Pergamon

Tetrahedron Letters 39 (1998) 761–764

TETRAHEDRON
LETTERS

A Simple and Efficient Method for the Preparation of Pyridine-*N*-oxides II.[1]

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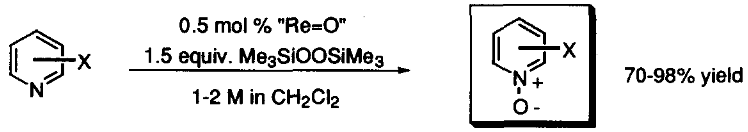
Received 17 October 1997; accepted 7 November 1997

Abstract: *Oxidation of pyridines with bis(trimethylsilyl)peroxide in the presence of catalytic amounts of inorganic rhenium derivatives gives high yields of their analytically pure N-oxides by simple work-ups, typically a filtration or a Kugelrohr distillation.*

We wish to report on a simple and efficient method for the *N*-oxidation of pyridine catalyzed by various inorganic rhenium derivatives using bis(trimethylsilyl)peroxide (BTSP) as the stoichiometric oxidant.[2]

We reported recently that pyridines are oxidized in high yields to their *N*-oxides by 30% aqueous H_2O_2 in the presence of catalytic amounts of methyltrioxorhenium (MTO).[1] This This procedure was developed out of an earlier study on ligand effects on the MTO-catalyzed epoxidation of alkenes, where we observed that pyridines were oxidized to their corresponding *N*-oxides, but *only* near the end of the epoxidation as the olefin concentration approaches zero.[3] Having just found that MTO can be replaced in the epoxidation process by cheaper and more readily available inorganic rhenium catalysts, provided aqueous H_2O_2 is replaced by BTSP (its "anhydrous" equivalent),[4] we decided to investigate the effectiveness of this new system for the oxidation of pyridines.[1,5] Oxidation of methyl isonicotinate by BTSP in the presence of MTO or various inorganic rhenium derivatives such ReO_3, Re_2O_7, and $HOReO_3$ gave high yields of its *N*-oxide (95-98 % isolated yields) while $ReCl_3$ and $NaOReO_3$ gave only trace amounts of oxidation products even after several days.

Scheme 1



"Re=O" : MTO, ReO_3, Re_2O_7, and $HOReO_3$

Since trace water is crucial to turnover frequencies in the epoxidation of alkenes with BTSP, its effect on the rate of this pyridine oxidation was examined.[6] The presence of 3Å molecular sieves slowed down the reaction especially in the case of ReO_3, but did not stop it in

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PII: S0040-4039(97)10619-0

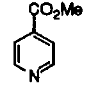
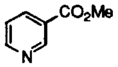
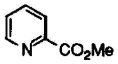
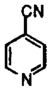
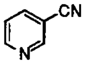
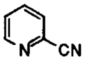
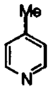
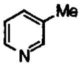
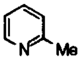
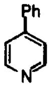
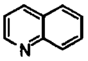
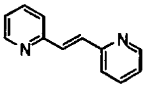
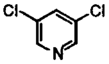
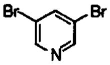
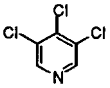
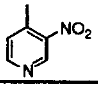
contrast to the related epoxidation.[4,6] However, using an excessive amount of water was also detrimental to catalysis in the present system. We found that the optimal water content was between trace amounts (if any) to 15 mol %, higher contents leading to lower conversions.

The commercial 65-70% solution of perrhenic acid in water was found to be a convenient source of both Re and water,[7] and the following procedure is recommended for all substrates unless otherwise noted (*vide infra* and Table): a mixture of methyl isonicotinate (2.74 g, 20 mmol), and perrhenic acid (17 µl, 25 mg, 0.1 mmol) in CH_2Cl_2 (3.0 mL) was treated with 6.0 mL of bis(trimethylsilyl)peroxide (30 mmol) and stirred for 6 h at 24 °C (water bath). The reaction mixture was diluted with hexanes (4 mL), cooled to 0 °C, and filtered. The resulting solid was washed with cold hexanes (2x4mL) and dried *in vacuo* to give 3.00 g (98%) of an analytically pure *N*-oxide.

