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One Pot Catalyzed Synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(*2H*)-yl) Thiourea and Its Antimicrobial Activity

Vandana Singh*, Jadveer Singh, Preeti, Arvind Kumar Pandey, Sneha Joshi, Lalit Mohan Dwivedi, Nauseen Fatima and Shailendra Tiwari

*Department of Chemistry, University of Allahabad, **INDIA**

Email: vschemau@gmail.com

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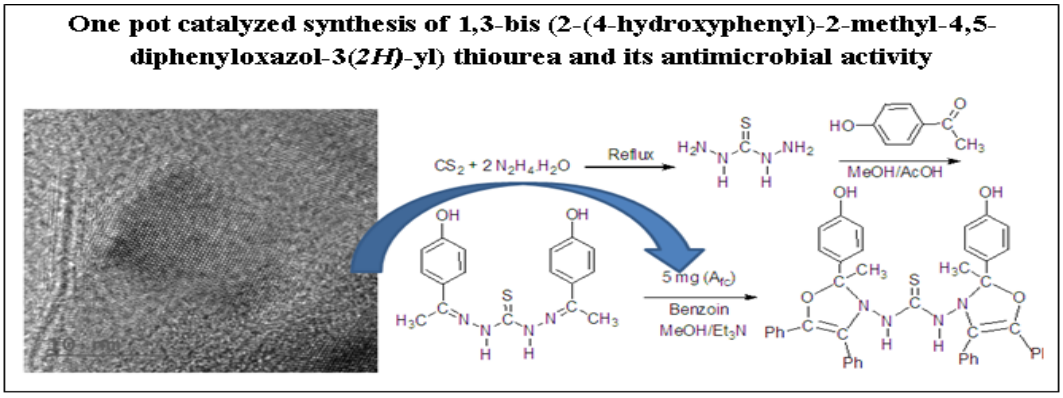
ABSTRACT

Aloevera-Fe^0-Nps-Silica nanohybrid (A_{fc}) catalyzed synthesis and antimicrobial activity of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea is being reported in the present communication. The catalyst was designed by integrating zerovalent FeNps (ZVI Nps) with Aloevera polysaccharide (AVP)-silica hybrid hydrogel. The synthesis of this new oxazole derivative (TO_x) was performed in a single step using three components (thiocarbonohydrazide, 4-hydroxy acetophenone, and benzoin) both through catalyzed and uncatalyzed routes. The catalyzed reaction led to 99.5 % product yield as compared to 49 % yield of the uncatalyzed reaction. The structure of TO_x was established using C H N analysis, FTIR, and ^1H NMR spectroscopy. The catalyst was easily recycled for the synthesis. TO_x exhibited fairly good antimicrobial actvity against different strains of pathogenic bacteria and fungi. The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) of TO_x were determined using positive and negative controls.

Graphical Abstract



Keywords: Aloevera-Fe^0-Nps-Silica nanohybrid, heterogeneous catalyst, oxazole nucleus, thiourea derivative, antimicrobial activity.

