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Mild and efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by a new polystyrene-bound Mn(TPP)Cl

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Abstract—Mild and efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by Mn(TTP)Cl supported on polystyrene-bound imidazole is reported. This heterogeneous catalyst is of great stability and reusability in the oxidation of 1,4-dihydropyridines with sodium periodate without significant loss of its catalytic activity.

1,4-Dihydropyridines are calcium antagonists,[1] antitubercular agents,[2] and neuropeptide Y Y1 receptor antagonists.[3] They possess neuroprotective,[4] platelet antiaggregation,[5] and antidiabetic[6] activities. Aromatization of 1,4-dihydropyridines has received considerable attention owing to the fact that 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver.[7] In addition, the corresponding pyridine derivatives show antihypoxic and antiischemic activites.[8] Additionally, dihydropyridines are often produced in a synthetic sequence and have to be oxidized to pyridines.[9] Numerous reagents and procedures have been recommended for this purpose, such as NO,[9] ferric or cupric nitrates on a solid support (clayfen or claycop),[10] ceric ammonium nitrate,[11] clay-supported cupric nitrate accompanied by ultrasound promotion,[12] manganese dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[13] nitric oxide,[14] bismuth nitrate pentahydrate,[15] pyridinium chlorochromate (PCC),[16] tetrakis-(pyridine) cobalt(II) dichromate (TPCD),[17] nicotinium dichromate,[18] *S*-nitrosoglutathione,[19] N_2O_4 complex of 18-crown-6,[20] diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents,[21] $KMnO_4$,[22] CrO_3,[23] HNO_3,[24] HNO_2,[25] *tert*-butylhydroperoxide,[26] silica gel supported ferric nitrate (silfen),[8] N_2O_3,[27] photochemical oxidation,[28] inorganic acidic salts, sodium nitrite or nitrate,[29–32] and Mn(TPP)Cl/$(n\text{-}Bu)_4NIO_4$.[33]

Despite these intensive efforts, most of the reported oxidation procedures require long reaction times, utilize strong oxidants in large excess, afford products with only modest yields, and non-reusability of the catalyst. Therefore, the development of more effective methods for aromatization of 1,4-dihydropyridines is still necessary.

Metalloporphyrins have been successfully used as models for the cytochrome P-450 enzyme with respect to the oxidation of organic compounds such as hydrocarbons.[34–36] Development in this area is based on different strategies with the aim of designing selective, stable, and high turnover catalytic systems.[37] Several simple oxidants such as iodosylbenzene, hypochlorite, *m*-chloroperbenzoic acid, hydrogen peroxide, and periodates have been extensively studied in oxygenation reactions catalyzed by metal complexes in order to understand the mechanism of cytochrome P-450 monooxygenation enzyme.[38–43] Great efforts have been made to the chemical modification of metalloporphyrin microenviron-

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Keywords: Dihydropyridines; Metalloporphyrin; Supported catalyst; Periodate; Oxidation.

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ment in the studies of cytochrome P-450 model. One way is to immobilize the metalloporphyrins onto solid supports. Such immobilization not only modifies the metalloporphyrin microenvironment, but also increases the catalytic activity of metalloporphyrins, and let to prepare the catalysts which are easier to handle and easily separate from reaction medium. Among the models of metalloporphyrin microenvironment, the polystyrene derivatives are often utilized, because they can provide suitable microenvironment for the 'accommodation' of porphyrin catalytic center.

Recently, we have reported the oxidation of 1,4-dihydropyridines with tetra-*n*-butylammonium periodate catalyzed by homogeneous Mn(TPP)Cl.[33] In this paper, we report the efficient oxidation of 1,4-dihydropyridines with sodium periodate at room temperature catalyzed by a Mn(TPP)Cl supported on polystyrene-bound imidazole, Mn(TPP)Cl-PSI (Scheme 1).

Chloromethylated polystyrene surface modification with imidazole to give the PSI was carried out through the method described by Alvarez-Builla and co-workers.[44] The supported MnP was prepared by stirring a suspension of the support, (PSI), in a solution of MnP in toluene as solvent, because of better solvation and swelling of the polymer in it. The free manganese porphyrin was removed by subsequent washing of the catalyst with toluene, dichloromethane, and acetone, respectively (Fig. 1).

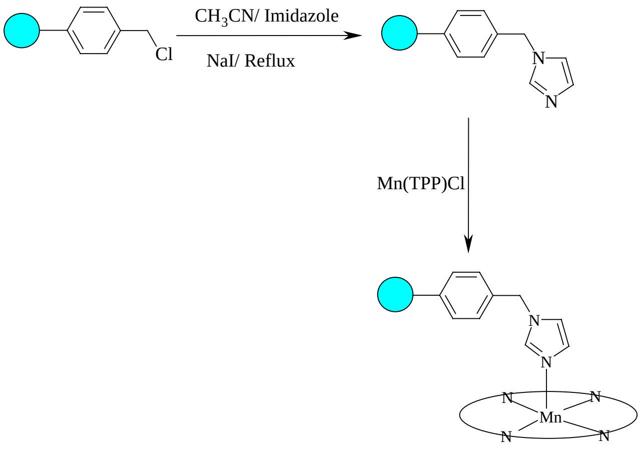


Figure 1. The preparation of supported catalyst used in this study.

