Present section describes the Aloevera-Fe\(^0\)Nps-Silica nanocomposite catalyzed single step three component (thiocarbonohydrazide, 2-hydroxy benzophenone, and benzoin) synthesis of 1,3-bis (2-2-hydroxyphenyl)-2-methyl, 4,5-diphenyl oxazol-3(2H)-yl thiourea. The catalyzed reaction led to 99.5% product yield which was nearly double of the yield that was obtained in the identical uncatalyzed reaction. The structure of the new oxazole derivative was determined using elemental analysis, FTIR, and \(^1\)H NMR spectroscopy.

**INTRODUCTION**

The catalyzing role of iron [135,136] and iron nanoparticles [137,138] is known for many organic transformations. Iron is good catalytic substitute of noble metal catalysts because of its low cost and ubiquitous nature. Iron salts are known for catalyzing [139-142] the synthesis of heterocyclic nuclei but the use of zerovalent iron nanoparticles is yet not reported. In principle Fe\(^0\)Nps can offer great deal in terms of yield and product selectivity because of their large surface to volume ratio. Nevertheless spent nanocatalysts can be easily separated and recycled since they exhibit better retention of catalytic activity than their bulk counterparts [143]. The synthesis of stable small sized Fe\(^0\)Nps involves tedious and sophisticated steps [144] as the
small sized nanoparticles have a tendency to agglomerate in water to form micron scale or larger aggregates. To circumvent the problem of agglomeration, nanoparticles are either capped with suitable polymer [145] or immobilized [146] on a solid support. The current trend is to use environmental friendly alternatives of synthetic polymers. Dhupar et al have used Mangifera indica leaf extract for synthesizing and stabilizing the crystalline zerovalent iron nanoparticles [147]. Polysaccharides are appropriate natural capping materials for stabilizing the nanoparticles, but impregnation of nanoparticles in polysaccharide templated silica matrix can furnish temperature resistant, stable, and recyclable heterogeneous nanocatalysts [148]. The oxazole nucleus is the key building blocks for synthesizing many natural products, pharmaceuticals, and the synthetic intermediates [149-151]. In an attempt to understand the catalytic performance of the synthesized nanocomposite, the catalyzed synthesis of 1,3-bis (4,5-diphenyl-2-methyl-2-(2‘-hydroxyl phenyl) oxazol-3(2H-yl) thiourea was done in a single step using thiocarbonohydrazide, 2-hydroxyl acetophenone, and benzoin. The selection of the target heterocyclic nucleus was based upon the reported biological activity of thiourea coupled oxazole moieties [152,153].
The present study presents a simplistic two step approach for the synthesis of Aloevera-Fe\textsuperscript{0}Nps-Silica nanocomposite (AFS\textsubscript{4}). AFS\textsubscript{4} has been evaluated as a efficient catalyst for the synthesis of the thiourea coupled oxazole derivative (>99% yield) where it catalyzed the reaction both in terms of yield and the reaction time.

**RESULTS AND DISCUSSION**

**The catalytic activity of the AFS\textsubscript{4}**

The catalytic activity of the AFS\textsubscript{4} has been monitored for one pot three component synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea for which thiocarbonohydrazide 1, 4-hydroxy acetophenone 2, and benzoin 3 were taken in methanol and refluxed for 2 h along with catalyst (AFS\textsubscript{4}) and triethyl amine. 1 was synthesized by a known method [154], where carbon disulphide was directly added to excess of hydrazine hydrate (3M) at its boiling point.

The reaction mixture was poured over crushed ice after removal of the catalyst. The solid mass thus obtained was filtered and recrystallized from aq. ethanol, yield 7.5 g (corresponding to 99.5%), m.p. 105 °C. A schematic diagram for the synthesis of the 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea is depicted as Scheme 5. The same
product was obtained for uncatalyzed reaction but now product yield was just 3.6 g (49%) and the completion of the reaction required 4 h reflux time. The catalyst was recycled after washing with water and in second cycle the product yield in the catalyzed reaction was 6.4 g (85%).