The simplicity of the procedure, *i.e.* isolation by filtration, and the importance of *N*-oxides as synthetic intermediates led us to investigate the scope of this process.[8] Both electron poor or electron rich pyridines give high yields of their *N*-oxides (see Table), and the reaction works well under high concentration (2 M) for those *N*-oxides which crystallized out. However, in the case of 3-picoline (Entry 8), which formed an *N*-oxide that did not precipitate, it was necessary to work under more dilute conditions to avoid phase separation and hence lower conversion.[9] In this case, evaporation of the reaction mixture followed by bulb-to-bulb distillation afforded 3-picoline-*N*-oxide in a 98% yield. In general, *para* or *meta* substituents do not significantly affect the reaction course while *ortho* ones show peculiar characteristics depending on their nature. For example, oxidation of methyl picolinate induced slow decomposition of BTSP into O_2 resulting in low conversion (Entry 3) while 2-cyanopyridine gave its *N*-oxide in a 92% yield (Entry 6). Also, 2-picoline showed poor conversion independently of the amount of perrhenic acid catalyst used (0.5 to 5 mol %). In fact, it is worth noting that increasing the amount of perrhenic acid, which is a 65-70% solution in water, increases the amount water as well, which has been shown to be detrimental to catalysis (*vide supra*). Therefore switching from aqueous perrhenic acid to solid ReO_3 (1 mol%) allowed isolation of 2-picoline-*N*-oxide in a 93% yield after bulb-to-bulb distillation. These results are in sharp contrast with our previously reported system where all *ortho* substituted pyridines required at least 5 mol % catalyst, *i. e.* MTO, to reach full conversion.[1] Finally, more electron deficient pyridines also gave high yields of their *N*-oxides (Entry 12-16).

Overall, this method allows for the preparation of a wide range of *N*-oxides with a simple work-up, typically a filtration or a distillation. These reactions are run very concentrated (1-2 M in CH_2Cl_2) and use inexpensive inorganic rhenium derivatives in combination with a safe and environmentally benign oxidizing agent, *i. e.* BTSP.[2] This study has further confirmed that water is responsible for deactivation of the inorganic Re species in the oxidation catalysis, which most of the time prevents the use of aqueous H_2O_2.[10]

Table. Perrhenic Acid-Catalyzed Oxidation of Pyridines with Bis(trimethylsilyl)peroxide.[a]

Entry	Pyridine	amount (mmol)	HOReO$_3$[b] (μL)	CH$_2$Cl$_2$ (mL)	BTSP (mL)	time (h)	yield (%)
1		20	17	4	6	6	98[c]
2		10	8.5	2	3	17	87
3		10	8.5	2	3	17	1:1[d]
4		20	17	4	6	6	91
5		20	17	4	6	6	96
6		10	8.5	2	3	15	92
7		10	8.5	2	3	9	89
8		20	17	10	6	8	98[e]
9		20	*f*	10	6	24	93[e]
10		10	8.5	5	3	17	91
11		20	17	10	6	17	90[e]
12		10	8.5	4	6	24	70[g]
13		20	17	3	6	20	90
14		10	8.5	5	3	24	88
15		20	17	10	6	24	75[h]
16		10	8.5	2	3	20	95

[a] Reaction conditions are given in the table, isolated yield after filtration unless otherwise noted. [b] 65-70% solution in water, amount shown corresponds to 0.5 mol%. [c] The reaction carried out with 0.1 mol% catalyst gave a 98% yield after 40 h. [d] by NMR. [e] Yield after bulb to bulb distillation. [f] 1 mol % of ReO$_3$ was used. [g] Yield of di-*N*-oxide, no epoxide was detected in the crude reaction mixture. [h] Evaporation of the filtrate followed by crystallization from a CH$_2$Cl$_2$/hexanes mixture provided an extra 15% yield of this *N*-oxide bringing the yield to 90%.

Acknowledgments. We are grateful to the National Institute for General Medical Sciences, the National Institutes of Health (GM 28384), the National Science Foundation (CHE 9521152), the W. M. Keck Foundation, and the Skaggs Institute for Chemical Biology for financial support. H. A. and C. C. are also grateful to the Swedish Natural Science Research Council, and the Association des Amis des Sciences for post-doctoral fellowships, respectively.

