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An efficient synthesis of heterocyclic *N*-oxides over molecular sieve catalysts☆

M. Ramakrishna Prasad, G. Kamalakar, G. Madhavi, S.J. Kulkarni*, K.V. Raghavan

Catalysis & Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract

The present work envisages an eco-friendly route for *N*-oxidation of heterocycles and selective mono *N*-oxidation of substituted pyrazines in good yields using 30% dilute H_2O_2 as an oxidant together with redox molecular sieves (TS-1, Ti–ZSM-5 (30), Ti–MCM-41) as catalysts in aqueous and non-aqueous medium as solvent. The TS-1 catalyst is shown good activity and selectivity in *N*-oxidation of substituted pyridines and pyrazines except –cyano substituted pyridines and pyrazines. The activity has been enhanced with TS-1 catalyst in aqueous medium in comparison with non-aqueous medium as solvent when electron-withdrawing groups are present. The solid catalysts displayed consistent activity for several cycles.

Keywords: Heterocycles; *N*-Oxides; Aqueous/non-aqueous media; Redox molecular sieves

1. Introduction

Preparation of heterocyclic *N*-oxides in a single step finds remarkable utilization as valuable organic intermediates in synthetic organic chemistry and also finds application in pharmaceutical industry [1]. *N*-Oxides hold a key position in the chemistry of heterocyclics. They offer functional group manipulation and structural modification possibilities, which are not accessible by other methods. The compounds are often obtained by the oxidation of heterocycles with acetic acid and hydrogen peroxide [2] ($AcOH/H_2O_2$), *m*-chloroperbenzoic acid [3] (MCPBA), monoperoxyphthalic acid [4], dioxiranes [5], hydrogen peroxide [6] and Caro's acid (H_2SO_5) [7]. More recently the synthesis of heterocyclic *N*-oxides using oxides of rhenium ($MeReO_3$) have been reported by Sharpless and coworkers [8,9]. The catalysts/reagents used were methyltrioxorhenium (MTO), ReO_3, Re_2O_7, $HOReO_3$, $MeReO_3$. These rhenium oxide reagents are water sensitive and undergo changes in the presence of water and so cannot be reused. Dilute hydrogen peroxide is poor oxidizing agent but an inexpensive and readily available oxidant and gives H_2O only as a by-product. Due to this reason there is recent upsurge in the research of this important organic transformation. We have recently reported the synthesis of *N*-oxides in organic solvents in a single step in a reaction time period of 24 h [10].

Molecular sieve catalysts are widely applied in petrochemical reactions as acidic catalysts and in the synthesis of speciality and fine chemicals including the synthesis of aromatics, heterocycles, aliphatic amines, ethers [11] and in oxidative transformations [12]. The recent development in the chemistry

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* Corresponding author. Tel.: +91-40-717-3874; fax: +91-40-717-3387/3757.
E-mail address: sjkulkarni@iict.ap.nic.in (S.J. Kulkarni).

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of zeolites is the incorporation of transition metal ions possessing redox characteristics into the framework of molecular sieves, which can give rise to the catalysts with shape selective oxidation properties. Redox molecular sieves having framework titanium, vanadium, iron or chromium find wide applications in many organic oxidative transformations [13–15]. Redox molecular sieves like titanium silicates with Mobil Five (MFI) topologies have been shown to possess unique catalytic properties in oxidation reactions like olefine epoxidations [16,17], hydroxylation of phenol to catechol and hydroquinone [18], oxidation of alkanes [19,20], conversion of carbonyl compounds to oximes [21,22], the oxidation of secondary amines to corresponding nitrones [23], hydroxylation of benzene, toluene and anisole [24a], epoxidation of cyclohexene, etc. Ti–ZSM-5 was used for the preparation of 2-, 3- or 4-pyridinecarboxaldehyde from corresponding picolyl alcohols [25]. One of the disadvantages of these titanium microporous catalyst is that their pore dimensions are too small to allow access to bulky reactants of the kind that dominate most of the chemical transformations which are of central importance in the fine chemical and pharmaceutical industries. A significant step in this direction, is the preparation and the use of Ti–MCM-41 in which the 'Ti' is incorporated (during synthesis) in the framework of mesoporous silica having a pore diameter of 30 Å [26a,27a]. The structured silica's (Ti–MCM-41) offer great advantages over modified silica gels because the former can be shape selective. Ti–MCM-41 catalysts have been described as potential catalysts for oxidative transformations of bulky organic substrates [26b,27b]. Herein we report the synthesis of heterocyclic *N*-oxides using redox molecular sieves and dilute hydrogen peroxide as oxidant in aqueous and non-aqueous medium as solvent.

2. Experimental

2.1. Preparation of catalysts

ZSM-5 ($SiO_2/Al_2O_3 = 30$) was obtained from Conteka, Sweden. Ti–ZSM-5 (30) was synthesized by post-synthetic modification of HZSM-5 (30). The catalyst was calcined at 800 °C for 10 h before modification. The calcined HZSM-5 (30) was refluxed with titanium isopropoxide (TIOP) in methanol as a solvent for about 6 h. The modified catalyst was dried at 100 °C and calcined at 400 °C for 4 h before use in liquid phase reaction. The incorporation of titanium was proved by solid state NMR which is reported in our earlier paper [25].

