A Simple and Efficient Method for the Preparation of Pyridine *N*-Oxides

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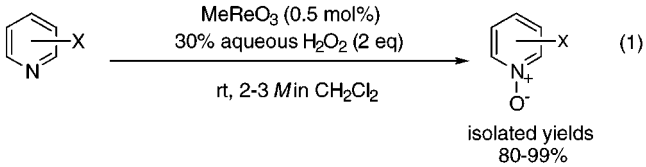
We report here on a practical and efficient method for the *N*-oxidation of pyridines to the corresponding *N*-oxides (eq 1). We have recently shown that the addition

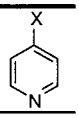


(1)

of 3-cyanopyridine improves the MTO-catalyzed epoxidation of terminal alkenes with 30% aqueous H_2O_2.[1,2] During this study, we have also observed that oxidation of the ligand to 3-cyanopyridine *N*-oxide was taking place late in the reaction.[3] In the absence of alkene, the use of 2 equiv of H_2O_2 with 0.5 mol % of MTO converted 3-cyanopyridine to its *N*-oxide, which was isolated in an analytically pure form (88% yield) by a simple extractive workup.[4] In the absence of MTO, under otherwise identical conditions, there was no sign of reaction even after several days. Oxidation of pyridines to the corresponding *N*-oxides can be achieved in many ways; however, methods depending on *m*CPBA as oxidant seem to be the most common.[5] Such peracid-based procedures are very reliable for most pyridines, but usually less so for electron deficient ones. In addition to its sometimes greater reactivity, this new method is performed very concentrated (>2 M in substrate) using an environmentally friendly oxidizing agent, *i.e.* 30% aqueous H_2O_2, and does not generate byproducts other than water so that workup is simple.

These features, along with the importance of *N*-oxides as synthetic intermediates, led us to investigate its scope

Table 1. MTO-Catalyzed Oxidation of Pyridines with 30% Aqueous H_2O_2[a]

Substituents (X)			
CN	94(24)[b]	86(17)[c]	79(17)[c]
CO_2Me	-	84(17)[c]	98(17)[c]
Acetyl	-	81(24)[c]	81(24)[c]
F	-	86(23)[d]	-
Cl	52[b,e]	84(17)[d]	82(5)[c]
Br	-	94(23)[d]	-
3'-Phenylpropyl	-	-	94(17)[d]
Me	90(24)[b]	92(24)[c]	96(24)[d]
MeO	-	-	87(15)[c]

[a] Conversion >99% unless otherwise noted, isolated yields in %, reaction time (h) in parentheses. [b] Using 5 mol% MTO. [c] Using 0.5 mol% MTO. [d] Using 0.2 mol% of MTO. [e] NMR yield, 10% of 2-chloropyridine remained unreacted after 40 h.

(Table 1). One notes that 3- and 4-substituted pyridines, regardless of their electronic nature, give high yields of the corresponding *N*-oxides using only 0.2−0.5 mol % of MTO. On the other hand, the most simple 2-substituted pyridines (Table 1, first column) require high catalyst loading, typically 5 mol %, to reach both full conversion and high yields. The latter pyridines also reveal little to no binding to MTO based on ^{1}H NMR experiments, which may suggest that coordination of the pyridine to the metal center is somehow helpful for achieving high turnovers.[1,6] However, the rates and catalyst loading in entries 1−4 in Table 2 indicate that with polysubstituted pyridines, the deleterious effect of a 2-substituent can be negated by other factors.

In our studies of the pyridine-assisted MTO-catalyzed epoxidation process,[1,2] we had found that higher concentrations of pyridine, instead of further accelerating the epoxidation catalysis actually retarded it by destroying the catalyst (vide infra). Hence, it was surprising to find that providing no olefin was present, MTO can be an excellent *and* quite stable catalyst for the oxidation of pyridines. If excessive amounts of pyridine (>20−50 mol

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(1) Copéret, C.; Adolfsson, H.; Sharpless, K. B. *Chem. Commun.* **1997**, 1565.

