REGULAR ARTICLE

W/HAP catalysed N-oxidation of tertiary amines with H_2O_2 as an oxidant

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Abstract. Synthesis of several *N*-oxides with tungsten exchanged hydroxyapatite (W/HAP) in the presence of 30% hydrogen peroxide (H_2O_2) as an oxidant is presented. A process with aqueous H_2O_2, a cheap and clean oxidant with an active catalyst is developed to reduce waste production and meet the requirements of green chemistry. Several tertiary amines have been efficiently oxidized to their corresponding *N*-oxides with excellent yields. The as-synthesized catalyst (W/HAP) is characterized using BET, FTIR, SEM, ICP-OES and XRD. Effect of catalyst loading, temperature and oxidants were studied. A kinetic model has been developed to determine the reaction rate at different temperatures and activation energy for the model reaction.

Keywords. *N*-oxides; Tertiary amines; Hydroxyapatite; Green oxidants; Kinetic study.

Abbreviations

A	Reactant species A, pyridine
B	Reactant species B, hydrogen peroxide
C	Product C, pyridine *N*-oxide
D	By-product D, water
C_A	Concentration of A (mol/lit)
C_B	Concentration of B (mol/lit)
$-r_A$	Rate of surface reaction of A (mol lit s^{-1})
K	Second order rate constant (lit^2. mol^{-1} sec^{-1} g^{-1})
W	Catalyst loading (g/lit)
C_{Ao}	Initial concentration of A, (mol/lit)
C_{Bo}	Initial concentration of B, (mol/lit)
X_A	Fractional conversion of A
M	Initial molar ratio of reactants B to A

1. Introduction

Pyridine is a six-membered heterocyclic nitrogen-containing compound. It occupies an important role in bioorganic and medicinal chemistry. Oxidation of pyridine to pyridine n-oxide has found novel applications in the field of chemistry due to its various uses in organic and inorganic chemistry.[1] The oxidation of nitrogen compounds results in the synthesis of versatile building blocks for organic synthesis.[2,3] Table 1 provides an insight into different catalysts used for the oxidation of heterocyclic nitrogen compounds to their *N*-oxides using H_2O_2 as an oxidant.

A greener catalytic oxidation method is one that utilizes dioxygen (O_2) or hydrogen peroxide as an oxidant. Aqueous H_2O_2 is an ideal oxidant because of its safety in storage and handling, high oxygen content, low production, and transportation cost, and is a green reagent that produces only water as a by-product.[1] Moreover, reactions performed in water are environmentally friendly. There is always a need to develop new processes to minimise the difference between atom utilization of actual and theoretical values for an increasingly global and environmental problem.[6]

Hydroxyapatite (HAP) [$Ca_{10}(PO_4)_6(OH)_2$] is a weak alkaline calcium phosphate. It has strong ion-exchange property, and it can be exchanged with the majority of metal ions. This property allows preparing the highly dispersed and stable metal-supported catalysts. The acidity and basicity on the surface of hydroxyapatite

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Table 1. Different types of catalysts used for N-Oxidation.

No.	Catalysts	Temperature (°C)	Time (h)	Yield (%)	Refs.
1	VS-1	60	12	90	[4]
2	TS-1	75	2	99	[5]
3	LDH-WO$_4$	r.t.	3–5	96	[6]
4	Mg-Al-O-tBu hydrotalcite	75	1–5	98	[7]
5	Redox molecular sieves	60	5–24	90	[8]
6	V$_x$Si$_{4x}$O$_{6.4x}$	80	3–12	45–99	[9]
7	Ru(PVP)/γ-Al$_2$O$_3$	r.t.	1–2	99	[10]
8	Poly(maleic anhydride-alt-1-octadecene)	90	7	93	[11]
9	MeReO$_3$	r.t.	6	90	[12]
10	*m*-Chloroperbenzoic acid	r.t.	1–24	87	[13]
11	Na$_2$WO$_4$ 2H$_2$O	− 5 and r.t.	3	40–89	[14]