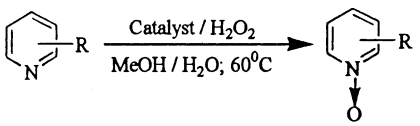
TS-1 (Si/Ti ∼ 33) was prepared by according to the procedure reported by Thangaraj et al. [28,29] with the gel composition tetraethoxy silane (TEOS): 0.03 TIOP:0.4 tetrapropyl ammonium hydroxide (TPAOH):20 H_2O. TEOS, TIOP and TPAOH (20% aqueous solution) were obtained from Fluka. After gel preparation, crystallization was performed in Teflon lined stainless steel autoclave for 7 days at 170 °C. After filtration the catalyst was washed with distilled water, dried and calcined at 550 °C. XRD, elemental analysis and FT-IR confirmed the catalyst structure. The catalyst was exchanged with 10% aqueous ammonium acetate solution twice and calcined at 450 °C before use. Ti–MCM-41 was prepared according to the procedure reported by Corma et al. [30] with the gel composition TEOS:0.15 $Ti(OEt)_4$:0.26 cetyltrimethyl ammonium bromide (CTAB):0.26 tetra ethyl ammonium hydroxide (TEAOH):24.3 H_2O. Titanium tetraethoxide, CTAB, TEAOH (20% aqueous solution) were obtained from Fluka. Crystallization was performed at 100 °C for 48 h. The occluded surfactant was completely removed by calcination. The BET surface area of the calcined catalyst was 744.1 $m^2\,g^{-1}$. The incorporation of the Ti in the framework of mesoporous silica proved by XRD, IR and solid state NMR techniques.

2.2. Oxidation of heterocycles: general procedure

A typical oxidation procedure is as follows. To a mixture of substrate (200 mg), catalyst (10 mg) and solvent water/MeOH (10 ml) at a temperature 60 °C, and 30% dilute hydrogen peroxide (1:2 or 1:4 M) was added dropwise. The reaction was monitored by thin layer chromatography. After the completion of the reaction, the catalyst was separated by filtration. Solvent was removed under reduced pressure and the product was separated by column chromatography (chloroform:methanol) using silica gel column. From entries 1 to 13 and 16 to 24, the product was

separated by column chromatography with solvent system (chloroform:methanol) and for entries 14–15 (acetonitrile:methanol) were used. The products have been characterized by their FT-IR, ^{1}H NMR, mass spectra and melting points. Infrared spectra were recorded on Nicolet 740 FT-IR either as film or KBr pellets. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz instrument in D_2O with TMS as an internal standard. Mass spectra were recorded on VG micromass 7070H and Fennigan Mat 1020 mass spectrometer. Thin layer chromatography was performed on silica gel 60 F_{254} plates procured from E-Merck. Column chromatography was performed using silica gel 60–120 mesh. All starting materials are used in the reaction are commercial grade.

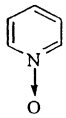
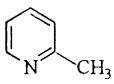
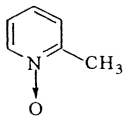
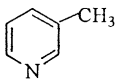
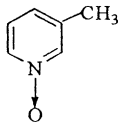
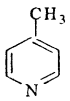
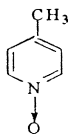
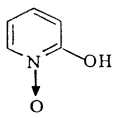
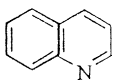
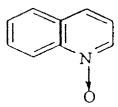
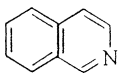
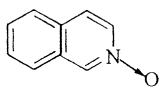
3. Results and discussion



Oxidation of substituted pyridines either containing electron-withdrawing groups like –CN, –Cl, vinyl or electron-donating groups such as methyl was carried out in non-aqueous and aqueous solvent media. The reaction conditions and the results are given in Tables 1 and 2. Ti–ZSM-5 (30) catalyst has shown good activity for the substrates having electron-donating substituents, but it is not much effective in oxidizing the substrates having electron-withdrawing groups in organic compound as a solvent (results presented entry 10 in Table 2). Whereas the present reactions proceeded efficiently in non-aqueous medium (methanol and acetone as co-solvent) over TS-1 catalyst and exhibited good activities with reaction duration of 24 h. In aqueous medium, we have recently observed that reaction could yield the respective *N*-oxide products with shorter times in comparison with our earlier report [10]. The TS-1 catalyst was tested for three cycles after reactivation and found same activity in the yields (Table 3). The blank reaction was also carried out in the absence of catalyst for 4-cyanopyridine with water as solvent showed little conversion in 3 h (Table 3). TS-1 being a siliceous zeolite is hydrophobic in nature. Organic substrates having good solubilities in aqueous media compete more efficiently for active oxidizing center when compared with organic solvent media. This is due to the facile diffusion of the substrate molecules through the channels of the molecular sieve in case of aqueous solvent wherein the substrate encounters a hindered diffusion in the case of organic solvent media. Due to this reason, reaction rates will be much greater in the aqueous media and this fact has been found to be advantageous for the present transformation (results depicted in Tables 1 and 2). Kumar and Bhaumik [24a,b] have also shown significant enhancement in the reaction rates in the hydroxylation of aromatics such as benzene, toluene, anisole and benzyl chloride in solvent free, triphase conditions over TS-1/H_2O system with high stirring rate (conventionally used biphase conditions in the presence of co-solvent). We have observed lesser yields in the case of pyridines having electron-donating groups to form picoline *N*-oxides when compare to the pyridines having electron-withdrawing groups. This dramatic change is significant in the aqueous medium as solvent, where the diffusion of reactants is more due to the hydrophobic channels of TS-1 catalyst. One of the possible reason is picolines are more basic when compared to pyridines having substituted electron-withdrawing groups. In recent past it has been reported that TS-1 posses considerable acidity [31] because of which more basic picolines get strongly adsorbed to these sites and will be difficult to undergo oxidation. In the case of Ti–ZSM-5 (30), synthesized by post-synthetic modification extraframework tetrahedral species like Ti (M^{n+})–O–Si (T) easily oxidizes picolines, all the substituted pyridines are smoothly oxidized without disturbing the functional groups. The high conversions are observed in shorter time periods for the pyridines having electron-withdrawing groups in water as solvent, this can also be correlated to the reactant polarity. The pyridines having electron-withdrawing groups have high reactant polarities, when compared to the picolines. This further enhances water as solvent where high rates of reaction observed for –CN, –Cl, –Br, –vinyl, –COOH, –$CONH_2$ substituted pyridines.