INTRODUCTION

Gram-positive [1] and Gram negative pathogens [2] are responsible for a broad array of bacterial infections such as diarrhoea, rheumatic soalmonellosis, leprosy, meningitis, pneumonia, food poisoning, extraintestinal, and intestinal wall infections. Antibiotics are unavoidable means for fighting these infections but the resistance of many pathogenic bacteria towards available antibiotics has emerged as the major threat to the human health [3]. Nevertheless fungal infections [4] are also of utmost concern as there is continous increase in the number of immunocompromised hosts i.e. patients suffering from AIDS or those undergoing anticancer chemotherapy or organ transplantation. In this scenario, the development of new biologically active molecules is needed. One pot synthesis of drug-like small molecules is important as they are important scaffolds for drug discovery processes. The one pot routes provide these scaffolds in fewer steps [5]. The use of catalyst for such syntheses may further add advantage in terms of better yields and shorter reaction time [6]. The catalyzed route may be very productive in terms of product yield and selectivity. The oxazole nucleus are the key building blocks for many natural products, pharmaceuticals and the synthetic intermediates [7-9]. The oxazole ring plays a vital role in designing the active drugs that have analgesic, trypanocidal pro-apoptotic, antifungal, anti-inflammatory, antidepressant, pesticidal, and antimicrobial activities. Thiourea and its derivatives are known to exhibit a wide variety of biological activities such as antiviral, antibacterial, and antifungal. They find extensive applications in the field of medicine, agriculture and analytical chemistry. The union of heterocyclic ring with thiourea linkage often results compounds with enhanced biological performance [10]. AVP of Aloevera gel consists of a backbone of β-(1→4)-D-mannosyl residues acetylated at C-2 and C-3 positions. It has 1:1 mannose monomer to acetyl ratio, while the backbone contains some side chains of mainly galactose that are attached to C-6 of the mannose units. The acemannan of Aloevera is likely to template exciting new silica hybrid as it is structurally unique amongst the plant mannans [11]. The catalyzing role of iron [12] and iron nanoparticles [13,14] 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 [15] the synthesis of few heterocyclic nuclei but the use of zerovalent iron nanoparticles (Fe^0Nps) is yet not reported in literature. In principle, Fe^0Nps can offer great deal in terms of product yield and selectivity because of their large surface to volume ratio. The spent nanocatalysts can be easily separated and recycled since they exhibit better retention of catalytic activity than their bulk counterparts [16]. The synthesis of stable small sized Fe^0Nps involves tedious and sophisticated steps [17] as the small sized nanoparticles have a tendency to agglomerate in water under neutral condition to form micron scale or larger aggregates and they also have a tendency for slow corrosion [18]. Nanoparticles are either capped [19,20] or immobilized [21] in a polymer network stucture to circumvent the problem of agglomeration. The impregnating nanoparticles with in polysaccharide templated silica matrix has emerged as a very useful technique for obtaining temperature resistant, stable and recyclable heterogeneous nanocatalysts [22,23]. In this light we have designed a novel catalyst from AVP, ZVI Nps and silica. The same has been utilized for synthesizing a new oxazole derivative; 1,3-bis (2-(4-hydroxyphenyl)-2-methyl, 4,5-diphenyl oxazol-3(2*H*-yl) thiourea (TO_x) in a one pot method. TO_x has been screened for its antimicrobial activity. The synthesis of the taget compound was planned due to reported biological activity of thiourea coupled oxazole moieties [24,25]. This catalyst invite sustainable approach for using polysaccharides derived nanocatalysts for synthesizing heterocyclic systems.

MATERIALS AND METHODS

Chemicals and instrumentation: TERRA-PURE^{TM}, 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. CS_2, hydrazine, 4-hydroxy acetophenone, Benzoin (Aldrich, USA) were used. UV/Vis Spectrophotometer UV 100 (Cyber lab, USA)

was used to observe the surface plasmon of zerovalent FeNps (ZVI Nps). All the melting points that were measured with a capillary apparatus are uncorrected. TEM analysis was done on FEI Technai U- Twin 20 instrument. HRTEM, EDX and elemental mapping was 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 using KBr pellets on a Perkin-Elmer model 400 FTIR spectrometer. ^{1}H 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. The bacterial and fungal stock cultures were incubated for 24 hours at 37°C on nutrient agar and potato dextrose agar (PDA) medium, respectively, following refrigeration storage at 4°C. The bacterial strains were grown in Mueller-Hinton agar (MHA) plates at 37°C (the bacteria were grown in the nutrient broth at 37°C and maintained on nutrient agar slants at 4°C). The fungal strains were grown in Sabouraud dextrose agar and PDA media, respectively at 28°C. The stock cultures were maintained at 4°C.

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 catalyst synthesis.

Synthesis of ZVI Nps: ZVI 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. The typical procedure for preparing ZVI Nps is described below:

Mango leaf extract (5 mL) was added to ferric nitrate solution (5 mL of 0.1 M) whereupon the yellow ferric nitrate solution immediately turned black due to the formation of ZVI Nps. The formation of ZVI Nps was confirmed by observing surface plasmon peak for ZVI Nps [26].

Synthesis of catalyst: The hybrid catalyst was synthesized by using 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. ZVI Nps 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 $^{\circ}$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 oxazole derivative

Synthesis of thiocarbonohydrazide: Thiocarbonohydrazide was synthesized by a known method where carbon disulphide was directly added to excess of hydrazine hydrate (3 M) at its boiling point. Thiocarbonohydrazide was periodically removed (60 % yield). The crude product was recrystallized with water (m.p. 168 ºC).

Synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(*2H)*-yl) thiourea: Thiocarbo nohydrazide (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 $A_{fc.}$ 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.

RESULTS AND DISCUSSION

Characterization of catalyst (A_{fc}): In FTIR spectrum (Fig. 1), the aloevera O-H and silica silanols are together seen as merged peak at 3444 cm.$^{-1}$ Carbonyl stretching peaks of O-acetyl ester is seen at 1734 cm^{-1} while other C-O stretching peak is seen masked with silica peaks below 1250 cm^{-1}. -C-CH_3 bending absorption is present at 1384 cm.$^{-1}$ Peaks due to SiO–H, Si–OH, and O–Si–O stretching are observed at 3398 cm^{-1} (merged with O-H peak), 1083 cm,$^{-1}$ and 798 cm^{-1} respectively.

