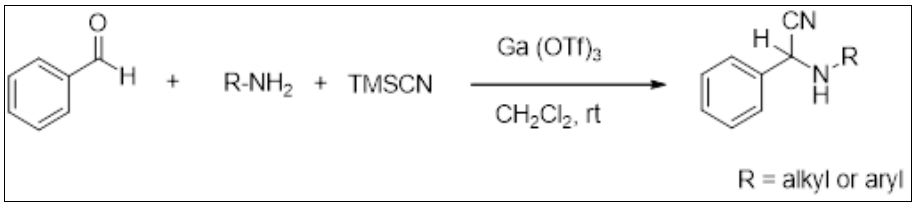
Clopidogrel (Plavix) is a platelet aggregation inhibitor used for treatment of ischemic strokes, heart attacks, atherosclerosis and also for the prevention of thrombosis after placement of intracoronary artery stents.

Review of Literature

Strecker reported the condensation of three compounds, an aldehyde, ammonia and hydrocyanic acid to afford α-aminonitriles for the preparation of alanine in 1850 (Strecker reaction) [10], this reaction has been significantly extended by the using of different catalysts, sources of cyano and amino groups, as well as various solvents [13]. This multi component conversion present one of the simplest and most significant methods for the preparation of amino acids [14, 15].

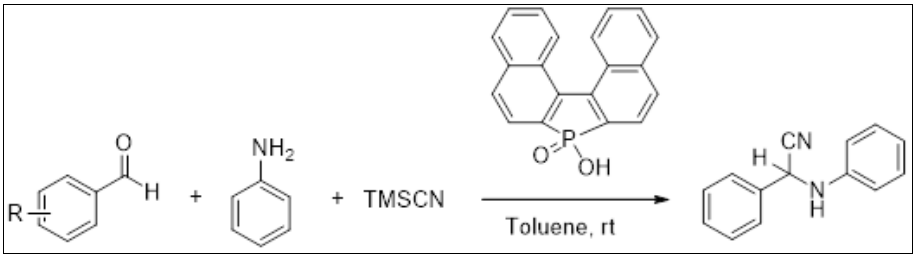
Therefore, over the past several centuries, several efforts have also been directed to the advancement of catalytic asymmetric approaches for the construction of optically active amino acids,[15] various examples of three-component Strecker reactions have been noticed and some of them have listed below.

Surya prakash *et al*., reported the synthesis of aminonitriles and their fluorinated analogs in high yield and purity by the Strecker reaction from the corresponding carbonyl compounds and amines with trimethylsilyl cyanide using gallium triflate in dichloromethane (Scheme 1) [16]. Examine with various nonfluorinated and fluorinated ketones reviews that the choice of suitable catalyst and the solvent system appropriate metal triflates as a catalyst and dichloromethane as a solvent performs a key role in the direct three component Strecker reactions of ketones.



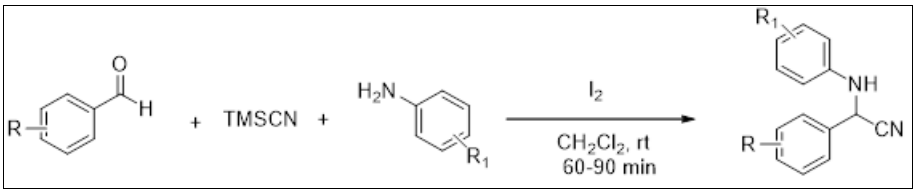
Scheme 1

Zhang *et al*., have developed a convenient and efficient onepot, three-component Strecker reaction of ketones, amines and trimethylsilyl cyanide in the presence of Brønsted acid (Scheme 2) [17]. A series of α-aminonitriles were synthesized in good to excellent yields. This method also provides a significant alternative route for the existing stepwise methodologies for the Strecker reaction.



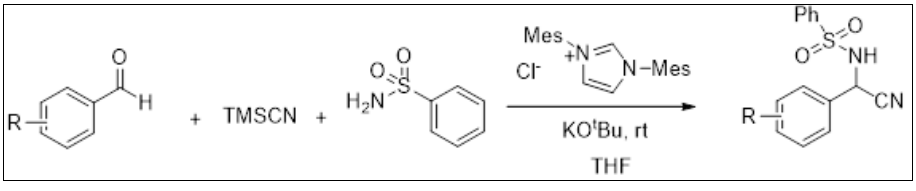
Scheme 2

Das *et al*., [18] reported the Strecker reaction of *N*-tosylaldimines with trimethylsilyl cyanide, used iodine as the catalyst at 25-30 °C to give protected α-aminonitriles in high yields.