It is observed in –CN substituted pyridines and pyrazines that oxidation and hydrolysis of cyano group occur simultaneously. The reactions are more

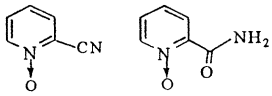
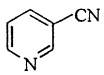
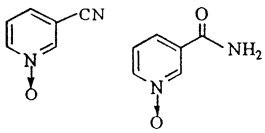
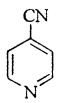
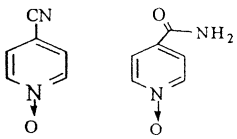
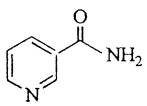
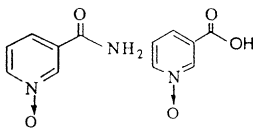
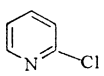
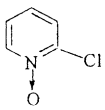
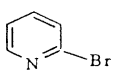
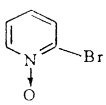
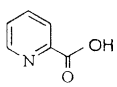
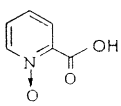
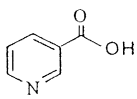
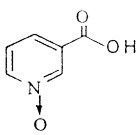
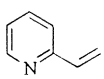
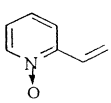
Table 1
Synthesis of pyridine *N*-oxides having electron-donating groups

Entry	Substrate	Time (h)	Product	Molar yields (%)	Specific activity (mmol $(g^{-1} h^{-1})$)[a]
1		16[b] 2.5[c]		91.9[d] 92.9[d]	14.5 93.9
2		5.0[b] 24[c]		92.9[e] 29.9[d]	39.9 2.7
3		6.0[b] 24[c]		95.7[e] 31.9[d]	34.3 2.8
4		5.0[b] 24[c]		94.8[e] 28.9[d]	40.8 2.6
5		25[b] –		91.9[d] –	7.7 –
6		24[b] –		34.6[f] –	2.2 –
7		24[b] –		51.8[f] –	3.3 –

[a] Specific activity: millimoles of the product obtained per gram of catalyst per hour; substrate:30% H_2O_2 = 1:2; amount of solvent = 10 ml.
[b] Methanol as solvent.
[c] Water as solvent.
[d] Catalyst is TS-1.
[e] Ti–ZSM-5 (30).
[f] Ti–MCM-41; catalyst is 5 wt.% of the substrate.

prone towards hydrolysis in aqueous medium than in non-aqueous medium (MeOH, acetone) as solvent and the results are presented in Table 2. Hydrolysis reaction is less pronounced in case of acetone as solvent. TS-1 catalyst has been well documented for epoxidation of lower olefines like propylene, butene, etc. [16,17]. To our surprise 2-vinyl pyridine has selectively resulted in *N*-oxidization without any trace of epoxidized products as observed in ^{1}H NMR. Sharpless and coworkers [8,9] have also reported selective *N*-oxidation of 2-vinyl pyridine with methyl rhenium trioxide catalyst.

Table 2
Synthesis of pyridine *N*-oxides having electron-withdrawing substituents

Entry	Substrate	Time (h)	Product	Molar yield (%)	Specific activity (mmol $(g^{-1}\,h^{-1})$)[a]
8		25[b] 2.0[c]		68.8 + 12.3 50.8 + 41.7	5.3 + 0.9 48.9 + 28.6
9		25[b] 2.0[c] 25[d]		60.4 + 36.5 43.4 + 54.4 73.2 + 11.5	4.6 + 2.8 41.7 + 52.2 5.6 + 0.9
10		25[b] 2.5[c] 3.0[c]		73.9 + 10.0 69.8 + 22.0 6.0 + 0.0[f]	5.7 + 0.8 53.6 + 16.8 3.8 + 0.0
11		24[b] 2.0[c]		97.9 + 0.0 0.0 + 95.5	6.7 82.0
12		24[b] 2.0[c]		91.0 98.0	6.7 86.3
13		– 2.0[c]		– 87.3	– 55.0
14		24[b] 2.5[c]		91.0 91.0	6.2 59.2
15		– 4.0[c]		– 90.5	– 36.8
16		24[b] 2.5[c]		95.0 86.8	7.5 66.0

[a] Specific activity = millimoles of the product obtained per gram of catalyst per hour; substrate:30% H_2O_2 = 1:2; amount of solvent = 10 ml.
[b] MeOH as solvent.
[c] H_2O as solvent.
[d] Acetone as solvent. [e] Catalyst is TS-1.
[f] Ti–ZSM-5 (30); catalyst is 5 wt.% of the substrate.