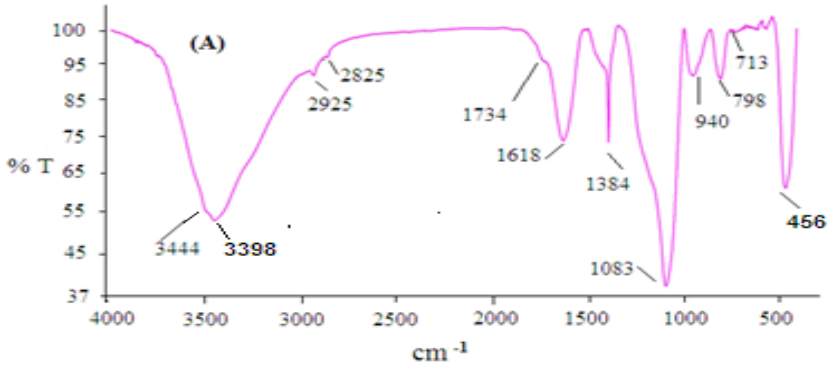


Fig. 1: FTIR spectra A_{fc}

FE-SEM imaging of the catalyst (A_{fc}) (Fig. 2(A&B)). exhibited layered hybrid surface enwrapped with nearly spherical to spherical shaped ZVI nanoparticles that are slightly agglomerated at places.

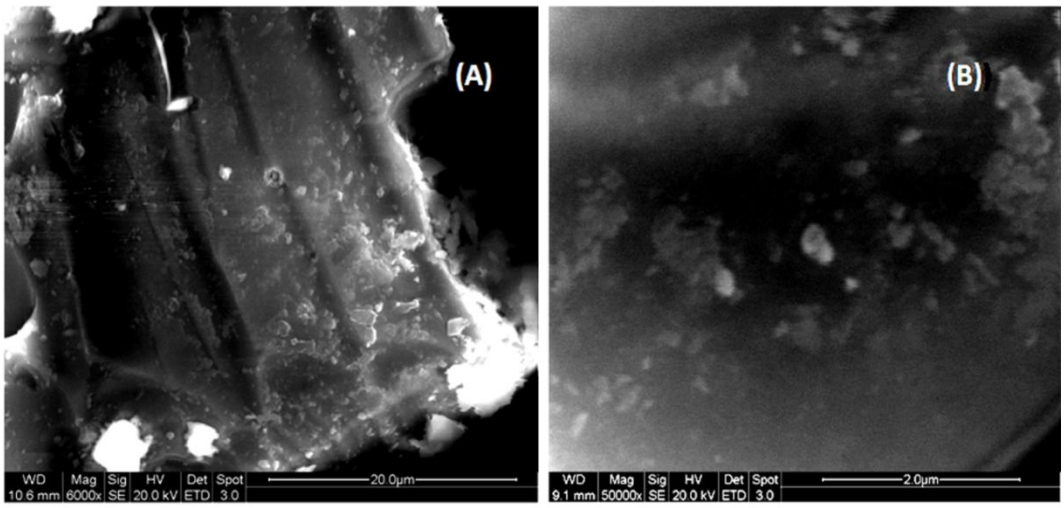


Fig. 2: (a) FE-SEM imaging of the A_{fc} (A) 6000X and (B) 50000X

TEM picture of A_{fc} (catalyst) is dipicted in Fig. 3, where particles are spherical to nearly spherical but slightly agglomerated ZVI Nps are seen scattered within the hybrid silica matrix. The TEM histogram prepared by IMAGE J software revealed that ZVI Nps are in the range of 1-11 nm, average particle size being ~5 nm (Fig. 3(A)). The hybrid matrix is uniform and throughout decorated with the ZVI Nps.