(2) (a) Rudolph, J.; Reddy, K. L.; Chiang, J. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 6185. (b) For a related catalytic system using bis(trimethylsilyl)peroxide as stoichiometric oxidant: Yudin, A. K.; Sharpless, K. B. *Ibid.* **1997**, *119*, 11536.

(3) It is worth pointing out that 3-cyanopyridine *N*-oxide slows down the rate of epoxidation.

(4) There have been several reports on MTO-catalyzed oxidations of amines and anilines: (a) Murray, R. W.; Iyanar, K.; Chen., J.; Wearing, J. T. *Tetrahedron Lett.* **1995**, *36*, 6415. (b) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7728. (c) Murray, R. W.; Iyanar, K.; Chen., J.; Wearing, J. T. *Tetrahedron Lett.* **1996**, *37*, 805. (d) Goti, A.; Nanelli, L. *Ibid.* **1996**, *37*, 6025. (e) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *J. Org. Chem.* **1996**, *61*, 8099. (f) Yamazaki, S. *Bull. Soc. Chem. Jpn.* **1997**, *70*, 877.

(5) (a) For a review on oxidation of pyridines, see: Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967; Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991. (b) For some examples of *N*-oxidation using peracids: Edwards, D. C.; Gillespie *Tetrahedron Lett.* **1966**, 4867. (c) For oxidation with a combination of hydrogen peroxides and acids/anhydrides: Chivers, G. E.; Suschitzky, H. *J. Chem. Soc., Chem. Commun.* **1971**, 28. Takabe, K.; Yamada, T.; Katagiri, T. *Chem. Lett.* **1982**, 1987. Tortorella, V. *J. Chem. Soc., Chem. Commun.* **1966**, 308. Kaczmarek; Balicki, R.; Nantka-Namirski, P. *Chem. Ber.* **1992**, *125*, 1965. (d) For oxidation with DMDO: Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. {e) For some examples of transition metal catalyzed oxidation of pyridines: Tolstikov, G. A.; Jemilev, U. M.; Jurjev, V. P.; Gershanov, P. B.; Rafikov, S. R. *Tetrahedron Lett.* **1971**, 2807. Cabre, C. J.; Palomo, C. A. *Afinidad* **1988**, *45*, 5111 (*Chem. Abstr.* **1989**, *111*, 77817). (f) The parent pyridine has been oxidized to its *N*-oxide by using anhydrous H_2O_2 in the presence of 8 mol % MTO: see ref 3c.

(6) This was probed by observing the difference in chemical shifts upon addition of 2 equiv of a ligand to a 20 mM solution of MTO in CD_2Cl_2: Copéret, C.; Sharpless, K. B. Unpublished results.

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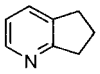
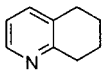
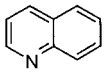
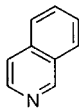
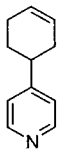
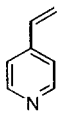
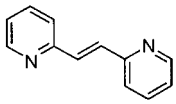
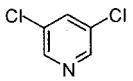
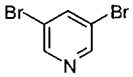
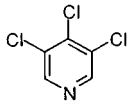
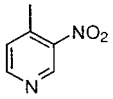
Table 2. Oxidation of Poly- and Alkenyl Substituted Pyridines

Entry	Pyridine	MTO (mol%)	time (h)	yield (%)[a]
1		0.5	5	88
2		5	12	99
3		0.5	3	98
4		0.5	15	92
5		1	4	80:20[b]
6		0.5	3.5	85[c]
7		1	12	78[c]
8		0.2	17	94
9		0.2	25	82
10		0.5	41	89
11		0.5	24	99

[a]conversion > 99% in all cases unless otherwise noted. [b]ratio of epoxide *vs.* starting material, <2% of the *N*-oxide was detected in the crude reaction mixture. [c]No epoxide was formed (< 1-2%) according to ^{1}H NMR spectroscopy on the crude reaction mixture.