Table 1. Effect of various oxidants on the oxidation of 4-phenyl derivative of 1,4-dihydropyridines

Oxidant	Solvent	Yield[a] (%)
$NaIO_4$	CH_3CN/H_2O	96
H_2O_2	CH_3CN	82
H_2O_2/urea	CH_3CN	47
NaOCl	CH_3CN	30
t-BuOOH	CH_3CN	25
n-Bu_4NIO_4	CH_3CN	22
t-BuOOH	*t*-BuOH/H_2O	34
$NaIO_4$	*t*-BuOH/H_2O	38

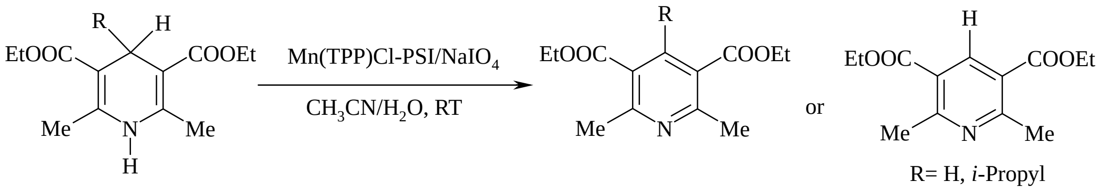
[a] Isolated yields.

Table 2. Effect of solvent on the oxidation of 4-phenyl derivative of 1,4-dihydropyridines

Solvent	Yield after 40 min[a] (%)
CH_3CN/H_2O	96
CH_3COCH_3/H_2O	78
CH_3OH/H_2O	52
CH_3CH_2OH/H_2O	47
t-BuOH/H_2O	38
$CHCl_3/H_2O$	17
CH_2Cl_2/H_2O	30
CCl_4/H_2O	8

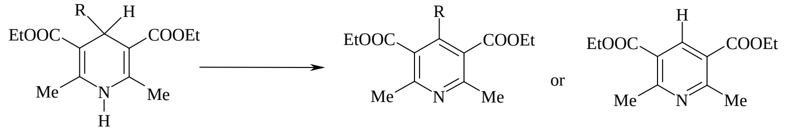
[a] Isolated yields.

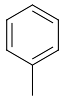
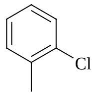
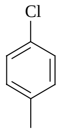
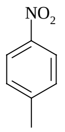
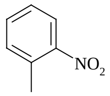
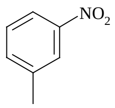
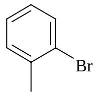
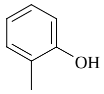
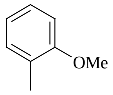
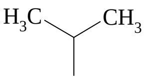
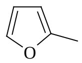
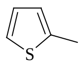
The high catalytic activity of this heterogeneous catalyst in the alkene epoxidation and alkane hydroxylation[45] prompted us to investigate its ability in the oxidation of 1,4-dihydropyridines with sodium periodate under mild reaction conditions. The oxidation of 1,4-dihydropyridines by Mn(TPP)Cl-PSI and sodium periodate yielded the corresponding pyridine derivative in 1:1 CH_3CN/H_2O as solvent, whereas trace amounts of product were detected when the identical reaction was carried out in the absence of periodate. The effect of other oxidants was also studied in the oxidation of 4-phenyl derivative of 1,4-dihydropyridines. The obtained results showed that $NaIO_4$ is more effective than H_2O_2, NaOCl, *t*-BuOOH, $(n\text{-Bu})_4NIO_4$, and UHP (Table 1). Also, we investigated the aromatization of 1,4-dihydropyridines as a test case in a mixture of EtOH, MeOH, CH_3COCH_3, CH_3CN, and *t*-BuOH (single phase systems), CH_2Cl_2, $CHCl_3$, and CCl_4 (two phase systems with *n*-Bu_4Br as phase transfer catalyst) with water as reaction media at ambient temperature. The results, which are summarized in Table 2, showed that the oxidation of 1,4-dihydropyridines in the 1:1 mixture of CH_3CN/H_2O led to a higher corresponding pyridine. The blank experiment, in the absence of catalyst, showed that the presence of catalyst is crucial in the oxidation reactions. All reactions proceeded efficiently within 40–80 min to provide the corresponding pyridines in excellent yields (Table 3). As shown in Table 3, oxidation of 4-isopropyl derivative was accompanied



Scheme 1.