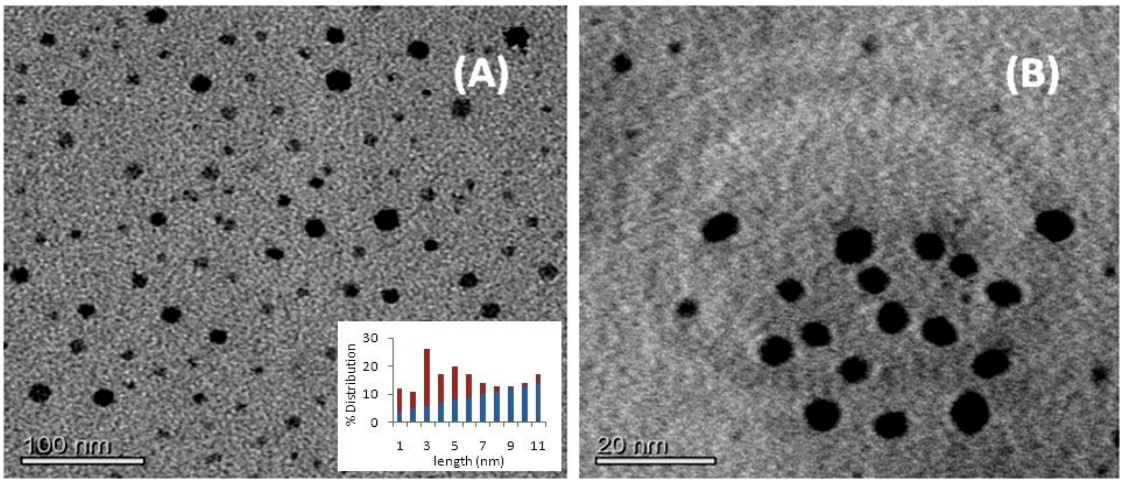


Fig. 3: Transmission Electron Micrographs of A_{fc} at different magnification (A) and (B); TEM histogram seen as inset of (A).

High resolution TEM (HRTEM) revealed fringes of regular lines within nearly spherical FeNps that are dispersed in silica matrix (Fig. 4(A&B)). The fine Fe^0 crystallites have a diameter of ~ 5 nm and its lattice fringes have the spacing of 0.282 nm which is in good agreement with the (110) plane of zerovalent iron nanoparticle [29]. HAADF image of A_{fc} depicted the chemical composition inside the nanocomposite at sub-nanometer resolution (Fig. 5(A-C)). The EDX mapping of elements in a selected area of A_{fc} (Fig. 4(D)), revealed the presence of Fe with other elements Si, C, O, N (constituent of mango leaf extract). This observation has confirmed the inclusion of ZVI in the composite. The SAED pattern indicate the poly crystalline nature of the catalyst matrix with embeded Fe^0 Nps.

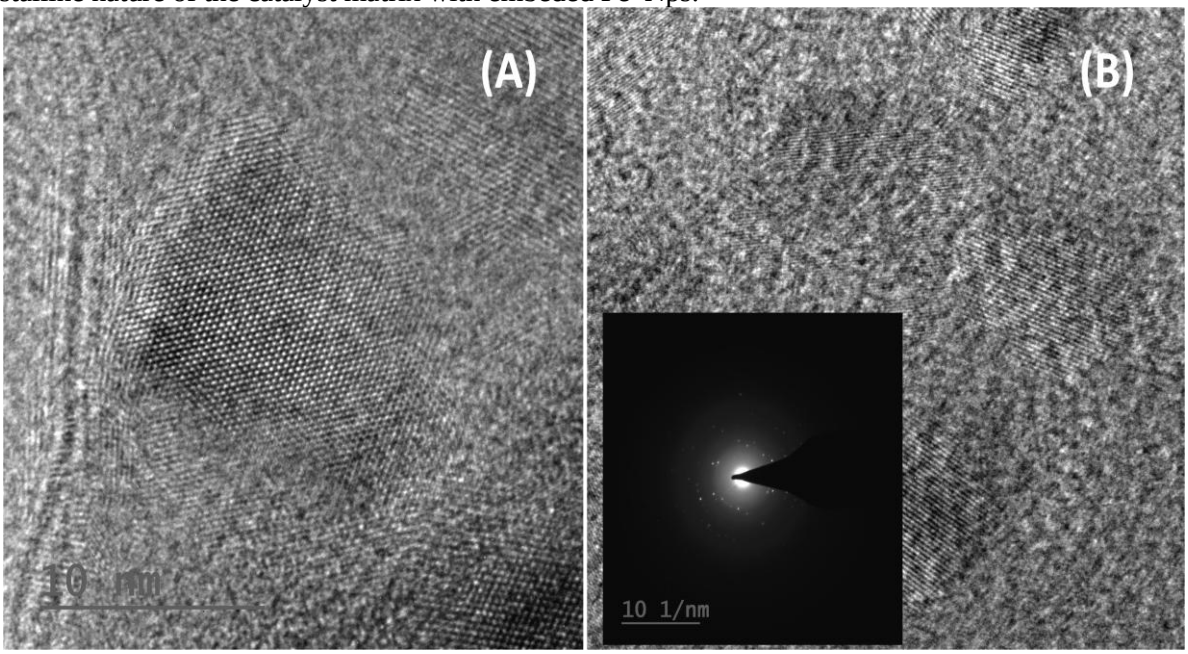


Fig. 4: High resolution TEM image (A) High Magnification of a single Fe(0) NP showing lattice fringes (B) HRTEM of A_{fc} with SAED pattern seen in inset

