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Ruthenium catalyzed oxidation of tertiary nitrogen compounds with molecular oxygen: an easy access to *N*-oxides under mild conditions

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A variety of tertiary nitrogen compounds have been efficiently oxidized to their corresponding *N*-oxides in excellent yields with molecular oxygen as a sole oxidant and ruthenium trichloride as catalyst.

Oxidation of tertiary nitrogen compounds is an important synthetic transformation as *N*-oxides find wide applications as oxidants,[1] and offer functional group manipulation and structural modification possibilities, which are not accessible by other methods.[2] Although a number of effective oxidants have been used to achieve this transformation, most of them suffer from drawbacks such as the use of stoichiometric amount of corrosive acids or toxic metallic compounds that generate undesirable waste.[3] In recent years the oxidation of tertiary nitrogen compounds with hydrogen peroxide using methyltrioxorhenium(VII),[4] manganese porphyrin,[5] flavin,[6] TS-1,[7] molecular sieves,[8] or tungstate-exchanged Mg–Al layered double hydroxide[9] as catalysts has been reported in pursuit to the development of ecofriendly synthetic methodologies.

Molecular oxygen is an attractive oxidant and development of synthetic methodologies using molecular oxygen as the sole oxidant is a rewarding goal both from environmental and economic points of view.[10] Due to the widest scope of oxidation states among the transition metals, ruthenium has proved to be the most versatile catalyst for organic transformations and has been used for epoxidation of alkenes, oxidation of alkanes and alcohols with molecular oxygen as oxidant.[11] However, to the best of our knowledge, there is no literature report on oxidation of tertiary nitrogen compounds to *N*-oxides with molecular oxygen as the sole oxidant.[12]

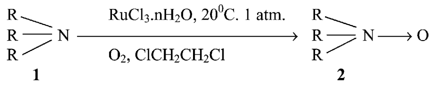
In continuation to our studies on oxidation with molecular oxygen as a primary oxidant,,[13] herein we report, a simple and convenient ruthenium catalyzed oxidation of tertiary nitrogen compounds to their *N*-oxides in near quantitative yields using molecular oxygen as the sole oxidant (Scheme 1).†

A wide variety of tertiary nitrogen compounds were oxidized to their corresponding *N*-oxides in near quantitative yields and results are summarized in Table 1. Pyridines containing electron donating groups were found to react faster and required lower reaction times, whereas pyridines bearing electron withdrawing groups required longer reaction times for their oxidation.

Results obtained on oxidation of 4-picoline to 4-picoline *N*-oxide using different solvents under similar conditions are summarized in Table 2. Among the solvents studied dichlorethane was found to be the best solvent for this reaction.

To evaluate the relative efficiency of various Ru-catalysts, we prepared a variety of ruthenium complexes[14] and studied the oxidation of 4-picoline under similar conditions employing 5 mol% of these catalysts; the results obtained are presented in Table 3. Among the catalysts studied dichlorotris(triphenylphosphine)ruthenium(II) was found to be most efficient catalyst. In blank experiments under similar conditions, no oxidation was observed in the absence of catalyst. The oxidation of 4-picoline to 4-picoline *N*-oxide was also studied at different temperatures and it was observed that an increase in temperature had only a marginal effect on an increase in the reaction rate.

Although the mechanism of this reaction is not clear at this stage, the reaction probably involves the formation of oxo-



Scheme 1 Tertiary nitrogen compounds **1** are efficiently oxidized to *N*-oxides **2** with molecular oxygen in the presence of catalytic amounts of ruthenium trichloride.