can be changed by adjusting the calcium-phosphorus ratio. The surface of HAP is rich in hydroxyl groups, so it has strong absorbability and can be modified by organic compounds with polar functional groups and better support for organometallic compounds. HAP is used widely for the dehydrogenation of hydrocarbons, oxidation of alcohols, C-C bond formation reactions, and reduction reactions such as hydrogenolysis.[15–20] Choudary B M [21] reported three-component coupling to prepare propargylamine from aldehyde, alkyne, and an amine using copper-hydroxyapatite (CuHAP) under mild reaction parameters. Another work reported by Choudary B M[22] includes N-arylation of imidazoles and other heterocycles with fluoroarenes and chloroarenes using copper-exchanged *tert*-butoxyapatite and copper-exchanged fluorapatite. Kantam M L[23] synthesized *N*-arylimidazoles and *N*-arylamines at room temperature in the presence of copper fluorapatite (CuFAP). A palladium-supported fluorapatite catalyst (PdFAP) gave high activity for Suzuki coupling of bromides and aryl iodides with chloroarenes and boronic acids at 130°C and room temperature, respectively. The catalyst was also successful for Heck olefination of chloroarenes.[24] Hydrogenation of levulinic acid to γ- valerolactone was successfully obtained by metal (Ru, Pt, Pd, Ni) supported hydroxyapatites.[16] Kaneda K[25] discussed the active metal sites on the apatite compounds that display novel catalytic activity in selective oxidations, carbon-dioxide chemical fixation, carbon-carbon bond formation.[22] Their further review includes high-performance apatite-based catalysts for liquid-phase organic synthesis and continuous flow systems. Fihri A and Solhy A[26] highlighted the application of hydroxyapatite in heterogeneous catalysis and its synthesis methods with the structural properties.

Recently, there is a review article by Kantam M L[27] on C-C and C-N bond-forming reactions catalysed by HAP. There are various methods to synthesize hydroxyapatite. A stoichiometric HAP can be obtained from a balanced molar ratio of the calcium and phosphate precursors and maintaining pH.[28]

Pyridine *N*-oxides have wide applications as auxiliary agents, synthetic intermediates, oxidants, protecting groups, and as ligands in catalysts and metal complexes.[11,29] Ghaleb A[30] successfully studied the structure-activity relationship for a new family of SARS-CoV 3CL pro-inhibitors, pyridine N-oxide derivatives. Pyridine N-oxide compounds have antiviral activity against SARS. They reported pyridine N-oxide antiviral compounds to be more potent against SARS-CoV-2 than chloroquine and hydroxychloroquine.

Herein, we report the N-oxidation of tertiary amines to the corresponding *N*-oxides using H$_2$O$_2$ as an oxidizing agent and tungsten exchanged hydroxyapatite (W/HAP) as a catalyst in water for three cycles at low temperature.

2. Experimental

2.1 *Materials*

All the chemicals were purchased from Oxford lab fine chem and used as received. The reaction progress was monitored by High performance liquid chromatography (Thermo Scientific, Ultimate 3000), Cosmosil C-18 column, 0.132 g of Sodium acetate buffer with 30% acetonitrile and 70% water, 0.6 mL/min of flow rate, 10 min total run time at the pressure of 65 bar. The surface area of the optimized catalyst was determined by Micromeritics ASAP 2000 instrument by

using Nitrogen adsorption-desorption isotherms. All the samples were degassed under vacuum for 4 h at 350 °C. ICP-OES is carried out by Agilent model: 5110. A Fourier Transform Infrared Spectrum (FTIR) of the catalysts was measured on a Perkin Elmer Spectrophotometer in the range of 400-4000 cm^{-1}. Scanning electron microscopy (SEM) was obtained on Philips XL, 30 SEM, The Netherlands. XRD was obtained from Shimadzu X-ray diffractometer-6100 LabX.

2.2 Catalyst synthesis

Hydroxyapatite was synthesized using the co-precipitation method.[22] 0.066 mol of calcium nitrate was dissolved in 60 mL of water, brought to 11-12 pH with concentrated ammonia solution and diluted to 120 mL. A solution of 0.04 mol of diammonium orthophosphate in 100 mL of water was prepared and brought to the pH of 11-12 using concentrated ammonia solution. The calcium solution was stirred at room temperature with the simultaneously addition of phosphate solution drop-wise over a period of 30 min and the milky solution was further stirred, boiled for 10 min at reflux. The precipitate was filtered, dried at 353 K overnight and calcined at 773 K for 3 h.