First step is the reaction of thiocarbonohydrazide 1 with 4-hydroxyacetophenone 2 to form corresponding shiff’s base 3 (Scheme 6). It can be speculated that the Fe$^{0}$Nps in AFS$_4$ catalyst, having vacant d orbitals acted as electrophile, thus induced more electrophilic character at carbonyl carbon atom of benzoin 4 (Catalytic Path-A) and/or at C-atom of azomethine 3 (Catalytic Path-B) respectively. Thus attack of nucleophile in either case became easier. This is the reason that the addition of the catalyst in this reaction reduced the reaction time period and increased the yield of the final product. Two possible mechanisms “Catalytic path- A” and “Catalytic path-B” are given in Scheme 7.
Scheme 5. Schematic diagram for the synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea

Scheme 6. Synthesis of Shiff’s base

In summary, an efficient, clean, and convenient one-pot three components synthesis of a new oxazole derivative; 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea was carried out through catalyzed and uncatalyzed routes. The catalyzed synthesis gave double yield.
(99%) as compared to the uncatalyzed reaction (45%). The catalyzed synthesis has an advantage of excellent yield and shorter reaction time and the catalyst was successfully used in the second cycle without compromising its activity. The catalyst (AFS₄) was designed from aloevera acetomannan which has Fe⁰Nps (of ~5 nm size) impregnated within aloevera-silica hybrid matrix. In the current study, Aloevera-Fe⁰Nps-Silica nanocomposite was found to be efficient catalyst for the synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea (TOₓ). The catalytic use of AFS₄ may be further extended for the synthesis of other similar heterocyclic derivatives.
Scheme 7. Plausible mechanistic pathways for the catalytic synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) Thiourea
Physical and Spectral data of synthesized 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) Thiourea (TOₓ)

<table>
<thead>
<tr>
<th>Property</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>DMF, DMSO, ethylacetate, acetone, ethanol; insoluble in benzene, toluene, hexane, cyclohexane, and chloroform</td>
</tr>
<tr>
<td>Melting point</td>
<td>105°C</td>
</tr>
<tr>
<td>$R_f$ (Solvent: ethylacetate)</td>
<td>0.44</td>
</tr>
<tr>
<td>IR (KBr)</td>
<td>3415 (O-H), 3375 (-NH), 3060, 2931 (C-H str.), 1689 (C=C str.), 1304 (C-N str.), 1304-1340 (C-H bending), 1261 (phenolic C-O phenolic str.), 1206 (C-O str.), 1068 (C-O str.), 1003 (N-N str.), 1200(C=S str.), 1490 (CH₃ as), 1388 (CH₃ s), 704, (C-H bend mono subst. Ar), 754 (C-H bend di subst. Ar ), 682-1003 (C-H bend Ar), 1600, 1490 and 1178 cm⁻¹ (C=C Ar.)</td>
</tr>
<tr>
<td>$^1$H NMR (DMSO-d₆):</td>
<td>δ 6.87-7.95 (m, aromatic H), 1.19 (s, CH₃), 6.31 (O-H), 6.27 (N-H)</td>
</tr>
<tr>
<td>Elemental Analysis</td>
<td>Anal. Calcd for C₄₇H₄₂N₄O₄S; C, 73.90; H, 5.20; N, 7.67; Found C, 73.75; H, 5.25; N, 7.70.</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