Table 3
Reusability of TS-1 catalyst[a]

Entry	Catalyst cycles	Time (h)	Molar yield (%)	Specific activity (mmol (g^{-1} h^{-1}))
1	I run	2.5	89.8 (1)	69.0
2	II run	2.5	89.8 (1)	69.0
3	III run	2.5	89.8 (1)	69.0
4	Blank[b]	3	9.0	5.8

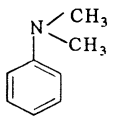
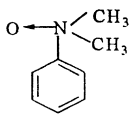
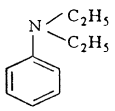
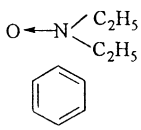
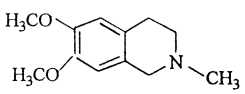
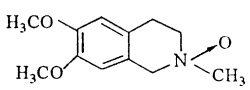
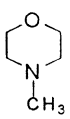
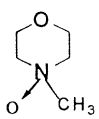
[a] Reaction conditions: substrate = 4-cyanopyridine (0.5 g); substrate:30% H_2O_2 = 1:2; amount of solvent = 5 ml (water); (1) 4-cyanopyridine *N*-oxide.
[b] Reaction carried out without catalyst.

Quinoline and *N*,*N*-dimethylaniline like compounds cannot be oxidized over microporous titanium silicates. The pore diameter of the above catalyst is less (5.6×5.4 Å^2) which hinder these substrates to enter into the channels of the catalyst. In view of the above, Ti–MCM-41 (30 Å) catalyst was employed for the oxidation of these compounds and the products were obtained in quantitative yields and the results are given in Table 4.

3.1. Selective N-oxidation of cyano substituted pyridines

From literature [32] it is known that –cyano substituted compounds acts as catalysts in oxidation reactions at certain pH values (i.e. pH = 8, basic conditions) by forming an intermediate called 'peroxycarboximidic' acid. The mechanism of the formation of amides as by-products in the oxidation of cyano substituted pyridines has been discussed in the same report where the hydrogen peroxide reacts with –cyano under controlled conditions to generate peroxycarboximidic acid intermediate (cyanopyridine carboximidic acid); either by proceeding through cyclization or by reacting with any available reducing agent, it forms pyridine amide *N*-oxide as by-product (detailed mechanism described by Payne [32]). It is mentioned that the same reaction path is more or less common to the 2,3,4-cyanopyridines. In the present studies, the results showed in the Table 2 for cyanopyridines are also shown pyridinamide *N*-oxides

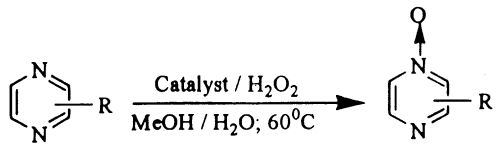
Table 4
N-Oxidation of tertiary amines

Entry	Substrate	Time (h)	Product	Molar yields (%)	Specific activity (mmol (g^{-1} h^{-1}))[a]
17		7[b] –		89.0[d] –	21.0 –
18		7[b] –		94.8[d] –	18.1 –
19		17[b] –		91.0[d] –	5.2 –
20		5.0[b] 9.0[c]		98.0[e] 85.0	38.8 18.7

[a] Specific activity = millimoles of the product obtained per gram of catalyst per hour; substrate:30% H_2O_2 = 1:2; amount of solvent = 10 ml; catalyst is 5 wt.% of the substrate.
[b] MeOH as solvent.
[c] H_2O as solvent.
[d] Ti–MCM-41.
[e] Catalyst is TS-1.

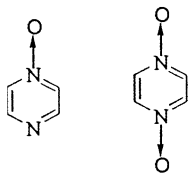
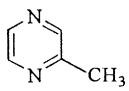
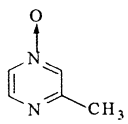
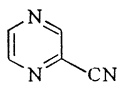
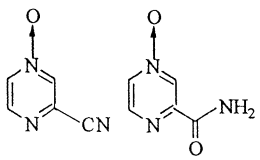
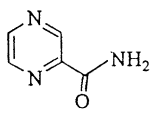
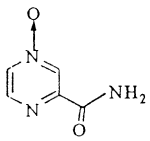
as by-products in agreement with the reaction mechanism discussed above. The formation of the 'carboximidic acid' intermediate may be one of the possible reasons for the completion of the reactions in less time periods in case of cyano substituted pyridines, when water as solvent. The compounds having electron-withdrawing substituents other than –cyano also showed completion of reaction in similar time period in aqueous medium. Hence the catalyst (TS-1) effect cannot be ruled out, i.e. hydrophobicity of the catalyst made reaction to complete in less time period in aqueous medium. Here in the present system, it is also observed that formation of amide disappeared as the quantity of solvent is reduced. In entry 10 (Table 2), solvent (10 ml, water) is 50 times to the substrate (0.2 g, 4-cyanopyridine) where the amide is present. In Table 3, solvent (5 ml) is 10 times to substrate (0.5 g) where the formation of amide is not found. The present results showed that the amount of solvent (water) might be effecting the formation of amide under the conditions studied here.