2.3 Tungstate exchanged hydroxyapatite

To 1 g of hydroxyapatite, 100 mL of sodium tungstate solution was added (1.87 mM. 0.616 g) and stirred at 293 K for 24 h. The catalysts were filtered off, washed, and dried at 353 K overnight.[6,31,32] The tungsten content in the W/HAP catalyst was found to be 0.0340 Wt.%.

2.4 Procedure for the N-Oxidation reaction

N-Oxidation of pyridine to pyridine N-Oxide was performed in a 50 mL glass reactor equipped with a 6-blade pitched turbine impeller. The reactor was immersed in an oil bath with PID controller to maintain the temperature of the oil bath. 2 mmol of pyridine was reacted with 6 mmol of 30% hydrogen peroxide (H_2O_2) in the presence of W/HAP catalyst and 10 mL of water, 1200 rpm at 353 K for 20 h. The initial sample was collected when the reaction reached the desired temperature. Samples were taken out at fixed intervals up to 20 h and centrifuged to separate the catalyst particles. The reaction is depicted in Scheme 1.
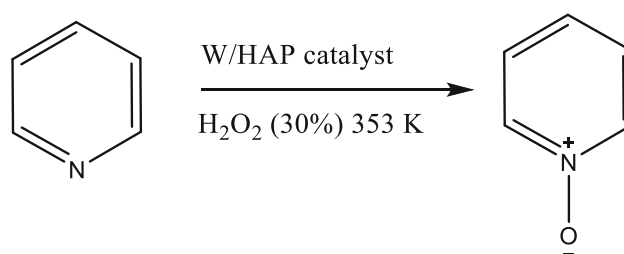
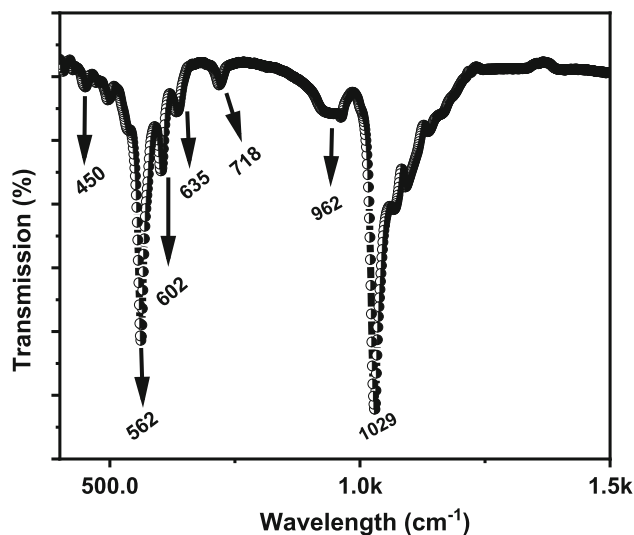**Scheme 1.** N-oxidation of Pyridine to Pyridine N-Oxide.