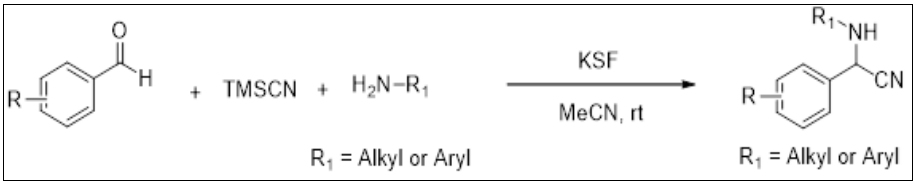
Scheme 3

The first method for Strecker reaction of aldimines by adding TMSCN in the presence of a *N*-heterocyclic carbene as a nucleophilic catalyst is described by the Toyohiko Aoyama gtoup (Scheme 4) [19]. A variety of aliphatic and aromatic aldimines were converted to corresponding α-amino nitriles.



Scheme 4

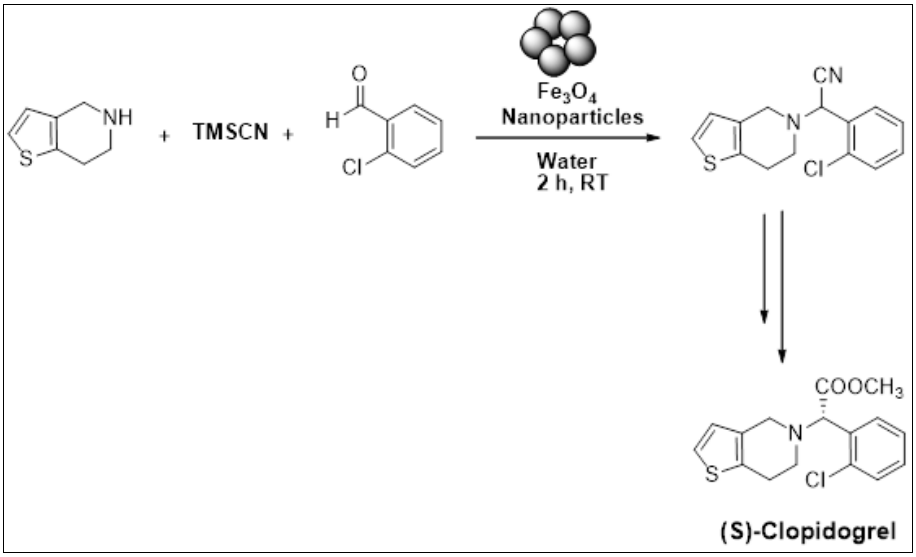
Aldehydes and amines undergo nucleophilic addition with trimethylsilyl cyanide in the presence of montmorillonite KSF clay gave α-aminonitriles in excellent yields (Scheme 5) [20].



Scheme 5

Present work

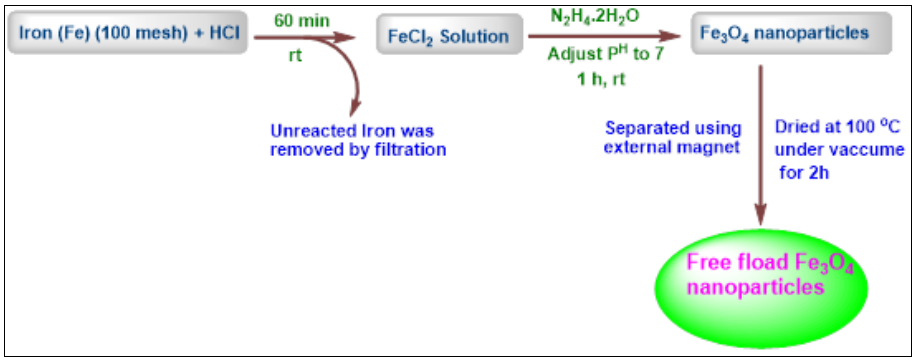
Herein, we report a new method for the preparation of iron oxide (ferric oxide) Fe_3O_4 nanoparticles has been developed and the prepared nanoparticles were used for the three-component Strecker-type reaction of different amines and aldehydes with Trimethylsilyl cyanide (TMSCN) in water at room temperature to afford the corresponding α-aminonitries and the synthesis of Clopidogrel (Scheme 6).