3.2. Selective mono N-oxidation of substituted pyrazines



In the reactions of substituted pyrazines with 1:4 M ratio of substrate to oxidant, it was observed that mono *N*-oxidation is more favorable but simple pyrazines formed mono *N*-oxide and *N*,*N*-dioxide, the fact can be ascribed to the small pore size of the zeolite and the results are given in Table 5.

Table 5
N-Oxidation of pyrazines[a]

Entry	Substrate	Time (h)	Product	Molar yields (%)	Specific activity (mmol (g^{-1} h^{-1}))
21		5[b] 2[c]		72.8 + 17.1 49.2 + 45.7	36.4 + 8.5 61.5 + 57.1
22		5[b] 2[c]		58.2 53.1	24.7 56.3
23		6[b] 5[c]		56.5 + 13.2 25.8 + 45.2	17.9 + 4.2 9.8 + 17.2
24		– 3[c]		– 93.8	– 50.8

[a] Catalyst is TS-1; substrate:30% H_2O_2 = 1:2; amount of solvent = 10 ml; catalyst is 5 wt.% of the substrate.
[b] MeOH as solvent.
[c] Water as solvent.

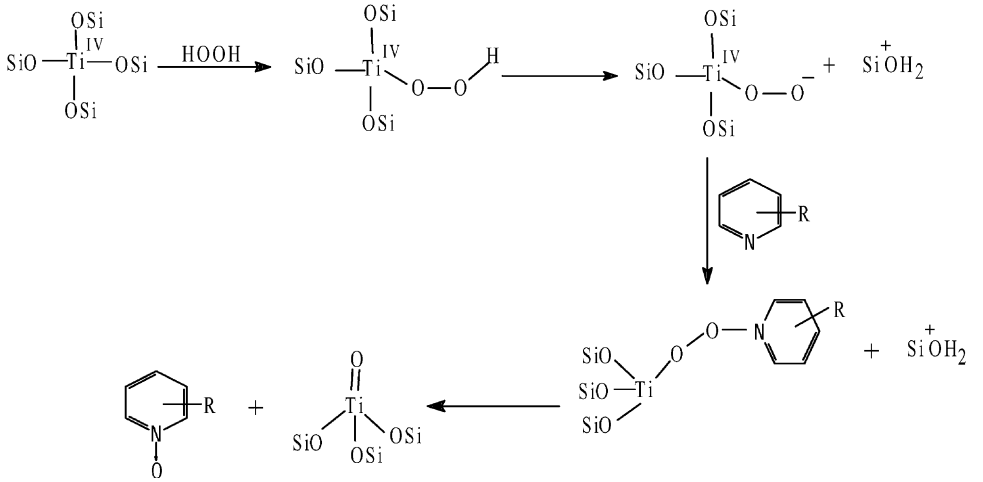


Fig. 1. A plausible mechanism for the oxidation of heteroaromatics to corresponding *N*-oxides over titanium silicate (TS-1) molecular sieves using H_2O_2 as oxidant.

The mechanism of the titanium silicate catalyzed *N*-oxidation reaction is as shown in Fig. 1. The novel activity of the catalyst assumed due to site isolation of monomeric Ti^{IV} centers, which are probably tetrasilanoxytitanium (IV) species [12]. The factor influencing the type of reactivity displayed by the catalyst is the strong hydrophobic nature of channels, thus facilitating selective adsorption of the hydrophobic substrate rather than water. Second important factor is the effect of confinement of the active site to a cavity of molecular dimensions. In Ti–MCM-41, Ti species present in the mesoporous framework are predominantly in tetrahedral coordination with a possibility of some Ti sites in six coordination state [27b] and the oxidation activity is believed due to site isolated Ti species present in mesoporous framework.

4. Conclusion

In summary, a simple methodology for the synthesis of heterocyclic *N*-oxides is described with cheap oxidizing agent 30% dilute H_2O_2 and water as solvent in a single step. This accelerated process is catalyzed by a small amount of reusable TS-1 as catalyst (5 wt.%). The present methodology, in which the only by-product is water, is eco-friendly. The high activity of TS-1 (Si/Ti = 33) is due to the large number of site isolated 'Ti' active centers per unit volume. Water is non-toxic and eco-friendly solvent and gave very good yields in less time.

4.1. Structural data of organic compounds

Pyridine N-oxide ***(1)***. Colorless solid, which becomes liquid by exposing in atmosphere, m.p.: 62–63 °C (lit. [2]). The compound purified over silica column ($CHCl_3$:MeOH, 9:1). FT-IR (KBr) 3076, 1470, 1265, 1176, 1020, 840, 775, 680 cm^{-1}. ^1H NMR (200 Hz, D_2O): δ 7.4 (m), 8.3–8.4 ppm (m). MS (EI) *m*/*z* 95 (82, M^+), 78 (100), 51 (71), 39 (35).

2-Picoline N-oxide ***(2)***. Hygroscopic oil (easily liquefied) (lit. [2]). The crude product was separated over silica column with MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3030, 1369–1515, 1190–1282, 1111, 1052, 699, 780, 763 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 2.52 (3H, s, $-CH_3$), 7.1–7.3 (3H, m, aromatic), 8.2–8.29 ppm (1H, m, aromatic). MS (EI) *m*/*z* 109 (M^+, 94), 92 (100), 65 (80.5), 51 (20.6), 39 (31.3).