Chemicals and instrumentation

TERRA-PURE™, USA certified spray dried aloevera inner leaf powder regular, 200 x (Specific gravity- 0.997- 1.004) was used after reprecipitation in ethanol. Tetramethoxysilane (TMOS), iron (III) nitrate nanohydrate, methanol, acetic acid (MERCK, India) were used. Methanol extra pure (LOBA Chemie) was used. Mango leaves were locally collected from Allahabad University campus and were powdered after drying in shade. CS₂, hydrazine, 4-hydroxyacetophenone, Benzoin (Aldrich, USA) were used. UV/Vis Spectrophotometer UV 100 (Cyber lab, USA) was used to observe the surface plasmon of Fe⁰Nps. All the melting points that were measured with a capillary apparatus are uncorrected. TEM analysis was done on FEI Technai U- Twin 20 instrument. HR-TEM, EDX, and elemental mapping were conducted using a FEI Titan G2 60-300 TEM (HR-TEM) instrument. X-ray diffraction (Cu Kα source) of the powdered sample was carried out on a XRD Pananalytical X-Pert Pro X-ray powder diffractometer. Elemental analysis was done on Haraeus Carbo Erba 1108 elemental analyzer. IR spectra were recorded in KBr on a Perkin-Elmer model 400 FTIR spectrometer. ¹H NMR spectra were recorded at ambient temperature using a
500 MHz (ZEOL-500) NMR spectrometer in DMSO-d$_6$. All the experiments were performed in triplicate and the results reported are the average of three experiments.

**Purification of Aloevera polysaccharide**

A homogenous solution was obtained by stirring aloevera powder (2 g) in distilled water (25 mL) for 15-20 min. This solution was precipitated with ethyl alcohol (200 mL) to obtain the aloevera polysaccharide. The polysaccharide was dried and reprecipitated thrice to obtain the pure polysaccharide (AVP) that was dried and used for the nanocomposite synthesis.

**Synthesis of Fe$^0$Nps**

Fe$^0$Nps were prepared using mango leaf extract. Mango leaf extract was prepared by boiling 1.0 g dried mango leaf powder with 25 mL of distilled water till the volume was reduced to 10 mL. Mango leaf extract (5 mL) was added to ferric nitrate solution (5 mL of 0.1M) whereupon the yellow ferric nitrate solution immediately turned black due to the formation of Fe$^0$Nps. The formation of Fe$^0$Nps was confirmed by appearance of surface plasmon peak for Fe$^0$Nps.
Synthesis of catalyst

The hybrid catalyst was synthesized by sol gel approach for which 0.2 g AVP was dissolved in 7 mL distilled water. To this solution 1.0 mL TMOS and 1.0 mL MeOH were added. Fe⁰Nps solution (3 mL) was added to this mixture after 10 min of stirring on a magnetic stirrer at room temperature and the mixture was stirred till the hydrogel was formed (180 min). It was dried overnight in an electric oven at 45°C and powdered well before use.

Recycling of catalyst

The catalyst (10 mg) was stirred with 5 mL distilled water at 100 rpm on a magnetic stirrer, filtered, dried and was reused in the requisite amount (0.005 g) for the synthesis of TOx as described below.

Synthesis of thiocarbonohydrazide

Thiocarbonohydrazide 1 was synthesized by adding carbon disulphide to excess of hydrazine hydrate (3M) at its boiling point. 1 was periodically removed (60% yield). The crude product was recrystallized with water (m.p. 168°C).
Synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea

Thiocarbonohydrazide (1.06 g, 0.01M), 4-hydroxy acetophenone (2.72 g, 0.02M), and benzoin (4.24 g, 0.02M) were dissolved in 30 mL of methanol. To this solution 0.005 g of catalyst and two drops of triethyl amine were added and the mixture was refluxed for 2 h. It was filtered hot to remove the catalyst. The excess solvent was removed in a rotary evaporator and the reaction mixture was poured over crushed ice. The solid mass thus obtained was filtered and recrystallized from aq. ethanol and dried (yield 7.5 g).

The identical reaction was performed in absence of AFS$_4$. The product formation was monitored by TLC (solvent: ethylacetate). The product yields were determined for both the catalyzed and uncatalyzed reaction. The identities of the products obtained through the catalyzed and uncatalyzed procedure were determined by their melting points, FTIR, $^1$H NMR, and TLC. The solubility of the products in various organic solvents was also determined.