Table 1 Oxidation of tertiary nitrogen compounds to *N*-oxides

Entry	Substrate	Reaction time/h	Yield[a] (%)
1	4-Picoline	6	95
2	2-Picoline	6	94
3	3-Picoline	8	90
4	Pyridine	8	85
5	4-Cyanopyridine	15	79
6	2-Cyanopyridine	20	75
7	3-Cyanopyridine	15	65
8	Quinoline	20	40
9	Isoquinoline	20	60
10	*N*,*N*-Dimethylaniline	8	98
11	*N*,*N*-Diethylaniline	8	94
12	2-Hydroxypyridine	12	52
13	Triethylamine	6	98
14	*N*-Methylmorpholine	12	70

[a] Isolated yield.

Table 2 Oxidation of 4-Picoline to 4-Picoline *N*-oxide with different solvents

Entry	Substrate	Solvent	Reaction time/h	Conversion[a] (%)
1	4-Picoline	Methanol	12	50
2	4-Picoline	Ethanol	12	60
3	4-Picoline	Acetone	20	0
4	4-Picoline	Dichloroethane	6	98

[a] Conversion was determined by HPLC using a C_{18} Bondapack reverse phase column (4.6 × 250 mm, 10μm), methanol as eluent (0.5 mL min^{-1}).

Table 3 Oxidation of 4-picoline to 4-picoline *N*-oxide with different catalysts

Entry	Substrate	Catalyst	Reaction time/h	Conversion[a] (%)
1	4-Picoline	$RuH(CO)(OCOMe)(PPh_3)_2$	12	42
2	4-Picoline	$RuCl_2(PPh_3)_4$	12	42
3	4-Picoline	$RuCl_2(PPh_3)_3$	5	100
4	4-Picoline	$RuH_2(CO)(PPh_3)_3$	8	91
5	4-Picoline	$RuCl_3 \cdot nH_2O$	6	98
6	4-Picoline	—	12	0

[a] Conversion was determined by HPLC using a C_{18} Bondapack reverse phase column (4.6 × 250 mm, 10 μm), methanol as eluent (0.5 mL min−1).

ruthenium species[11a,15] from ruthenium and molecular oxygen followed by oxygen transfer to tertiary nitrogen, which yields the corresponding *N*-oxide.

In summary we have demonstrated, for the first time, that ruthenium catalyzed oxidation of tertiary nitrogen compounds with molecular oxygen as the sole oxidant yields *N*-oxides in excellent yields under mild conditions. The simplicity of the system, easy separation of the catalysts, simple workup and excellent yields make this method an attractive, environmentally acceptable synthetic tool for the oxidation of tertiary nitrogen compounds to their corresponding *N*-oxides.

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Notes and references

† *Experimental procedure*: all the substrates and solvents are commercially available. A typical procedure for the oxidation of tertiary nitrogen compound to its *N*-oxide is as follows: molecular oxygen was bubbled into a stirred solution of 4-picoline (0.93 g, 10 mmol) and $RuCl_3 \cdot nH_2O$‡ (0.103 g, 5 mol%) in dichloroethane (10 ml) in a 50 ml double necked round bottomed flask. The progress of reaction was monitored by TLC (SiO_2). At the end of reaction, the catalyst was removed by filtration and the reaction mixture thus obtained was purified by passing through a column of basic alumina using dichloromethane/MeOH (95:5) as eluent. Removal of the solvent and usual workup gave 4-picoline *N*-oxide (0.92 g, 95% yield). Similarity other *N*-oxides were prepared and the reaction times required and yields obtained are shown in Table 1. The products were identified by comparing their physical and spectral data with those of authentic compounds reported in the literature.

For comparing the efficiency of various solvents, experiments were similarly conducted with different solvents and the residues obtained after passing through the basic alumina column were analyzed by HPLC. For comparing the efficiency of various catalysts, experiments were carried out with different Ru-catalysts under similar conditions and the residues obtained after passing through the basic alumina column was analyzed by HPLC.