3-Picoline N-oxide ***(3)***. Hygroscopic oil (lit. [2]). The crude product was separated over silica column with MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3030, 1470–1408, 1282, 1162, 1020, 943, 787, 746, 675 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 2.28 (3H, s, $-CH_3$), 7–7.29 (2H, quintet, J = 9.3 Hz, J =

4.65 Hz), 8.0–8.08 ppm (2H, d, $J = 9.3$ Hz). MS (EI) *m/z* 109 (M^+, 90), 92 (100), 65 (75), 51 (25), 39 (25).

*4-Picoline N-oxide (**4**)*. White crystals, m.p.: 182 °C (lit. [33]). The crude product was separated over silica column with MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 2941, 1428–1492, 1176–1250, 1041, 854, 757 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.43–7.48 (2H, d, $J = 7.05$ Hz), 8.14–8.2 ppm (d, 2H, $J = 7.05$ Hz). MS (EI) *m/z* 109 (M^+, 100), 92 (92), 65 (70), 51 (33), 39 (31).

*2-Hydroxy pyridine N-oxide hydrate (**5**)*. Colorless needles (recryst. MeOH), m.p.: 148–150 °C. The crude product was purified over silica gel column in MeOH:$CHCl_3$, 0.2:9.8. FT-IR (KBr) 2941–2857, 2439, 1639, 1538, 1369, 1176, 1142, 892, 847, 757 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 6.20 (t, 1H, $J = 6.73$ Hz, $J = 6.9$ Hz), 6.51 (d, 1H, $J = 9.04$ Hz), 7.38 (t, 1H, $J = 9.04$ Hz, $J = 6.73$ Hz), 7.90 ppm (d, 1H, $J = 6.94$ Hz). MS (EI) *m/z* 129 (M^+, 15), 113 (92.5), 93 (7.5), 78 (100), 59 (26.2), 51 (43.7), 39 (32.5), 36 (52.5).

*Quinoline N-oxide (**6**)*. Colorless solid, m.p.: 52–55 °C. The crude product was purified over silica gel column in MeOH:$CHCl_3$, 0.2:9.8. FT-IR (KBr) 3448, 3030, 1492, 1428, 1388, 1298, 1265, 1219, 1204, 1176, 1136, 1086, 1052, 1010, 877, 826, 763, 722 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.1–7.8 (m, 4H), 8.1 (m, 2H), 8.5 ppm (d, 1H, $J = 10.8$ Hz). MS (EI) *m/z* 145 (M^+, 5), 129 (100), 102 (20), 76 (6.1), 51 (10.7).

*Isoquinoline N-oxide (**7**)*. Colorless solid, m.p.: 105–108 °C. The crude product was purified over silica gel column in MeOH:$CHCl_3$, 0.2:9.8. FT-IR (KBr) 3040, 3025, 1612, 1562, 1428, 1369, 1315, 1250, 1190, 1176, 1111, 909, 813, 746, 729 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.55–7.85 (m, 4H), 7.9 (d, 1H, $J = 10.2$ Hz), 8.1 (d, 1H, $J = 10.2$ Hz), 8.7 ppm (s, 1H). MS (EI) *m/z* 145 (M^+, 4.7), 129 (100), 102 (23.8), 76 (11.9), 51 (16.6).

*2-Cyanopyridine N-oxide (**8a**)*. White solid (recryst. MeOH). The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 3400–2900 (broad), 2229, 1443, 1271, 1166, 1050, 860, 750 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.7–7.9 (2H, m, $J = 5.6$ Hz), 8.22–8.32 (1H, d, $J = 5.6$ Hz), 8.4–8.5 ppm (1H, d, $J = 5.6$ Hz). MS (EI) *m/z* 122 (7.5, M^+), 120 (25), 95 (33.8), 78 (100), 52 (28.8), 51 (40.0), 39 (32.5).

*2-Pyridine amide N-oxide (**8b**)*. White solid (recryst. acetone), m.p.: 160–161 °C (lit. [34], 160–161 °C). FT-IR (KBr) 2900–3400 (broad), 1685, 1589, 1396, 1311, 1086, 1007, 956, 767 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.7–7.9 (2H, m, $J = 5.6$ Hz), 8.22–8.32 (1H, d, $J = 5.6$ Hz), 8.4–8.5 ppm (1H, d, $J = 5.6$ Hz). MS (EI) *m/z* 138 (M^+, 58.7), 122 (7.5), 120 (25.0), 95 (33.8), 78 (100), 52 (28.8), 51 (40.0), 39 (32.5).

*3-Cyano pyridine N-oxide (**9a**)*. White solid (recryst. MeOH), m.p.: 188–189 °C. The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 3350–2900 (broad), 2220, 1481, 1201, 1151, 1025, 934, 742.1 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.78 (1H, t, $J = 7.4$ Hz), 8.11 (1H, d, $J = 8$ Hz), 8.58 (1H, d, $J = 9$ Hz), 8.82 ppm (1H, d). MS (EI) *m/z* 120 (21.25), 104 (7.5), 64 (11.2), 44 (100).