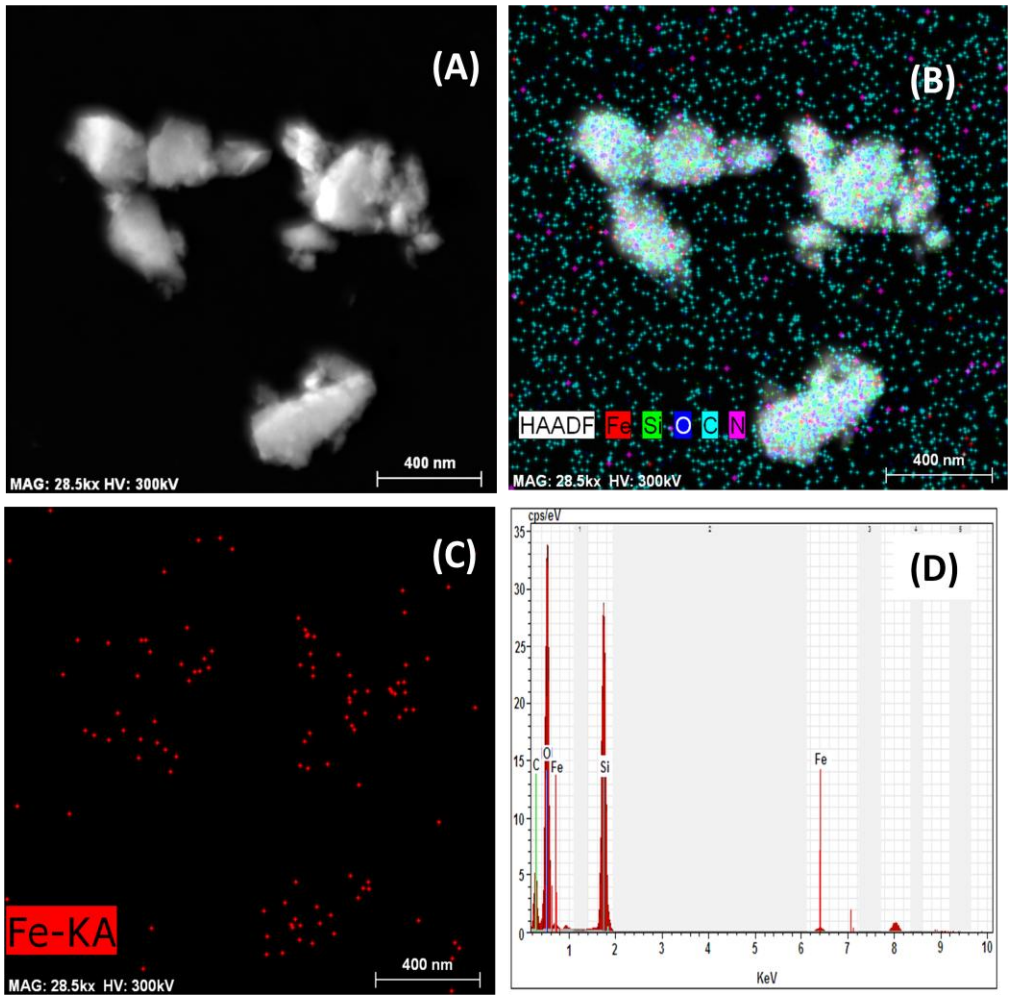


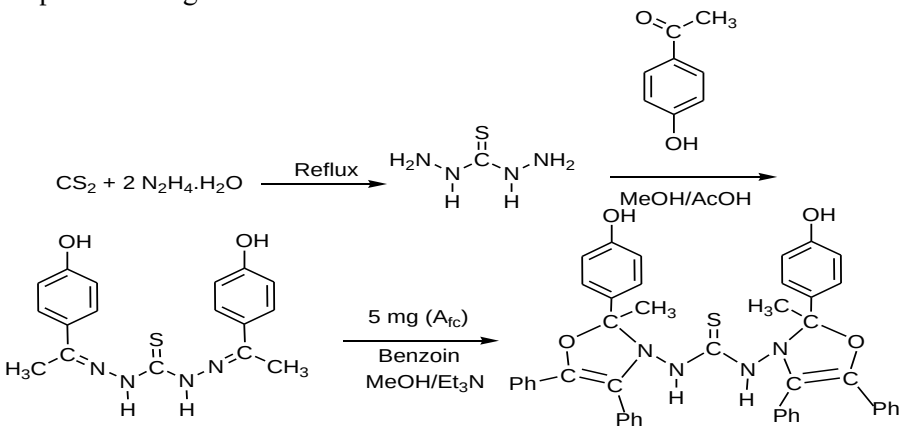
Fig. 5: (A&B) HAADF HR-TEM image of A_{fc} and its corresponding elemental mappings for (C) Fe, (D) The corresponding EDX spectrum taken from the whole area of (A).