‡ One of the referees suggested to prepare purified ruthenium trichloride (by treating the commercial ruthenium trichloride with conc. HCl and a few drops of ethanol) and $K_2[RuCl_5(H_2O)]$ from commercial ruthenium trichloride and use them as catalysts in these reactions. Accordingly we studied the oxidation of 4-picoline, 2-picoline and pyridine by using purified ruthenium trichloride and $K_2[RuCl_5(H_2O)]$ as catalysts under similar conditions; *N*-oxide yields and reaction times were found to be comparable to those for commercial $RuCl_3 \cdot nH_2O$.

1 (*a*) V. Van Rheenen, D. Y. Cha and W. M. Hartley, *Org. Synth. Coll. Vol.*, 1988, **6**, 342; (*b*) M. Schroder, *Chem. Rev.*, 1980, **80**, 187; (*c*) L. Ahrgren and L. Sutin, *Org. Proc. Res. Dev.*, 1997, **1**, 425; (*d*) S. V. Ley, J. Norman, W. P. Griffith and S. P. Marsden, *Synthesis*, 1994, 639; (*e*) V. Franzen and S. Otto, *Chem. Ber.*, 1961, **94**, 1360; (*f*) S. Suzuki, T. Onishi, Y. Fujita, H. Misawa and J. Otera, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3287; (*g*) A. G. Godfrey and B. Ganem, *Tetrahedron Lett.*, 1990, **31**, 4825; (*h*) W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625.

2 (*a*) A. C. Cope and E. Ciganek., *Org. Synth. Coll. Vol.*, 1963, **4**, 612; (*b*) A. C. Cope and E. R. Trumbull., *Org. React.*, 1960, **11**, 317; (*c*) *Ullmann's Encyclopedia of Industrial Chemistry*, VCH, Germany, 5th edn., 1993, vol. A-22, pp. 399–428.

3 For representative reports see: (*a*) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, 1954, **76**, 1286; (*b*) E. C. Taylor and A. J. Crovetti, *Org. Synth. Coll. Vol.*, 1963, **4**, 828; (*c*) P. Brougham, M. S. Copper, D. A. Cummerson, H. Heaney and N. Thompson, *Synthesis*, 1987, 1015; (*d*) R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, 1985, **50**, 2847; (*e*) M. Ferrer, F. Sanchez-Baeza and A. Messeguer, *Tetrahedron*, 1997, **53**, 1587.

4 (*a*) C. Coperet, H. Adolfsson, T.-A. V. Khuong, A. K. Yudin and K. B. Sharpless, *J. Org. Chem.*, 1998, **63**, 1740; (*b*) Z. Zhu and J. H. Espenson, *J. Org. Chem.*, 1995, **60**, 1326; (*c*) Y. Jiao and H. Yu., *Synlett.*, 2001, **1**, 73.

5 A. Thellend, P. Battioni, W. Sanderson and D. Mansuy, *Synthesis*, 1997, 1387.

6 (*a*) K. Bergstad and J. E. Backvall, *J. Org. Chem.*, 1998, **63**, 6650; (*b*) S. Ball and T. C. Bruice, *J. Am. Chem. Soc.*, 1980, **102**, 6498.

7 D. J. Robinson, P. McMom, D. Bethell, P. C. Bulmanpage, C. Sly, F. King, F. E. Hangcock and G. J. Hutching, *Catal. Lett.*, 2001, **72**, 233.