*4-Cyanopyridine N-oxide (**10a**)*. White solid (recryst. MeOH), m.p.: 182–183 °C. The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 2941, 2231, 1470, 1282, 1176, 1030, 847, 709 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.9–8.0 (2H, d, $J = 8$ Hz) 8.4–8.46 ppm (2H, d, $J = 8$ Hz). MS (EI) *m/z* 122 (10.4), 120 (M^+, 100), 104 (20.8), 65 (41.8), 64 (43.3), 38.0 (29.8).

*4-Pyridineamide N-oxide (**10b**)*. Colorless solid (recryst. H_2O), m.p.: 311–312 °C (lit. [34], 312–313 °C). The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 3367, 3149, 1681, 1397, 1233, 1119, 1025, 840, 700 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.9 (2H, d, $J = 8$ Hz), 8.4 ppm (2H, d, $J = 8$ Hz). MS (EI) *m/z* 138 (M^+, 57), 122 (6), 120 (25), 95 (38), 78 (100).

*Nicotinamide N-oxide (**11**)*. White solid (recryst. H_2O), m.p.: 284–285 °C (lit. [34], 285–286 °C). The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 3333–2857 (broad), 1695, 1490, 1388, 1234, 1162, 1030, 934, 746, 650 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.72 (1H, t, $J = 7.4$ Hz, $J = 7.4$ Hz), 8.08 (1H, d, $J = 8$ Hz), 8.46 (1H, d, $J = 6$ Hz), 8.7 ppm (s, 1H). MS (EI) *m/z* 138 (100), 122 (23.5), 106 (8.8), 94 (7.3), 78 (22.0), 63 (13.2), 50 (17.9), 44 (22.3), 39 (29.8).

*2-Chloro pyridine N-oxide hydrate (**12**)*. Rhombs (recryst. ether/EtOH), m.p.: 66–67 °C (lit. [35], 66–68 °C). The crude product was purified by silica gel column in MeOH:$CHCl_3$, 2:8. FT-IR (KBr) 3409–2843.6, 1644, 1589, 1463, 1284, 1207, 1052.1,

1012, 857, 770 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.5–7.6 (1H, t, $J = 3$ Hz, $J = 8$ Hz), 7.65–7.75 (1H, t), 7.8–7.87 (1H, d), 8.44–8.5 ppm (1H, d, $J = 8$ Hz). MS (EI) *m/z* 145 (M^+, 15), 131 (28.8), 129 (100), 111 (23.8), 95 (11.3), 95 (11.3), 66 (36.3), 55 (12.5), 39 (81.25).

2-Bromopyridine N-oxide ***(13)***. Colorless crystals (recryst. ether), m.p.: 135–136 °C (lit. [36], 135–136 °C). The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3560–2823 (broad), 1644.3, 1465, 1411, 1271, 1228, 1132, 839, 767 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.88(2H, t, $J = 11.1$ Hz, $J = 5.4$ Hz), 8.28–8.4 (1H, $J = 11.1$ Hz), 8.8–8.9 ppm (1H, t). MS (EI) *m/z* 175 (M^+, 33.8), 173 (37.5), 94 (12.5), 78 (23.8), 66 (60), 63 (25), 39 (100).

2-Picolic acid N-oxide ***(14)***. White solid (cryst. EtOH, H_2O), m.p.: 161–164 °C (lit. [34], 163–164 °C). The crude product was separated over silica column in MeOH:ACCN, 2:8. FT-IR (KBr) 3030–2857 (broad), 1724–1515, 1428, 1282, 1250, 1149–1123, 980, 847, 746, 632 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 8.6–8.8 (2H, dd, $J = 16$ Hz, $J = 5.3$ Hz), 8.3–8.46 (1H, d, $J = 5.3$ Hz), 8.06–8.2 ppm (1H, d, $J = 5.3$ Hz). MS (EI) *m/z* 139 (M^{+1}, 7.5), 124 (16.3), 106 (27.5), 95 (27.5), 80 (49.0), 79 (100), 78 (100), 77 (40), 76 (37.5), 75 (31.3).

3-Picolic acid N-oxide ***(15)***. White solid (recryst. EtOH), m.p.: 260–262 °C (lit. [34], 259–260 °C). The crude product was purified by silica gel column in MeOH:ACCN, 2:8. FT-IR (KBr) 3125–2857 (broad), 1724, 1492–1408, 1333–1265, 1219–1136, 1111–1063, 1020, 925, 757, 675 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 7.68–7.73 (1H, t), 8.05–8.1 (1H, d, $J = 5.26$ Hz), 8.23–8.25 (1H, d, $J = 2.6$ Hz), 8.7 ppm (1H, s). MS (EI) *m/z* 138 (M^+, 100), 122 (32.5), 108 (7.5), 94 (23.8), 78 (35.0), 66 (31.3), 63 (36.3), 53 (35), 51 (32.5), 44 (47.5), 39 (81.25).

2-Vinyl pyridine N-oxide ***(16)***. Yellow colored hygroscopic solid. The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3571, 3030, 1851, 1587, 1428, 1298, 1197, 1133, 1020, 987, 884, 741 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 5.94 (olefinic 1H, d, $J_{AX} = 11.9$ Hz), 6.2 (olefinic 1H, d, $J_{BX} = 19$ Hz), 7.32 (aromatic 1H, quartet, $J_{AB} = 3$–4 Hz), 7.6 (aromatic 1H, t, $J^1_{AA} = 2$ Hz), 7.82 (1H, t, $J^1_{AA} = 4$ Hz, $J_{AB} = 2$ Hz), 7.98 (1H, d, $J^1_{AA} = 4$ Hz), 8.4 ppm (H, d). MS (EI) *m/z* 121 (M^+, 86.3), 92 (100), 78 (68.8), 65 (75), 51 (43.8), 49 (38.8).