The catalytic activity of the A_{fc}: The catalyst synthesis involved AVP templated polymerization of tetramethoxysilane in presence of ZVI Nps which were synthesized by reducing Fe^{+3} salt with aqueous extract of dry powdered mango leaf according to a previously known method [26]. The selection of H_2O: TMOS: MeOH ratio was based upon our previous experience [27] with similar materials derived from other polysaccharides. The catalyst was obtained using 0.2 g of purified [28] AVP, 1.0 mL TMOS, 1.0 mL MeOH, and 10 mL water (which included the water content in the Nps solution). The purpose of impregnation of ZVI Nps in AVP templated silica was to avoid agglomeration of nanoparticle during the catalyzed reaction of the oxazole nucleus and easy recovery of the catalyst for the recycling. The selection of AVP as the templating agent was based on its unique structural characteristics among the plant mannan polysaccharides. The catalyst (A_{fc}) has polycrystalline nature having both AVP and silica matrix with embeded Fe^0 Nps of ~5 nm diameter.

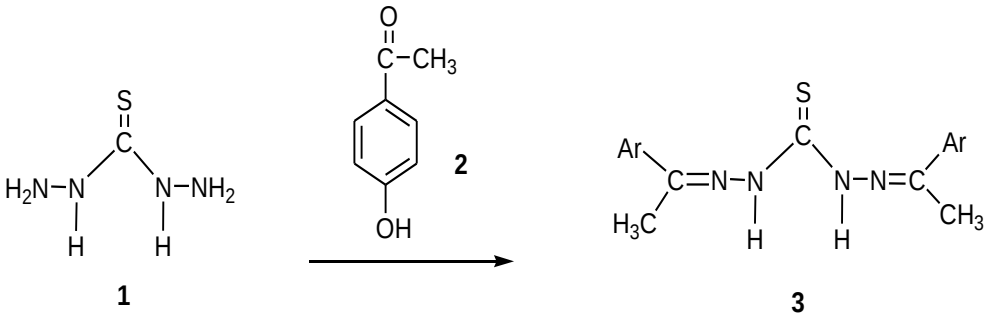
The catalytic activity of the A_{fc} has been monitored for one pot three component synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(*2H)*-yl) thiourea (Scheme 1) for which thiocarbono hydrazide **1**, 4-hydroxy acetophenone **2** and benzoin **3** were taken in methanol and refluxed for 2 h along with catalyst (A_{fc}) and triethyl amine. **1** was synthesized by a known method [30], where carbon disulphide was directly added to excess of hydrazine hydrate (3 M) at its boiling point. **1** was periodically removed (60 % yield). The crude product was recrystallized with water (m.p. 168 ºC).

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 ºC. 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 1. 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 through washing with water and in second cycle the product yield in the catalyzed reaction was 6. 4 g (85%).