Table 3. Oxidation of Hantzsch 1,4-dihydropyridines with $NaIO_4$ catalyzed by Mn(TPP)Cl-PSI



Row	R	Time (min)	Yield[a] (%)
1	H	40	96
2	CH_3	50	95
3		50	97
4		80	96
5		55	96
6		70	93
7		90	92
8		100	93
9		120	91
10		80	92
11		80	95
12		40	96[b]
13		55	93
14		70	92

[a] Isolated yields; All products were identified by comparison with authentic samples (IR, ^1H NMR, and mp).

[b] The product is a dealkylated pyridine derivative.

Table 4. The results of [Mn(TPP)-PSI] catalyst recovery and the manganese leached in the oxidation of 4-phenyl derivative of 1,4-DHPs with sodium periodate

Run	Time (min)	Yield[a] (%)	Mn leached[b] (%)
1	40	96	0
2	40	95	0
3	40	94	0
4	40	94	0

[a] Isolated yield.

[b] Determined by atomic absorption spectroscopy.

by expulsion of this substituent gave dealkylated pyridine derivative (entry 12), which is previously reported by Ortiz de Montellano in the oxidation of 1,4-dihydropyrines by cytochrome P-450.[46] This approach shows that this synthetic model behaves as cytochrome P-450.

We also studied the recycling of the used Mn(TPP)Cl-PSI in the repeated oxidation reactions. After the first run, the polymer was recovered by filtration followed by washing with water and acetonitrile, and reused. The catalyst can be reused four consecutive times, without loss of its activity. No manganese was detectable in the filtrates by atomic absorption spectrometry (Table 4). The nature of the recovered catalyst has been followed by IR and solid state UV. The results indicated that the catalyst after reusing several times showed no change in its IR and solid state UV spectra.

Comparison of this system with the previously reported systems shows that the Mn(TPP)Cl-PSI/ $NaIO_4$ catalytic system has the following advantages: robustness of the catalyst, mild reaction conditions, and reusability of the catalyst without loss of its activity.

On the other hand, comparison of homogeneous Mn(TPP)Cl/$(n\text{-Bu})_4NIO_4$[33] with heterogeneous Mn(TPP)Cl-PSI/$NaIO_4$ shows that reaction times and yields are similar but the heterogeneous catalyst is a robust and recoverable catalyst.

All materials were of commercial reagent grade. The tetraphenylporphyrin ligand (H_2TPP) was prepared, metalated, and supported according to the literature procedures.[45,47,48] All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures.[49] ^1H NMR spectra were obtained with a Brucker AW80 (80 MHz) spectrometer.

All of the reactions were carried out at room temperature under air in a 25 mL flask equipped with a magnetic stirrer bar. A solution of $NaIO_4$ (2 mmol) in H_2O (10 mL) was added to a mixture of 1,4-dihydropyridines (1 mmol), Mn(TPP)Cl-PSI (20 μmol) in CH_3CN (10 mL). The progress of reaction was monitored by TLC until no starting material is detected by TLC. After the reaction was completed, the reaction mixture was filtered and the pyridine derivative was extracted with CH_2Cl_2 (2× 20 mL). The pyridine derivatives were obtained after evaporation of solvent. Further purification was followed by silica gel plate. IR and ^1H NMR spectral data confirmed the identities of the products.