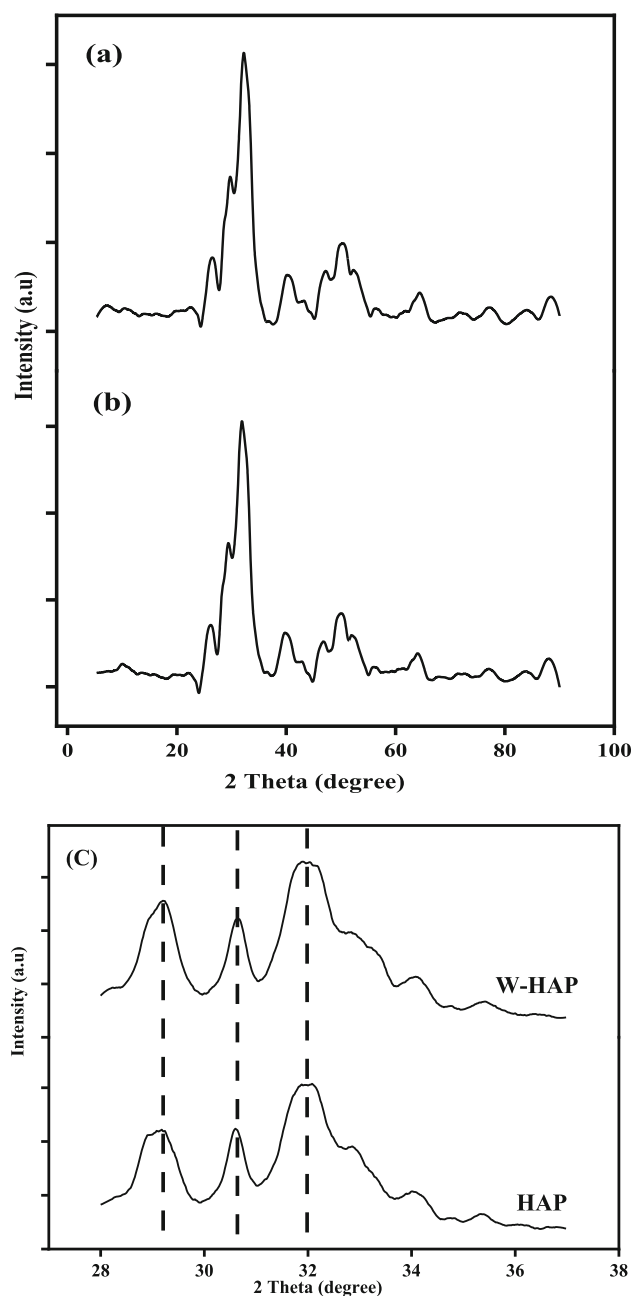## 3. Results and Discussion

3.1 Catalysts characterization

The Brunauer-Emmett-Teller (BET) surface area of W/HAP was measured to be 91.4 m^2/g, and the pore volume was 0.1318 cc/g. The nitrogen adsorption-desorption isotherm for W/HAP is shown in (Figure S1, SI) was found to be type IV with the characteristic of mesoporous material having a small plateau at high relative pressure.

The FTIR spectra (Figure 1) of W/HAP displays PO$_4$ vibrational frequencies in agreement with the literature,[33,34] bands were observed at 962 cm^{-1}, for the symmetric P-O stretching ϑ_1, at 1029 and 1060 cm^{-1} for the asymmetric P-O stretching ϑ_3. 450, 562, 602, 635, and 718 cm^{-1} for the O-P-O bending modes ϑ_3 and ϑ_4.

The SEM technique was used to investigate the size and shape of the synthesized material. The (Figure S2, SI) image (a) clearly indicates the particles are in the nanosize range. There are irregular agglomerates for the W/HAP sample from image (b) and literature.[35]

Figure 1. FTIR of W/HAP.

in corresponding with (229), (105), (350), (300), (100), (99), (95), (105), (106), (98), (97), (101).

3.2 Catalytic activity

2 mmol of pyridine was reacted with 6 mmol of 30% hydrogen peroxide (H_2O_2) in the presence of different catalysts and 10 mL of water at 353 K for 20 h. The conversion was 90 and 86%, respectively, with W/HAP and HAP. No by-products were formed in this reaction. The lowest conversion of 36% was found with FAP (Fluorapatite). Sodium tungstate and sodium molybdate afforded conversion of 70 and 75%, respectively. Whereas tungstate and molybdate loaded layered double hydroxides showed 58 and 44% conversion (Figure 3). A series of experiments were done using 5 wt% to 50 wt% of W/HAP catalyst, and 20 wt% catalyst gave 90% conversion (Figure 4). Catalyst loading was studied with respect to the limiting reactant. The optimization studies were conducted with 20 wt% of W/HAP catalyst (Figure 4).[36] The reaction was tested with different oxidants. 30% H_2O_2 was found to be the best oxidant for the reaction with 90% conversion, and the conversion was less with the use of 70% aqueous TBHP and air, as shown in (Figure 5). The reaction was studied at varying molar ratios of pyridine to H_2O_2 (Figure 6). We obtained an increase in yield with an increase in the amount of H_2O_2.[4] The speed of agitation was studied from 800 to 1200 rpm. There was a negligible difference in the rate of reaction and thus proves the absence of external mass transfer resistance in the reaction (Figure 7). Temperature study was carried out at 323, 333, 343, and 353 K. The highest conversion, 90%, was obtained at 353 K, and the lowest 60% at 323 K. Low conversion of 20% was obtained at room temperature, and water was found to be the best solvent for the reaction. Sample was analysed with time at all temperatures to determine the progress of the reaction as shown in (Figure 8). The TON and TOF are calculated as 5.05 and 0.25 h^{-1}, respectively.