N,N-Dimethyl aniline N-oxide ***(17)***. Yellow colored hygroscopic solid (lit. [37]). The compound purified over silica gel column with solvent system MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 2941, 1587, 1492, 1351, 1219, 1190, 1162, 1063, 1030, 1000, 943, 746, 689 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.32 (s, 6H), 7.18 (m, 3H), 7.55 ppm (m, 2H). MS (EI) *m/z* 137 (M^+, 51.2), 121 (37.5), 120 (48.7), 107 (22.5), 94 (63.7), 77 (93.7), 65 (43.7), 51 (70), 44 (100).

N,N-Diethyl aniline N-oxide ***(18)***. Brown color hygroscopic solid. The compound purified over silica gel column with solvent system MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 1369–1333, 1265, 1219, 1176, 1123, 1086, 990, 862, 793, 740, 684 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.15 (3H, t, $J = 7$ Hz), 3.34 (q, 2H, $J = 7$ Hz), 6.6 (m, 3H), 7.13 ppm (m, 2H). MS (EI) *m/z* 149 (M^+, 28.7), 134 (100), 106 (45), 77 (35), 51 (12.5), 44 (11.2).

6,7-Dimethoxy N-methyl tetrahydroisoquinoline ***(19)***. Hygroscopic solid. The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3446, 2969, 1646, 1507, 1461, 1353, 1230, 1120, 1092, 984, 876, 823 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 3.42 (s, 3H), 3.46 (t, 2H, $J = 6.7$ Hz), 3.66 (t, 2H, $J = 6.8$ Hz), 3.95 (s, 6H), 4.09 (s, 2H), 6.50 (s, 1H), 6.52 ppm (s, 1H). MS (EI) *m/z* 223 (M^+, 7.5), 206 (74.6), 190 (41.8), 164 (100), 150 (19.4), 121 (22.3), 77 (22.4), 50 (47.7), 36 (37.3).

Morpholine N-oxide ***(20)***. Colorless solid, m.p.: 180–183 °C. The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3571–2857, 1470, 1315, 1250, 1123, 1098, 990, 934, 862 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 3.19–3.3 (m, 2H), 3.25–3.33 (s, 3H), 3.5–3.68 (m, 2H), 3.88–3.98 (m, 2H), 4.07–4.22 ppm (m, 2H). MS (EI) *m/z* 117 (M^+, 7.5), 73 (78.8), 60 (100), 45 (43.8), 42 (68.8).

Pyrazine N-oxide ***(21a)***. Colorless solid (cryst. benzene), m.p.: 112–114 °C (lit. [38], 113–114 °C). The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3024, 1648, 1594, 1435, 1271, 1034, 1004, 860, 805 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 8.38 (2H, d, $J = 8$ Hz), 8.64 ppm (2H, d, $J = 8$ Hz). MS (EI) *m/z* 96 (100), 71 (7.5), 46 (68.8), 44 (55), 40 (22.5).

Pyrazine N,N-dioxide ***(21b)***. Colorless solid (cryst. MeOH), m.p.: 287–292 °C (lit. [38], 285–295 °C). The

crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3025, 1649, 1595, 1436, 1384, 1305, 1213, 1034, 1005, 861, 806 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 8.4 ppm (4H, s, symmetric aromatic hydrogens). MS (EI) *m/z* 112 (M^+, 100), 96 (50), 52 (25), 40 (20).

*2-Methyl pyrazine-4-N-oxide (**22**)*. Colorless solid, m.p.: 87–89 °C (lit. [38], 91–92 °C). The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3039, 2941, 1587, 1470, 1398, 1300, 1250, 1156, 1041, 829, 636 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 8.2–8.6 (2H, d, $J = 10.52$), 8.32 (1H, s) 8.35–8.4 ppm (1H, d, $J = 10.52$). MS (EI) *m/z* 110 (M^+, 100), 66 (15), 42 (15), 39 (25).

*2-Cyano pyrazine-4-N-oxide (**23a**)*. Colorless solid, m.p.: 155–156 °C (lit. [39], 157–159 °C). The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3020, 2930, 1580, 1433, 1300, 1250, 1020, 855, 810 cm^{-1}. ^1H NMR (D_2O, 200 MHz): δ 8.83–8.9 (m, 1H), 8.92–8.98 (m, 1H), 9.1–9.6 ppm (s, 1H). MS (EI) *m/z* 121 (97.5), 105 (100), 78 (55), 51 (15).

*Pyrazinamide N-oxide (**24**)*. Pale yellow solid, m.p.: 179.3–180 °C. The crude product was separated over silica column in MeOH:$CHCl_3$, 1:9. FT-IR (KBr) 3247, 1689, 1601, 1372, 1167, 1707, 1050, 1021, 876, 779, 652, 542 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO d_6, 200 MHz): δ 7.5–7.71 (2H, broad d, $–NH_2$), 8.56–8.62 (1H, m), 9.36–9.41 ppm (1H, m). MS (EI) *m/z* 123 (M^+, 77.5), 80 (100), 53 (75), 54 (66.3), 45 (31.3).

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