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1. C. Copéret, H. Adolfsson, T.-A. V. Khuong, A. K. Yudin, K. B. Sharpless, submitted for publication.
2. a) For the preparation of BTSP, see: P. G. Cookson, A. Davies, N. Fazal *J. Organometal. Chem.* **1975**, *99*, C31, M. Taddei, A. Ricci *Synthesis* **1986**, 633; b) for convenient large scale syntheses of BTSP: W. P. Jackson *Synlett.* **1990**, 536; P. Dembech, A. Ricci, G. Seconi, M. Taddei *Org. Synth.* **1997**, *74*, 84; J. P. Chiang, K. B. Sharpless, manuscript in preparation.
3. a) C. Copéret, H. Adolfsson, K. B. Sharpless *Chem. Commun.* **1997**, 1565; b) J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless *J. Am. Chem. Soc.* **1997**, *119*, 6185.
4. A. K. Yudin, K. B. Sharpless *J. Am. Chem. Soc.* in press.
5. a) For a review on oxidation of pyridines, see: E. Ochiai, *Aromatic Amine Oxides*, Elsevier, Amsterdam **1967**; A. Albini, S. Pietra *Heterocyclic N-Oxides*, CRC Press, **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: G. E. Chivers, H. Suschitzky *J. Chem. Soc., Chem. Comm.*, **1971**, 28; K. Takabe, T. Yamada, T. Katagiri *Chem. Lett.* **1982**, 1987; V. Tortorella *J. Chem. Soc., Chem. Comm.*, **1966**, 308; Kaczmarek, R. Balicki, P. Nantka-Namirski *Chem. Ber.* **1992**, *125*, 1965; d) for oxidation with DMDO: R. W. Murray, R. Jeyaraman *J. Org. Chem.* **1985**, *50*, 2847; e) for some examples of transition metal catalyzed oxidation of pyridines: G. A. Tolstikov, U. M. Jemilev, V. P. Jurjev, P. B. Gershanov, S. R. Rafikov *Tetrahedron Lett.* **1971**, 2807; C. J. Cabre, C. A. Palomo, *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: R. W. Murray, K. Iyanar, J. Chen., J. T. Wearing *Tetrahedron Lett.* **1996**, *37*, 805; g) For reports on the MTO-catalyzed oxidations of amines and anilines: R. W. Murray, K. Iyanar, J. Chen., J. T. Wearing *Tetrahedron Lett.* **1995**, *36*, 6415; Z. Zhu, J. H. Espenson *J. Org. Chem.* **1995**, *60*, 7728; see 3f; A. Goti, L. Nanelli *Tetrahedron Lett.* **1996**, *37*, 6025; R. W. Murray, K. Iyanar, J. Chen., J. T. Wearing *J. Org. Chem.* **1996**, *61*, 8099; S. Yamazaki *Bull. Soc. Chem. Jpn.* **1997**, *70*, 877.
6. In contrast to the epoxidation of alkenes, the oxidation of pyridines might not require the presence of water as pyridines themselves could assist the activation of BTSP by Re catalysts. It is however difficult to disprove that trace amounts of water would be enough to perform this activation.
7. 0.5 mol % of catalyst (65-70 % solution of perrhenic acid in water from Aldrich®) provides between 2.0-2.5 mol% of H_2O.
8. For a review on the use of *N*-oxides, see: 5a; A. K. Katritzky, C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Vol. 2, **1984**.
9. *N*-oxides, that are liquid or low melting, and the hexamethylsiloxane (formed concomitantly) are not miscible, which causes phase separation.
10. Oxidation of pyridines by aqueous H_2O_2 in the presence of inorganic Re derivatives is very slow (< 20% conversion after a few weeks). This is the striking difference between inorganic Re derivatives and MTO where the methyl group seems to be "protecting" the catalyst from deactivation in the presence of aqueous H_2O_2, see W. A. Herrmann, F. E. Kühn *Acc. Chem. Res.* **1997**, *30*, 169 and references cited therein.