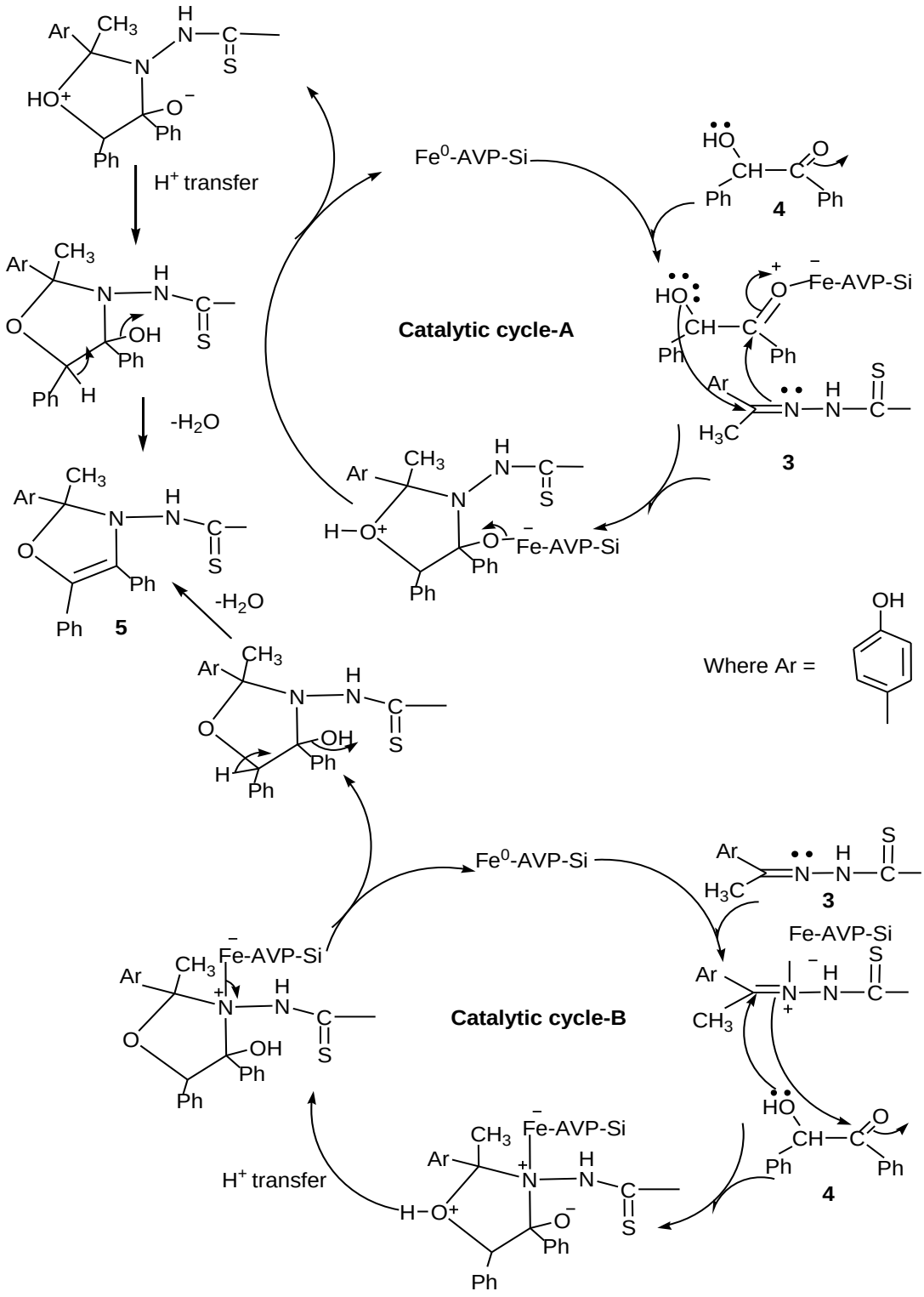
First step is the reaction of thiocarbonohydrazide **1** with 4-hydroxyacetophenone **2** to form corresponding shiff's base **3** (Scheme 2). We speculate that the Fe^0 of A_{fc} catalyst, having vacant d orbitals act as electrophile, thus induces more electrophilic character at carbonyl carbon atom of benzoin (Catalytic Path-A) **4** and/or at C-atom of azomethine (Catalytic Path-B) of **3** respectively. Thus attack of nucleophile in either case becomes easier. This is the reason that the addition of the catalyst in this reaction reduces reaction time period and increase the yield of the final product. Two possible mechanisms "Catalytic path-A" and "Catalytic path-B" are given in Scheme 3.



Scheme 1. Schematic diagram for the synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(*2H)*-yl) thiourea



Scheme 2. Synthesis of thiocarbonohydrazide



Scheme 3. Plausible mechanistic pathways for the catalytic synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl, 4,5-diphenyl oxazol-3(2*H)*-yl) thiourea

Physical and Spectral data of synthesized 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(*2H)*-yl) thiourea (TO_x):

Solubility	DMF, DMSO, ethylacetate, acetone, ethanol; insoluble in benzene, toluene, hexane, cyclohexane, and chloroform
Melting point	105°C
R_f (Solvent: ethylacetate)	0.44
IR (KBr)	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 (CH_3 as), 1388 (CH_3 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.)
^{1}H NMR (DMSO-d_6):	δ 6.87-7.95 (m, aromatic H), 1.19 (s, CH_3), 6.31 (O-H), 6.27 (N-H)
Elemental Analysis	Anal. Calcd for $C_{47}H_{42}N_4O_4S$; C, 73.90; H, 5.20; N, 7.67; Found C, 73.75; H, 5.25; N, 7.70.

Biological activity of oxazole derivative (TO_x): The synthesized oxazole derivative (TO_x) is a new compound and therefore we were prompted to screen its antibacterial and antifungal activities. Antibacterial activity of TO_x was screened against *E. coli* (ATCC-25922), Methicillin-resistant *S. aureas* (MRSA +ve), *Pseudomonas aeruginosa* (ATCC-27853), *Streptococcus pyogenes* and *K. pneumonia* (Clinical isolate) bacterial strains by disk diffusion method [31]. The Minimum Inhibitory Concentration (MIC) are summarized in Table. 1 and Table. 2 respectively.

The investigation of antibacterial screening data revealed that TO_x has fairly good bacterial inhibition against *S. Pyogenes*, Methicillin-resistant *S. aureas* (MRSA +ve), *P. Aeruginosa*, *K. Pneumonia*, and *E. coli* species. The compound showed antibacterial activity (MIC 12.5 µg mL^{-1}) against all bacterial strains except for *E. Coli* for which MIC was 25 µg mL^{-1}. The minimum bactericidal concentration (MBC) of the compound was two, three, or four fold higher than the corresponding MIC results.

