

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

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

Catalysis and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad-500 007, India.
E-mail: root@csiict.ren.nic.in

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Heterocyclic *N*-oxides have been synthesized in very high yields over redox molecular sieve catalysts in the presence of H₂O₂.

N-Oxides hold a key position in the chemistry of heterocyclics in that they offer functional group manipulation and structural modification possibilities, which are not accessible by other methods. Recently the synthesis of heterocyclic *N*-oxides using oxides of rhenium (MeReO₃) have been reported by Sharpless *et al.*^{1,2} The catalysts/reagents used were methyltrioxirhenium (MTO), ReO₃, Re₂O₇, HOREO₃, Me ReO₃. These rhenium oxide reagents are water sensitive and undergo changes in the presence of water and so cannot be reused. The compounds are often obtained by the oxidation of heterocycles with acetic acid and hydrogen peroxide³ (AcOH/H₂O₂), *m*-chloroperbenzoic acid (MCPBA),⁴ monoperoxyphthalic acid,⁵ dioxiranes,⁶ hydrogen peroxide⁷ and more recently Caro's acid (H₂SO₅).⁸ Dilute hydrogen peroxide is a poor oxidizing agent but an inexpensive and readily available oxidant and gives H₂O only as a by-product. Recently titanium-containing molecular sieves like TS-1, TiZSM-5 (prepared by post-synthetic modification) with MFI topologies and mesoporous materials like TiMCM-41 have been found to possess very good redox properties in catalyzing many oxidation reactions^{9–12} *e.g.* olefin epoxidation, hydroxylation, oxidation of alkanes and conversion of carbonyl compounds to oximes. TiMCM-41, by virtue of its bigger pore diameter and redox property, overcomes the barrier of spatial limitation and has been used to oxidize bigger molecules like 2,6-di-*tert*-butylphenol and cinnamyl alcohol. The preparation of *N*-oxides of mono binuclear heterocycles suffers mainly from the disadvantage of very low yields of product formation in spite of using very costly and stoichiometric amounts of reagents.¹³ Titanium-containing redox molecular sieves in the presence of an oxidant like H₂O₂ have the advantage of reusability, no catalyst separation problems, and no environmental disposal problems. In order to overcome problems associated with homogenous reactions, heterogeneous catalysts like molecular sieve materials were employed for the oxidation of heterocycles.

Titanium silicalite (TS-1), TiZSM-5(30) and TiMCM-41 are prepared^{14,12,15} in our laboratory by the procedures reported earlier. All these catalysts were characterized using XRD and FTIR analyses and the results are in accordance with the reported literature. Oxidation of substituted pyridines and quinolines and, substituted isoquinolines have been carried out and the results are presented in Table 1. In our studies it is observed that pyridines having electron donating substituent groups such as –CH₃, –OH or vinyl are oxidized rapidly in a single step to yield the corresponding *N*-oxides as the exclusive oxidation product when the substrate is treated with 5% wt/wt catalyst and 2 equiv. of 30% H₂O₂. However, pyridines containing electron withdrawing substituent groups like –CN, –NO₂ or –CONH₂ take comparatively longer to reach the quantitative reaction yield of the product. It can be understood that a peroxo species like Ti(μ-O₂) oxidizes the nitrogen of the heterocycle which results in the corresponding heterocyclic *N*-oxide. TiMCM-41 was used as catalyst for the oxidation of

Table 1 Oxidation of aromatic heterocycles: variation of substrate

Substrate	Yield of the product (%) (reaction time)	Substrate	Yield of the product (%) (reaction time)
2-Cyanopyridine	81.3 ^a (25 h)	2-Picoline	93.0 ^b (5 h)
3-Cyanopyridine	97.3 ^a (25 h)	3-Picoline	96.0 ^b (6 h)
4-Cyanopyridine	84.0 ^a (24 h)	4-Picoline	95.0 ^b (5 h)
2-Chloropyridine	91.0 ^a (24 h)	<i>N,N</i> -Dimethylaniline	89.0 ^c (7 h)
2-Carbamoylpyridine	98.0 ^a (24 h)	<i>N,N</i> -Diethylaniline	95.0 ^c (7 h)
2-Picolinic acid	91.0 ^a (24 h)	<i>N</i> -Methyl-3,4-dimethoxyisoquinoline	83.3 ^c (17 h)
2-Hydroxypyridine	92.0 ^a (25 h)	Quinoline	34.7 ^c (24 h)
2-Vinylpyridine	95.0 ^a (24 h)	Isoquinoline	52.0 ^c (24 h)