Scheme 6

Results and Discussion

Preparation of Fe_3O_4 Nanoparticles



Scheme 7

Preparation of ferric oxide nanoparticles were carried out as shown in above (Scheme 7) using Iron metal. In a typical procedure, Iron 50 gm (100 mesh) was added to 200 mL concentrated hydrochloride at room temperature and srirred for 60 min until the formation of clear solution. Unreacted Iron was separated by filtration and added hydrazine monohydrate ($N_2H_4 \cdot H_2O$) until the pH of the solution reached to 7.0. During this process of addition, it was observed that colour of the solution changed to black from brownish green, which indicates the formation of ferric oxide nanoparticles (Fe_3O_4) and completion of the reaction. The reaction mixture was stirred for a further period of 1 h and the black precipitate was separated using external magnet and repeatedly washed with distilled water. The formed ferric oxide Fe_3O_4 nanoparticles were subsequently dried in vacuum for 2 h at room temperature.

Characterization of the ferric oxide (Fe_3O_4) Nanoparticles

The prepared Fe_3O_4 nanoparticles characterized by XRD (X-ray Diffraction), TEM (transmission electron microscopy), and Infra-red spectroscopic methods. XRD pattern of the Fe_3O_4 is quite identical to pure magnetite and matched well with that of it (JCPDS No. 82-1533), indicating that the sample has a cubic crystal system (Figure 1). Further, the crystallite size calculated using Debye Scherrer formula is found to be ~19 nm.

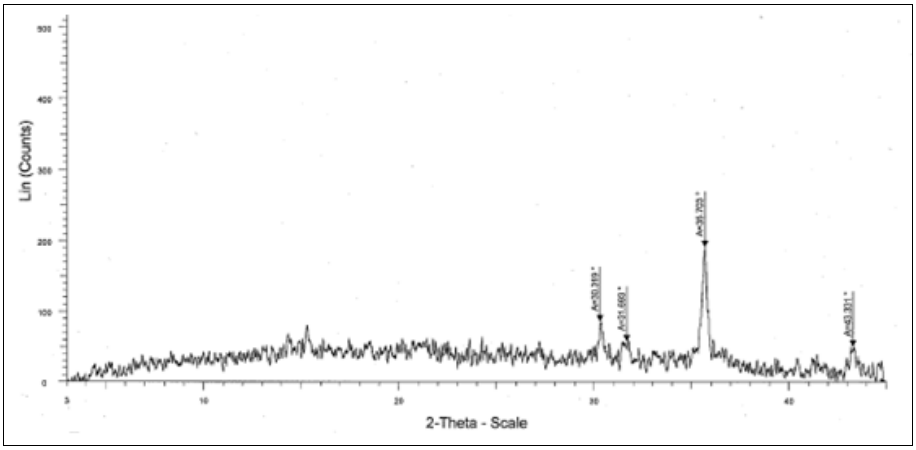


Fig 1: XRD pattern of ferric oxide (Fe_3O_4) nanoparticles

The TEM image of the Fe_3O_4 sample is presented in figure 2, which reveals that iron oxide powders consist of mainly spear shape and uniform in size. The size of ferric oxide nanoparticles about 15-20 nm in diameter and it is in consistent with the crystalline size found from the XRD pattern.

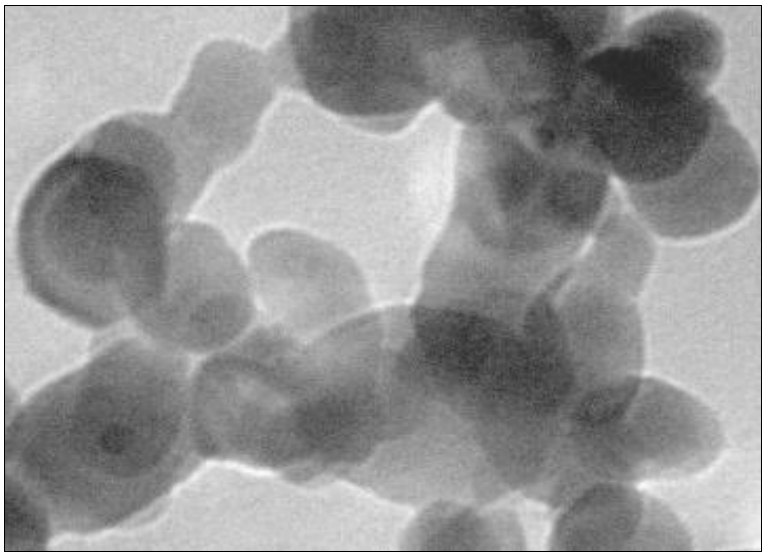


Fig 2: TEM image ferric oxide nanoparticles observed at 120 kV

The FT-IR spectra of ferric oxide nanoparticles were presented at Fig 3.