Table 1. Antibacterial activity of the compound

Diameter of zone of inhibition (mm)					
Gram positive bacteria			Gram Negative bacteria		
Compounds	*S. pyogenes*	MRSA [a]	*P. aeruginosa*	*K.pneumonia*	*E. coli*
TOx	19.5±0.3	16.1±0.5	24.4±0.2	15.3±0.2	20.1±0.3
Standard	22.0±2.0	21.0±0.2	31.0±0.3	19.0±0.2	27.0±0.2
DMSO	--	---	---	---	---

Positive control (standard); Ciprofloxacin and negative control (DMSO) measured by the halo zone test (Unit, mm) a Methicillin resistant *S. aureas*(MRSA +ve)

Table 2. MIC and MBC results of TO_x and positive control Ciprofloxacin

Diameter of zone of inhibition (mm)										
Gram positive bacteria					Gram Negative bacteria					
Compounds	*S. pyogenes*		MRSA [a]		*P. aeruginosa*		*K.pneumonia*		*E. coli*	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
TOx	12.5	25	12.5	25	12.5	25	12.5	50	25	50
Standard	12.5	12.5	6.25	12.5	12.5	25	6.25	25	6.25	12.5
DMSO	--	--	--	--	--	--	--	--	--	--

MIC(µg/mL) minimum inhibitory concentration, i.e the lowest concentration of the compound to inhibit the growth of bacteria completely.
MBC(µg/mL) minimum bactericidal concentration, i.e the lowest concentration of compound for killing the bacteria completely

Antifungal activity was also studied using the disk diffusion method. For assaying antifungal activity, *C. albicans, Aspergillus fumigatus, Penicillin marneffi and Trichophyton mentagrophytes* were re-cultured in DMSO by agar diffusion method [32].

The inhibitory results are presented in Table. 3 and Table. 4. The antifungal screening data showed fairly good fungicidal activity against *C. albicans, Aspergillus fumigatus, Penicillin marneffi and Trichophyton mentagrophytes* fungal strains. The compound showed maximum inhibition results against *C. albicans,* and *T. Mentagrophytes.* The MFC of the compound was found to be two, three, or four fold higher than the corresponding MIC results.

Table 4. Antifungal activity of compounds TOx

Compounds	*C. albicans*	*A. fumigates*	*T. mentagrophytes*	*P. marneffi*
TOx	18.1±0.3	15.7±1.2	18.3±0.7	12.1±0.2
Standard	30.0±0.2	27.0±0.2	24.0±0.3	20.0±0.5
DMSO	--	---	---	---

Positive control (Griseofulvin) and negative control (DMSO) measured by the halo zone test (Unit, mm).

Table 5. MIC and MFC of TOx

Compounds	*C. albicans*		*A. fumigates*		*T. mentagrophytes*		*P. marneffi*	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
TOx	25	100	25	50	25	50	25	100
Standard	6.25	25	12.5	12.5	6.25	25	12.5	25

MIC (µg mL^{-1}) minimum inhibitory concentration i.e the lowest concentration of the compound to inhibit the growth of fungus completely
MFC (µg mL^{-1}) minimum fungicidal concentration, i.e the lowest concentration of the compound for killing the fungus completely.

APPLICATIONS

In the current study, Aloevera-Fe^0-Nps-Silica composite were found to be an efficient catalyst for the synthesis of 1,3-bis (2-(4-hydroxyphenyl)-2-methyl-4,5-diphenyloxazol-3(2H)-yl) thiourea (TO_x). The synthesized new oxazole derivative (TO_x) showed fairly good antibacterial and antifungal activity.

CONCLUSIONS

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 activty. The catalyst (A_{fc}) was designed from Aloevera acetomannan which has ZVI Nps of ~5 nm size impregnated within aloevera-silica hybrid matrix. The A_{fc} showed fairly good antimicrobial activity. TO_x can be used as template for synthesizing several derivatives through modification to develop bioactive heterocyclic oxazole compounds while the catalyst may be useful for synthesizing the similar other hetrocyclic nuclei.

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AUTHORS' ADDRESSES

1. **Jadveer Singh**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: jadveer007@gmail.com
2. **Dr. Preeti**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: preetisrivastava.au@gmail.com
3. **Arvind Kumar Pandey**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: arvindauchem@gmail.com
4. **Sneha Joshi**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: snehajoshi008@gmail.com
5. **Lalit Mohan Dwivedi**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: dwivedilalitmohan@gmail.com
6. **Nauseen Fatima**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: nfsnrau786@gmail.com

7. **Dr. Shailendra Tiwari**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: drshailendratiwariau@gmail.com
8. **Prof. Vandana Singh**
Department of Chemistry, University of Allahabad, Allahabad-211002
E-Mail: vschemau@gmail.com