3.3 Substrate study

Substrates with structural diversity were studied at the optimized reaction conditions. We observed that all the aromatic nitrogen compounds were transformed into their corresponding *N*-Oxides, as shown in (Table 2).

Figure 2. XRD of **a** HAP and **b** W/HAP **c** Inset of **a** and **b** showing detailed view.

These agglomerates consist of fine crystallites that are not visible individually because of their small size. The surface of the particles was found to be rough from image (c).

The XRD data of hydroxyapatite well matched with the reported JCPDS #09-0432. The XRD of W/HAP catalyst matches with the reported data (JCPDS# 11-0693). The crystallinity of the catalyst can be confirmed by the peaks reflection at 32° and 34° and planes corresponding are (300) and (112), respectively.[34] The other peaks are at the reflection of 25°, 26°, 29°, 30°, 38°, 40°, 41°, 46°, 49°, 50°, 51°, 53° are

3.4 Reaction mechanism and kinetic model

The reaction mechanism is presumed to be similar to that reported in the literature.[6,37]

$$A + B \rightarrow C + D$$
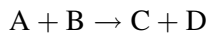
A = Pyridine, B = H_2O_2, C = Pyridine N-Oxide, D = Water

$$-r_A = \frac{-dC_A}{dt} = \frac{-dC_B}{dt} = K\, C_A C_B W$$

$$-r_A = C_{Ao} \frac{dX_A}{dt}$$
$$= K(C_{Ao} - C_{Ao} \cdot X_A)(C_{Bo} - C_{Ao} \cdot X_A)$$

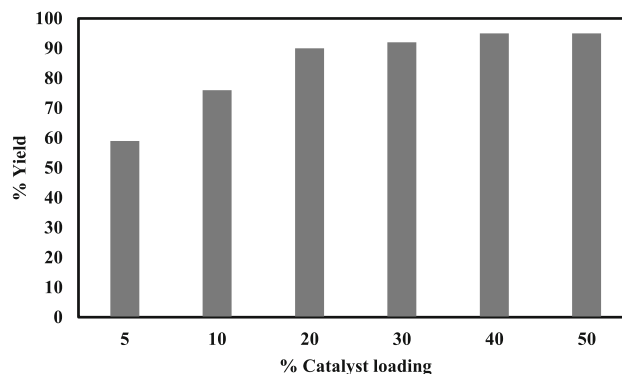Let $M = \frac{C_{Bo}}{C_{Ao}}$ be the initial molar ratio of reactants, we obtain

$$-r_A = C_{Ao} \frac{dX_A}{dt} = KC_{Ao}^2(1 - X_A)(M - X_A)$$

Integrating the above equation, we get

$$\int_{C_{Ao}}^{C_A} \frac{dX_A}{(1 - X_A)(M - X_A)} = KC_{Ao}W \int_0^t dt$$

$$\ln \frac{M - X_A}{M(1 - X_A)} = KC_{Ao}(M - 1)Wt \tag{1}$$

Plotting the above equation as a graph with the slope as $K\,C_{Ao}\,(M\text{-}1)\,W$,

Figure 4. Effect of catalyst loading on yield of pyridine N-oxide. Reaction conditions: Pyridine: 2 mmol, oxidant: 6 mmol, W/HAP, 10 mL water, 1200 rpm, 353 K, 20 h.