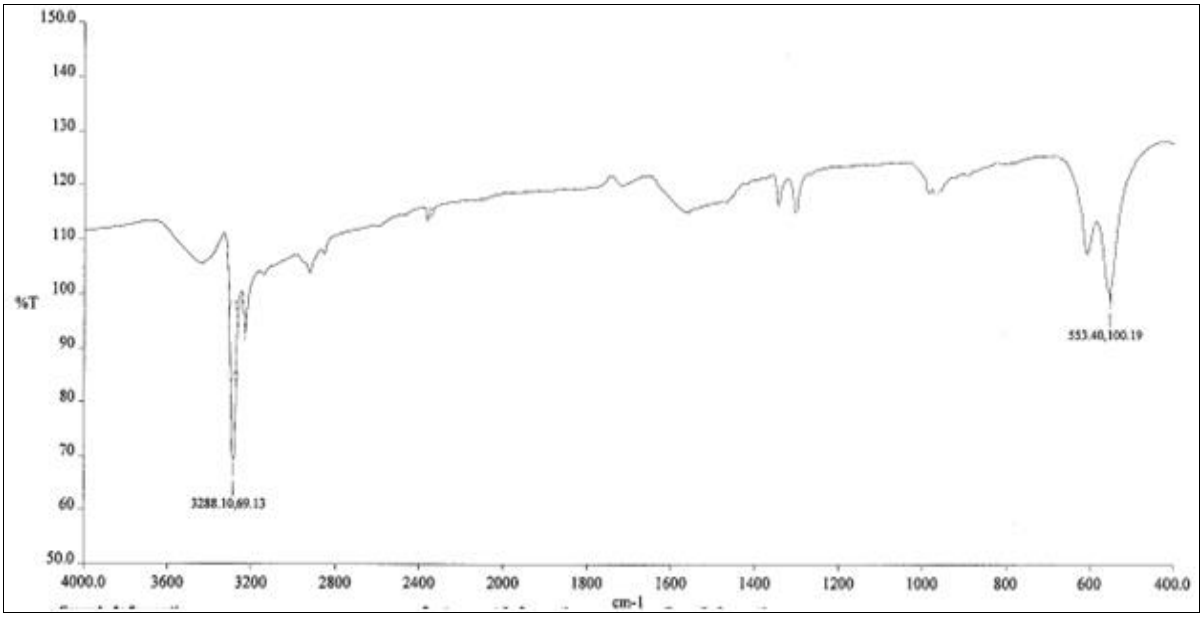
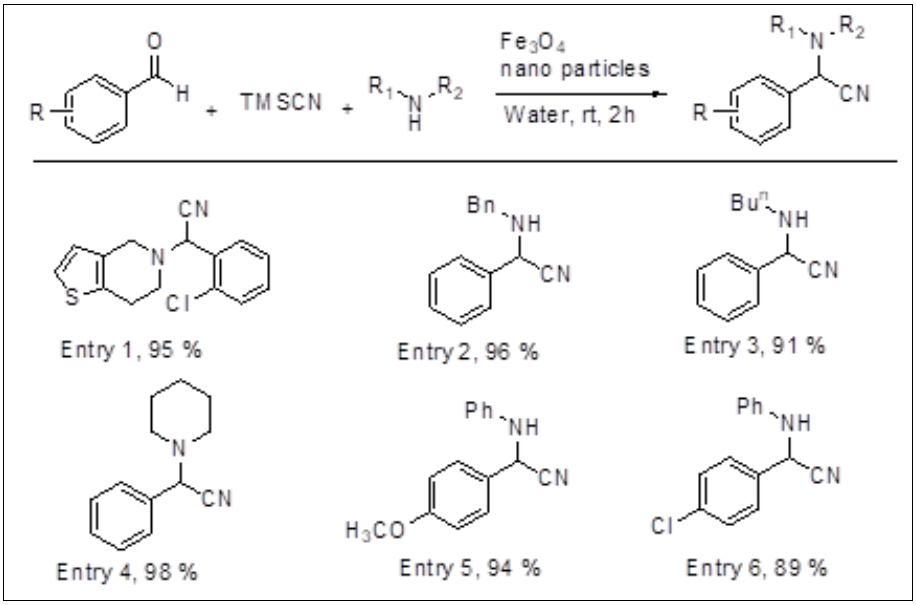


Fig 3: The FT-IR spectra of ferric oxide nanoparticles

The peak at ~3288 cm^{-1} is attributed to the stretching vibrations of OH, which is assigned to OH absorbed by Fe_3O_4 nanoparticles. And the peak at 553 cm^{-1} is attributed to the Fe-O bond vibration of ferric oxide.