%) are present *during epoxidation* (eq 2), MTO catalyst decomposes more rapidly.[7,8]

$$MeReO_3 \xrightarrow[Pyridine]{H_2O_2} MeOH + HOReO_3{\bullet}2Py \qquad (2)$$

In light of these trends, we were not surprised to find that the olefinic pyridine [4-(3′-cyclohexenyl)pyridine, entry 5, Table 2] undergoes epoxidation (not *N*-oxidation), but with poor turnover.[9] By contrast, for the entries 6 and 7, having conjugated alkene substituents, the *N*-oxidation pathway dominates and no epoxides were detected. Finally, *N*-oxidation of more electron deficient pyridines was also achieved in high yields (entries 8−11, Table 2).

In conclusion, a simple and efficient procedure for the oxidation of pyridines to their *N*-oxides has been developed.[10] Moreover, the fact that the MTO catalyst is especially vulnerable to pyridine-mediated destruction *only* when it is catalyzing olefin epoxidation seems to offer an important mechanistic clue. This phenomenon and other ligand effects in these MTO-catalyzed epoxidations are under investigation.[11]

Experimental Section

All reagents and solvents were purchased and used without further purification. All reaction were carried out at 24 °C (water bath) in scintillation vials or Erlenmeyer flasks under air.

General Procedure. A representative procedure for the oxidation of pyridines is as follows: a mixture of methyl isonicotinate (13.7 g, 100 mmol) and MTO (125 mg, 0.5 mmol) in CH_2Cl_2 (40 mL) was treated with 20 mL of 30% aqueous H_2O_2 (200 mmol) and stirred for 6 h at 24 °C. The biphasic reaction mixture was then treated with a catalytic amount of MnO_2 (25 mg) and stirred until oxygen evolution ceased (1 h). Following phase separation, the water layer was extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 15.0 g (98%) of an analytically pure solid: ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 7.75−7.95 (m, 2 H), 8.05−8.3 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 52.99, 125.36, 126.88, 129.38, 138.93, 142.61, 163.31; high-resolution MS calcd for $C_7H_7NO_3$ (M + 1) 154.0504, found 154.0508.

Supporting Information Available: ^{1}H, and ^{13}C NMR, and mass spectrometry data of all *N*-oxides (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(7) For a comprehensive study on the base-induced decomposition of MTO, see: Abu-Omar, M. M.; Hansen, P. J.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 4966.

(8) The MTO catalyst decomposes into MeOH plus the bis(pyridine) adduct of perrhenic acid, which is not an epoxidation catalyst: Yudin, A. K.; Sharpless, K. B. Unpublished results.

(9) The high "pyridine" concentration brings on the "olefin-dependent" catalyst destruction.

(10) Later we found that the combination of bis(trimethylsilyl) peroxide as stoichiometric oxidant and inorganic rhenium derivatives as catalysts could also oxidize pyridines into their *N*-oxides, see: Copéret, C.; Adolfsson, H.; Chiang, J. P.; Yudin, A. K.; Sharpless, K. B. *Tetrahedron Lett.*, in press.

(11) For other results on the MTO-catalyzed epoxidation of alkenes, see: Hoechst AG (Herrmann, W. A.; Marz, D. W.; Kuchler, J. G.; Weichselbaumer, G.; Fischer, R. W.) DE 3.902.357, 1989; Herrmann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1638−1641; ARCO Chemical Technology (Crocco, G. L.; Shum, W. P.; Zajacek, J. G.; Kesling, H. S., Jr.) US 5.166.372, 1992. Herrmann, W. A.; Fischer, R. W.; Rauch, M. U.; Scherer, W. *J. Mol. Catal.* **1994**, *86*, 243−266. Al-Ajlouni, A. M.; Espenson, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 9243−9250. Pestovsky, O.; van Eldik, R.; Huston, P.; Espenson, J. H. *J. Chem. Soc., Dalton Trans. 2* **1995**, 133−137. Herrmann, W. A. *J. Organomet. Chem.* **1995**, *500*, 149. Adam, W.; Mitchell, C. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 533−535. Boelow, T. R.; Spilling, C. S. *Tetrahedron Lett.* **1996**, *37*, 2717−2720. Al-Ajlouni, A. M.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 3969−3976. Herrmann, W. A.; Correia, J. D. G.; Rauch, M. U.; Artus, G. R. J.; Kühn, F. E. *J. Mol. Catal.* **1997**, *118*, 33.