Graph of $ln\, \dfrac{M - X_A}{M(1 - X_A)}$ V/s Time:

The experimental data were used to verify the validity of the equation (1) and plotted as shown in (Figure 9). Using equation (1), plots were made for different temperatures with respect to time, and the rate constants were calculated mentioned in (Table 3). These rate constants were used for the calculation of activation energy by plotting an Arrhenius plot (Figure 10) as 50 Kcal/mol, which supports the fact that the N-oxidation of pyridine was kinetically controlled.
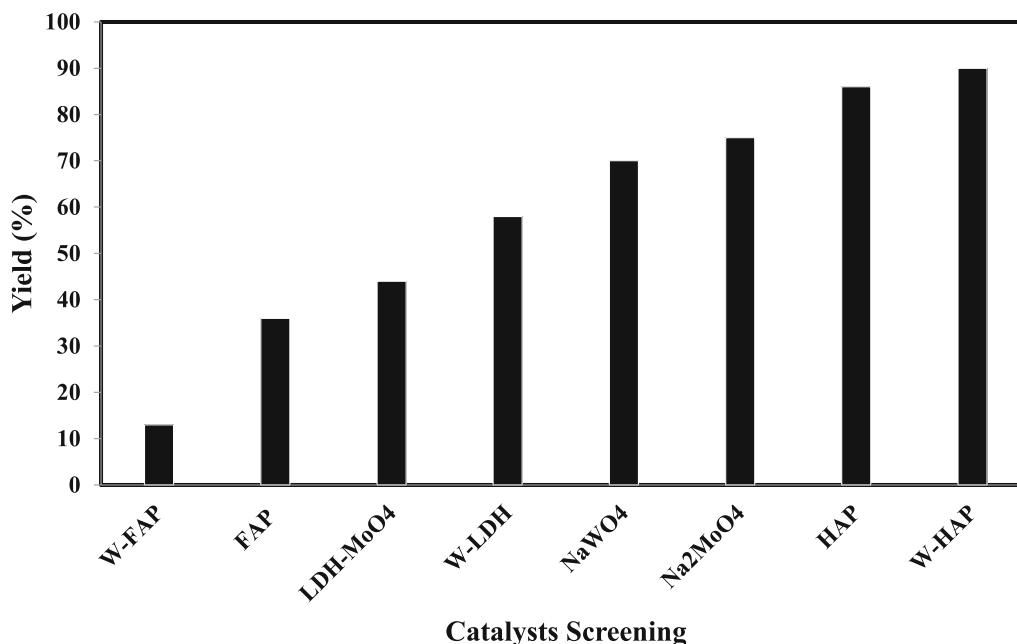
Figure 3. Effect of different catalysts on the yield of Pyridine N-oxide. Reaction conditions: Pyridine: 2 mmol, H_2O_2: 6 mmol, catalyst: 200 mg, 10 mL water, 1200 rpm, 353 K, 20 h.
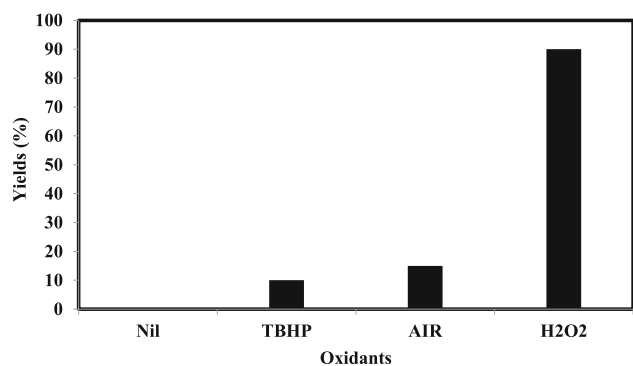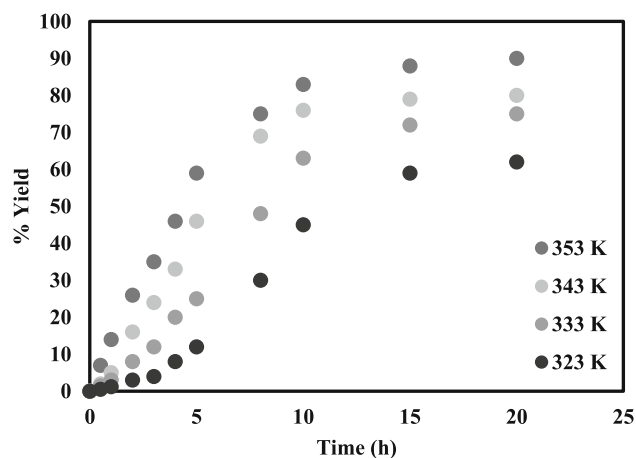
Figure 5. Effect of different oxidants on the yield of Pyridine N-Oxide. Reaction conditions: Pyridine: 2 mmol, oxidant: 6 mmol, 20% W/HAP, 10 mL water, 1200 rpm, 353 K, 20 h.
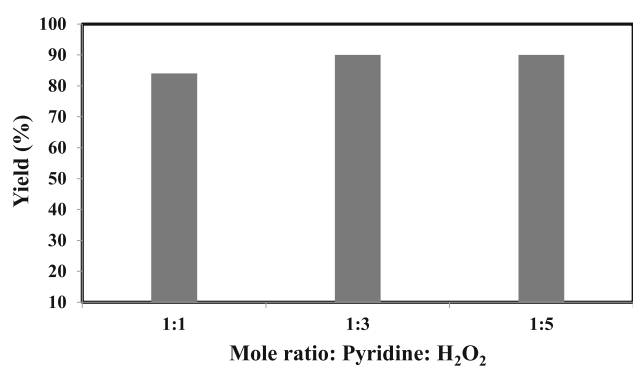
Figure 6. Effect of mole ratio on the yield of Pyridine N-Oxide. Reaction conditions: Pyridine: 2 mmol, 20% W/HAP, 10 mL water, 1200 rpm, 353 K, 20 h.
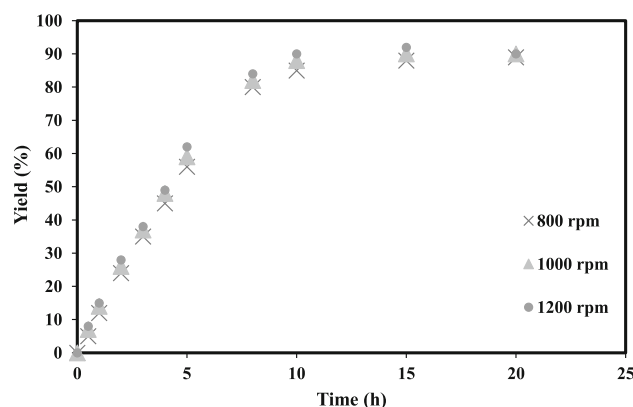