After preparing the catalyst successfully, to explore the potential activity of ferric oxide nanoparticles as a catalyst we subJected in the synthesis of α-aminonitriles via Strecker reaction as the formed products were intermediates in the synthesis of anti-platelet drug Clopedogrel. At the outset of this study, no example of reported for Strecker reaction under aqueous conditions using Fe_3O_4 nanoparticles, despite the potential inherent stability and activity of such materials.

Table 1. Synthesis of aminontriles using different aldehydes, amines and TMSCN using ferric oxide nanoparticles under aqueous conditions.

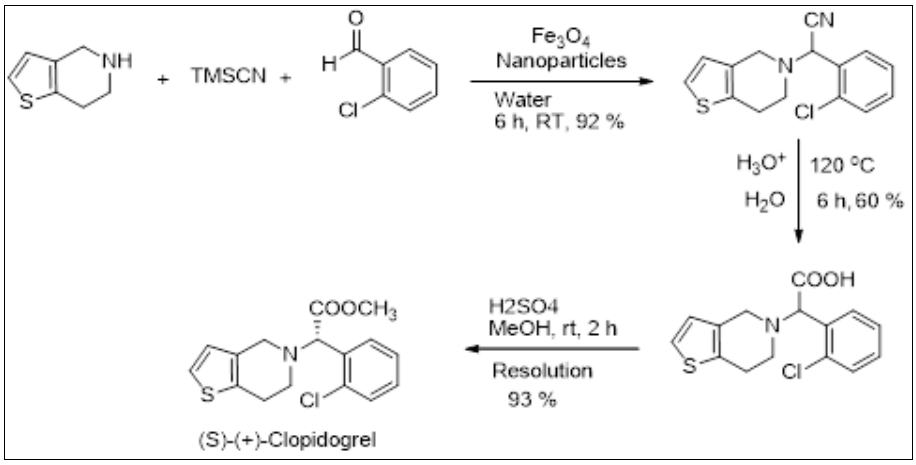


Reaction parameters

Aldehyde (1 mmol), amine (1 mmol), TMSCN (1.2 mmol), Fe_3O_4 (10 mol %), H_2O (3 ml).

We studied various amines in combination with different aldehydes were used to prepare variety of α-aminonitriles in table 1. The aldehyde used in this study includes benzaldehyde, 4-methoxy benzaldehyde, 4-chloro benzaldehyde and all of them gave good yield tabulated as entries 3-6 in table 5.1. Furthermore, both alkyl and aryl amines were equally reactive and gave in excellent yields tabulated as entries 1-3 in table 5.1. Encouraged with this results next we explored the synthesis of 2-(2-chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c]pyridin-5(4H)-yl)acetonitrile, followed by the antiplatelet drug Clopidogrel as shown in Scheme 1.

The synthesis starts with the Strecker reaction of 4,5,6,7-tetrahydrothieno [3,2-c]pyridine, 2-chloro benzaldehyde and TMSCN to give 2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5 (4H)-yl) acetonitrile. Thus formed cyanide was hydrolyzed acid, followed by ester and resolution gives the product Clopidogrel.



Scheme 1

Synthesis of Clopidogrel using Fe_3O_4 nanoparticles.

Reuse of Catalyst

The catalyst recovered by using external magnet and washed several times with water and followed by ethyl acetate and then finally by ether and dried for further reuse. The catalyst showed consistent activity and yield even upto five cycles.