^a TS-1. ^b TiZSM-5(30). ^c TiMCM-41. Products were characterized by MS, NMR and IR techniques, catalyst was washed and reused. Product was corresponding *N*-oxide.

quinolines, isoquinolines and *N,N*-dimethylaniline and the products were obtained in quantitative yields. The effect of varying the solvent was also studied for this reaction and the results are presented in Table 2. Methanol, acetone and acetonitrile were found to be better solvents than dichloromethane and chloroform with TS-1 as catalyst. The performance of the catalysts was also studied for 3-cyanopyridine and the results are presented in Table 3. TS-1 and TiZSM-5(30) gave better yields of the product, indicating the better redox system of the materials reported. The effect of varying the reaction temperature for the oxidation of 3-cyanopyridine was studied and the results are presented in Table 4. Methanol at a reaction temperature of 60 °C gave the optimum yield of the product.

All the starting materials and solvents were obtained commercially. A typical oxidation of a substituted pyridine was

Table 2 Oxidation of 3-cyanopyridine: variation of solvent

Solvent	Isolated yield(%) of <i>N</i> -oxide	Reaction time (h)
Acetone	85.1	25
Methanol	97.3	24
Acetonitrile	90.9	25
DCM	—	25

Reaction temp. 60 °C, substrate; oxidant $\frac{1}{2}$; catalyst TS-1.

Table 3 Oxidation of 3-cyanopyridine: variation of catalyst

Catalyst	Isolated yield(%) of <i>N</i> -oxide	Reaction time (h)
TiZSM-5(30)	73.3	26
TS-1	97.3	25
TiMCM-41	53.0	25

Reaction temp. 60 °C; substrate; oxidant = $\frac{1}{2}$, solvent methanol.

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Table 4 Oxidation of 3-cyanopyridine: variation of reaction temperature

Reaction temp. °C	Isolated yield(%) of <i>N</i> -oxide	Reaction time (h)
Room temp.	22.7	23
40	38.8	24
50	52.9	24
60	97.0	25

Substrate: oxidant = $\frac{1}{2}$, solvent methanol; catalyst TS-1.

carried out as follows. A mixture of 4-cyanopyridine (10.0 g, 0.096 mol) and TS-1 (500 mg) in 40 ml of methanol as solvent was refluxed in the presence of 30% aq. H₂O₂ (19.8 ml, 0.192 mol) for 24 h. The progress of the reaction was monitored by TLC. Once the reaction was complete the catalyst was removed by filtration and the product isolated from the solvent by vacuum evaporation. The isolated product by this procedure, contained exclusively the corresponding *N*-oxide as observed from the ¹H NMR and mass spectra. 4-Cyanopyridine gave 9.6 g of corresponding *N*-oxide without any trace of the by-product. The products were also confirmed by mass and ¹H NMR techniques.

Notes and references

- 1 C. Copéret, H. Adolfsson, J. P. Chiang, A. K. Yudin and K. Sharpless, *J. Org. Chem.*, 1998, **63**, 1740.
- 2 C. Copéret, H. Adolfsson, T.-A. V. Khuong, A. K. Yudin and K. B. Sharpless, *Tetrahedron Lett.*, 1998, **39**, 761.
- 3 V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 1954, **76**, 1286.
- 4 P. Albini, *Heterocyclic N-oxides*, ed. B. Raton, CRC Press, FI, 1991, p. 31.
- 5 P. Brougham, M. S. Cooper, D. A. Cummersoni, H. Heaney and N. Thompson, *Synthesis*, 1987, 1015.
- 6 R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847.
- 7 G. B. Payne, P. H. Deming and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 659.
- 8 J. G. Robke and E. J. Behrman, *J. Chem. Soc. D*, 1971, 2867.
- 9 J. M. Thomas, *Nature*, 1994, **368**, 289.
- 10 R. A. Sheldon, *CHEM TECH*, 1991, **21**, 566.
- 11 A. Corma, M. Domine, J. A. Gaibam, J. L. Jorda, M. T. Navarro, F. Rey, J. P. Pariente, J. Tsui and L. T. Nemeth, *Chem. Commun.*, 1998, 2211.
- 12 G. Kamalakar, S. J. Kulkarni and K. V. Raghavan, *Microporous Mesoporous Mater.*, 1999, **29**, 283.
- 13 W. C. E. Arends, R. A. Sheldon, M. Wallau and U. Schuchardt, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1144.
- 14 B. Notari, *Stud. Surf. Sci. Catal.*, 1991, **60**, 343.
- 15 A. Corma, M. T. Navarro, J. P. Pariente and F. Sanchez, *Stud. Surf. Sci. Catal.*, 1994, **84**, 69.