Figure 7. Effect of speed of agitation on the yield of Pyridine N-Oxide. Reaction conditions: Pyridine: 2 mmol, oxidant: 6 mmol, 20% W/HAP, 10 mL water, 353 K, 20 h.

Figure 8. Effect of temperature on the yield of Pyridine N-oxide. Reaction conditions: Pyridine: 2 mmol, H_2O_2: 6 mmol, 20% W/HAP, 10 mL water, 1200 rpm, 20 h.
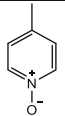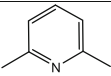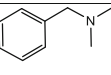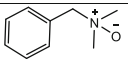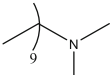
3.5 *Reusability of catalyst*

The reusability of catalysts was studied. The catalyst was separated by centrifuging the reaction mixture after the reaction. The catalyst separated was refluxed in water for 5 h to remove the adsorbed materials from the catalyst surface and dried at 373 K overnight. There was no loss of catalyst during the separation process. The catalyst was used three times. During the third use, we observed a slight decrease in conversion. The leaching experiments were also performed after each cycle, and the amount of tungsten was determined after each cycle. There was marginal leaching of tungsten after each cycle. This must be the reason for a slight decrease in the performance of the catalyst (Figure 11).

4.   Conclusions

A simple and efficient procedure is developed for the synthesis of *N*-oxides using eco-friendly H_2O_2 as an oxidant and reusable W/HAP catalyst. Several catalysts were studied among which W/HAP was found to be the best catalyst among all the screened catalysts. The as-prepared and optimized catalyst was characterized by various analytical techniques such as N_2 adsorption-desorption, SEM, XRD, ICP-OES and

Table 2. *N*-Oxidation of various tertiary amines in the corresponding *N*-Oxide.