Conclusion

In conclusion, a new method for the preparation of ferric oxide or Iron oxide or Fe_3O_4 nanoparticles has been synthesized, then characterized by, TEM (transmission

electron microscopy), XRD (X-ray diffraction) and Infra-red spectroscopic methods. The Fe_3O_4 nanoparticles efficiently catalyzed the three-component Strecker-type reaction of different amines and aldehydes with trimethylsilyl cyanide in water at room temperature to afford the corresponding α-aminonitriles in excellent yields. Furthermore, the reaction was used for the synthesis of Clopidogrel. Due to its super magnetic behavior catalyst is completely recoverable by applying external magnetic field, re-used up to five times without losing its catalytic activity,

Experimental

General information

All solvents and chemicals bought from Loba chemicals, S.D Fine, and Sigma-Aldrich. For column chromatography purification, run with ACME silica gel mesh size 100–250 mesh. TLC thin-layer chromatography performed with the help of Merck-precoated silica gel 60-F_{254} plates. Perkin-Elmer, Spectrum GX FTIR spectrometer use for IR spectra for all compounds. Varian- 400 MHz, Bruker-Avance 300 MHz Spectrometer use for record of Proton NMR and C^{13} NMR spectra's and their chemical shifts are measured in ppm. Finnigan LCQ Advantagemax use for ESI mass spactra and Shimadzu GC-MS QP2010 Plus use for EI mass spectra.

TECNAI FE12 TEM instrument use for Iron oxide morphology, shape, and size, Rikagu diffractometer use for XRD spectra.

Preparation of Nanocrystalline Fe_3O_4

Synthesis of Fe_3O_4 nanoparticles were carried out as shown in scheme using Iron metal. In a typical procedure, Iron 50 gm (100 mesh) was added to 200 mL concentrated hydrochloride at room temperature and stir for 60min until the formation of clear solution. Un-reacted Iron was separated by filtration and added hydrazine monohydrate ($N_2H_4 \cdot H_2O$) until the pH of the solution reached to 7.0. During this process of addition, it was observed that color of the solution changed to black from brownish green, which indicates the formation of Fe_3O_4 nanoparticles and completion of the reaction. The reaction mixture was stirred for a further period of 1hr and the black precipitate was separated using external magnet and repeatedly washed with distilled water. The formed Fe_3O_4 nanoparticles were subsequently dried in vacuum for 2 hr at room temperature.

Experimental procedure for the strecker reaction

TMSCN (1.2 mmol) was added to a solution of 1.0 mmol of an appropriate aldehyde and 1mmol of amine in 3mL water in the presence of 10mol% of the catalyst (Fe_3O_4 nanoparticles). The reaction mixture was stirred at 25-30 °C for 120 minutes, reaction is monitoring by TLC thin layer chromatography when the reaction complies, separate catalyst by external magnet, reaction mass was extracted with dichloromethane (2X10mL) and purified by column chromatography.

Spectral data for the selected products

1. **2-Phenyl-2-(phenylamino) acetonitrile (Table 1, entry 1)**
   ^{1}H NMR (300 MHz): δ 4.67 (br s, 1H), 5.36 (s, 1H), 6.72 (d, J = 7.8Hz, 2H), 6.84 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 8.0 Hz, 2 H), 7.37-7.44 (m, 3H), 7.52-7.55 (m, 2H); 13C NMR (75 MHz) δ 50.1, 114.1, 118.1, 120.2, 127.2, 128.4, 129.2, 129.4, 134.0, 144.7. ESI MS (m/z): 209 $(M + H)^+$.

2. **2-(4-Chlorophenyl)-2-(phenylamino) acetonitrile (Table 1, Entry 6)**
   ^{1}H NMR (CDCl3, 300 MHz): δ 4.04 (brs, 1H), 5.43 (s, 1H), 6.77 (d, J = 7.4 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 2H), 7.44 (d, J = 5 Hz), 7.55 (d J = 7.5 Hz). ESI MS (m/z): 242 $(M)^+$, 244 (M+2).

3. **2-(2-Chlorophenyl)-2-(6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-yl) acetonitrile (Table 1)**
   IR (KBr): ν 2823, 2359, 1575, 1473, 1332, 1167, 1131, 1015, 752 cm^{-1}. ^{1}H NMR (CDCl3, 300 MHz): δ 2.71 – 2.97 (m, 4H), 3.52 (d, 1H, J = 6.2 Hz), 3.28 (d, 1H, J = 6.2 Hz), 5.72 (s, 1H), 6.83 (d, 1H, J = 7.3 Hz), 7.38 (d, 1H, J = 7.2 Hz), 7.42 – 7.61 (m, 3H), 7.69 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): 25.5, 47.8, 49.5, 59.1, 115.8, 124.0, 125.9, 127.8, 130.4, 130.9, 131.3, 131.4, 132.9, 133.1, 134.1. ESI MS (m/z): 288 (M +H).

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