8 M. R. Prasad, G. Kamalkar, G. Madhavi, S. J. Kulkarni and K. V. Raghvan, *Chem. Commun.*, 2000, 1577.

9 B. M. Choudhary, B. Bharathi, C. V. Reddy, K. M. Lakshmi and K. V. Raghavan, *Chem. Commun.*, 2001, 1736.

10 (*a*) Y. Nishiyama, Y. Nakagawa and N. Mizuno, *Angew. Chem., Int. Ed.*, 2001, **40**, 3639; (*b*) J. M. Thomas, R. Raja, G. Sankar and R. G. Bell, *Acc. Chem. Res.*, 2001, **34**, 191; (*c*) C. Dobler, G. M. Mehltretter, U. Sundermeier and M. Beller, *J. Am. Chem. Soc.*, 2001, **122**, 10289; (*d*) J. T. Groves and R. Quinn, *J. Am. Chem. Soc.*, 1985, **107**, 5790; (*e*) S. Davis. and R. S. Drago, *J. Chem. Soc., Chem. Commun.*, 1990, 250; (*f*) R. J. David, S. J. Pugsley and S. Matthew, *J. Am. Chem. Soc.*, 2001, **123**, 7475; (*g*) W. Partenheimer, in *The Activation of Dioxygen and Homogeneous Catalytic Oxidation*, ed. D. H. R. Barton, A. E. Martell and D. T. Sawyer, Plenum Press, New York, 1993; (*h*) Y. Nishiyama, Y. Nakagawa and N. Mizuno, *Angew. Chem.*, 2001, **40**, 3639; (*i*) K. Noboyuki, M. Yasunari, T. Nishimura and S. Uemura, *J. Org. Chem.*, 2001, **66**, 6620.

11 (*a*) T. Naota, H. Takaya and S. Murahashi, *Chem. Rev.*, 1998, **98**, 2599; (*b*) A. Miyata, M. Murakami, R. Iric and T. Katsuki, *Tetrahedron Lett.*, 2001, **42**, 7067; (*c*) T. Konda, T. Okada and T. Mitsudo, *J. Am. Chem. Soc.*, 2002, **124**, 186; (*d*) J. E. Marko, P. R. Giles, M. Tsukazaki, I. Chelle-Regnaut, C. J. Urch and S. M. Brown, *J. Am. Chem. Soc.*, 1997, **119**, 12661.

12 There are two literature reports on oxidation of tertiary nitrogen compounds to *N*-oxides using a molecular oxygen–aldehyde system: (*a*) R. S. Dongre, T. V. Rao, B. K. Sharma, B. Sain and V. K. Bhatia, *Synth. Commun.*, 2001, **31**, 167; (*b*) F. Wang, H. Zhang, G. Song and X. Lu, *Synth. Commun.*, 1999, **29**, 11.

13 (*a*) T. V. Rao, B. Sain, K. Kumar, P. S. Murthy, T. S. R. Prasada Rao and G. C. Goshi, *Synth. Commun.*, 1998, **28**, 319; (*b*) B. Sain, P. S. Murthy, T. V. Rao, T. S. R. Prasada Rao and G. C. Goshi, *Tetrahedron Lett.*, 1994, **35**, 5083; (*c*) T. V. Rao, B. Sain, P. S. Murthy, T. S. R. Prasada Rao, A. K. Jain and G. C. Joshi, *J. Chem. Res. (S)*, 1997, 300; (*d*) T. V. Rao, B. Sain, P. S. N. Murthy, G. C. Joshi and T. S. R. Prasada Rao, *Stud. Surf. Sci. Catal.*, 1998, **113**, 921; (*e*) S. L. Jain and B. Sain, *J. Mol. Catal.*, 2001, **176**, 101.

14 For the preparation of $RuH(CO)(OCOMe)(PPh_3)_2$, $RuCl_2(PPh_3)_4$, $RuCl_2(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$ from $RuCl_3 \cdot 3H_2O$, see: (*a*) A. Dobsen, S. D. Robinson and M. F. Uttley, *Inorg Synth.*, 1977, **17**, 126; (*b*) P. S. Hallman, T. A. Stephenson and G. Wilkinson, *Inorg. Synth.*, 1970, **12**, 238; (*c*) N. Ahmad, J. J. Levison, S. D. Robinson and M. F. Uttley, *Inorg Synth.*, 1974, **15**, 48.

15 (*a*) J. T. Groves and R. Ouinn, *J. Am. Chem. Soc.*, 1985, **107**, 5790; (*b*) M. M. T. Khan and R. S. Shukla, *J. Mol. Catal.*, 1988, **44**, 85.