Sr. No	Substrate	Product	Yield (%)
1			90[a]
2			89[a]
3			47[a]
4			69[a]
5			20[a]
6			94[b]
7			92[b]
8			89[b]
9			94[b]
10			92[b]
11			91[b]

Reaction conditions: Pyridine: 2 mmol, H_2O_2: 6mmol, 10 mL water, 1200 rpm, 353 K, 20% W/HAP, 20 h

[a]Substrates analysed by HPLC

[b]Substrates analysed by GC
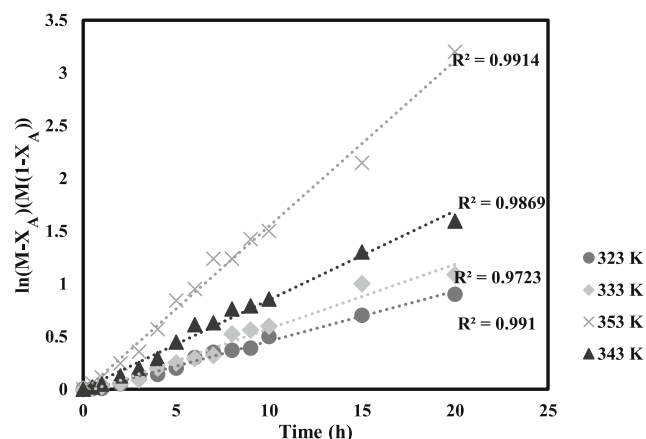
Figure 9.   Plot of $\ln(M-X_A)(M(1-X_A))$ Vs Time.

Table 3.   Rate constants at different reaction temperature.

Temperature (K)	(K) $lit^2.$ mol^{-1} sec^{-1} g^{-1}
323	0.00686
333	0.009440
343	0.01326
353	0.03709

Figure 10.   Activation energy by Arrhenius plot.

FTIR. A broad substrate study was done and a kinetic study was also carried out.

Supplementary Information (SI)

Supplementary Information contains the nitrogen adsorption-desorption isotherm and SEM images of W/HAP catalyst, LCMS and GCMS data of products. Supplementary information is available at www.ias.ac.in/chemsci.
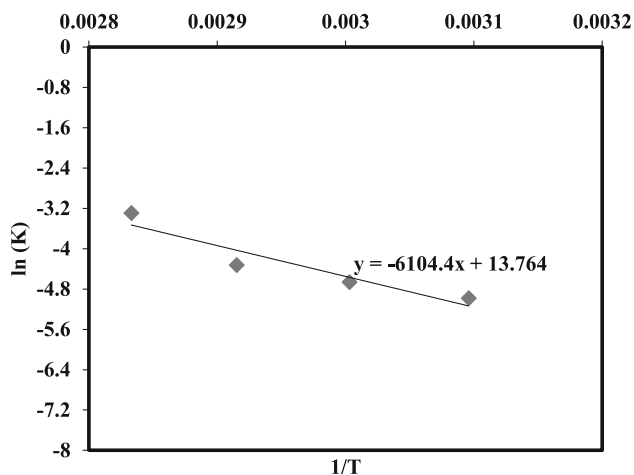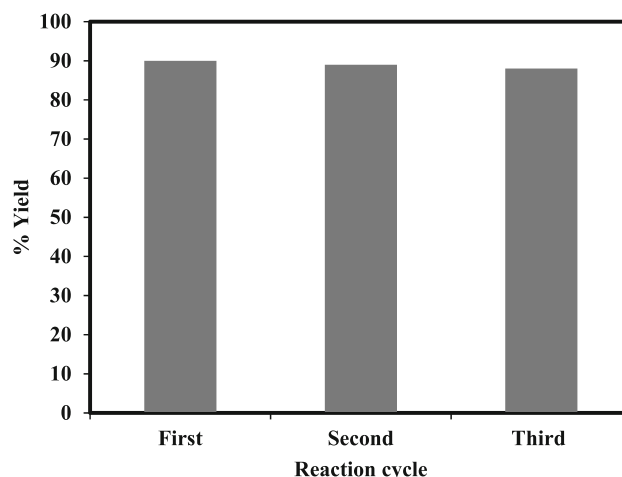

Figure 11.   Catalyst Reusability study. Reaction conditions: Pyridine: 2 mmol, H_2O_2: 6 mmol, 10 mL water, 353 K, 1200 rpm, 20% W/HAP, 20 h.

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