References and notes

1. (a) Zamponi, G. W.; Stotz, S. C.; Staples, R. J.; Andro, T. M.; Nelson, J. K.; Hulubei, V.; Blumenfeld, A.; Natale, N. R. *J. Med. Chem.* **2003**, *46*, 87; (b) Visentin, S.; Rolando, B.; Di Stilo, A.; Frutterro, R.; Novara, M.; Carbone, E.; Roussel, C.; Vanthuyne, N.; Gasco, A. *J. Med. Chem.* **2004**, *47*, 2688; (c) Zarghi, A.; Sadeghi, H.; Fassihi, A.; Faizi, M.; Shafiee, A. *Farmaco* **2003**, *58*, 1077; (d) Peri, R.; Padmanabhan, S.; Rutledge, A.; Singh, S.; Triggle, D. J. *J. Med. Chem.* **2000**, *43*, 2906.
2. Kharkar, P. S.; Desai, B.; Gaveria, H.; Varu, B.; Loriya, R.; Naliapara, Y.; Shah, A.; Kulkarn, V. M. *J. Med. Chem.* **2002**, *45*, 4858.
3. (a) Poindexter, G. S.; Bruce, M. A.; Breitenbucher, J. G.; Higgins, M. A.; Sit, S.-Y.; Romine, J. L.; Martin, S. W.; Ward, S. A.; McGovern, R. T.; Clarke, W.; Russell, J.; Antal-Zimanyi, I. *Bioorg. Med. Chem.* **2004**, *12*, 507; (b) Poinder, G. S.; Bruce, M. A.; LeBoulluec, K. L.; Monkovic, I.; Martin, S. W.; Parker, E. M.; Iben, L. G.; McGovem, R. T.; Ortiz, A. A.; Stanley, J. A.; Mattson, G. K.; Kozlowski, M.; Arcuri, M.; Zimanyi, I. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 379.
4. Klusa, V. *Drugs Future* **1995**, *20*, 135.
5. Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Drugs Future* **1992**, *17*, 465.
6. (a) McCormack, J. G.; Westergaard, N.; Kristiansen, M.; Brand, C. L.; Lau, J. *Curr. Pharm. Des.* **2001**, *7*, 1457; (b) Ogawa, A. K.; Willoughby, C. A.; Raynald, B.; Ellsworth, K. P.; Geissler, W. M.; Myer, R. W.; Yao, J.; Georgianna, H.; Chapman, K. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3405.
7. (a) Boer, R.; Gekeler, V. *Drugs Future* **1995**, *20*, 499; (b) Sabitha, G.; Kiran Kumar Reddy, G. S.; Srinivas Reddy, Ch.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129.
8. Khadikar, B.; Borkat, S. *Synth. Commun.* **1998**, *28*, 207.
9. Itoh, T.; Nagata, K.; Matsuya, Y.; Miyazaki, M.; Ohsawa, A. *J. Org. Chem.* **1997**, *62*, 3582.
10. Balogh, M.; Hermecz, I.; Meszaros, Z.; Laszlo, P. *Helv. Chim. Acta* **1984**, *67*, 2270.
11. Pfister, J. R. *Synthesis* **1990**, 689.
12. Maquestiau, A.; Mayence, A.; Eynde, J. J. V. *Tetrahedron Lett.* **1991**, *32*, 3839.
13. Eynde, J. J. V.; Delfosse, F.; Mayence, A.; Van Haverbeke, Y. *Tetrahedron* **1995**, *51*, 6511.
14. Itoh, T.; Nagata, K.; Okada, M.; Ohsawa, A. *Tetrahedron Lett.* **1995**, *36*, 2269.
15. Mashraqui, S. H.; Karnik, M. A. *Synthesis* **1998**, *9*, 713.
16. Eynde, J. J. V.; Mayence, A.; Maquestiau, A. *Tetrahedron* **1992**, *48*, 463.
17. Wang, B.; Hu, Y.; Hu, H. *Synth. Commun.* **1999**, *29*, 4193.
18. Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R.; Sobhani, S. *Synth. Commun.* **2000**, *30*, 1661.
19. Mao, Y. Z.; Jin, M. Z.; Liu, Z. L.; Wu, L. M. *Org. Lett.* **2000**, *2*, 741.
20. Zolfigol, M. A.; Zebarjadian, M. H.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R.; Shamsipur, M. *Synth. Commun.* **2001**, *31*, 929.
21. Sadeghi, M. M.; Memarian, H. R.; Momeni, A. R. *J. Sci. Islamic Repub. Iran* **2001**, *12*, 141.
22. Eynde, J. J. V.; Orazio, R. D.; Van Haverbeke, Y. *Tetrahedron* **1994**, *50*, 2479.
23. Grinsteins, E.; Stankevice, B.; Duburs, G. *Kim. Geterotsikl. Soedin* **1976**, 1118.
24. (a) Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1986**, *29*, 1596; (b) Garcia, O.; Delgado, F. *Tetrahedron Lett.* **1993**, *34*, 623.

25. (a) Love, B.; Snader, K. M. *J. Org. Chem.* **1965**, *30*, 1914; (b) Huntress, E. H.; Shaw, E. N. *J. Org. Chem.* **1948**, *13*, 674.
26. Chavan, S. P.; Dantale, S. W.; Kalkote, U. R.; Jyothirmai, V. S.; Kharul, R. K. *Synth. Commun.* **1998**, *28*, 2789.
27. Hantzsch, A. *Annalen* **1982**, 215.
28. Memarian, H. R.; Sadeghi, M. M.; Aliyan, H. *Indian J. Chem.* **1998**, *37B*, 219.
29. Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, *30*, 551.
30. Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Memarian, H. R.; Mohammadpoor-Baltork, I. *J. Chem. Res. Synop.* **2000**, 167.
31. Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Memarian, H. R.; Mohammadpoor-Baltork, I. *Synth. Commun.* **2000**, *30*, 2945.
32. Zolfigol, M. A.; Kiany-Borazjani, M.; Sadeghi, M. M.; Mohammadpoor-Baltork, I.; Memarian, H. R. *Synth. Commun.* **2000**, *30*, 3919.
33. Moghadam, M.; Nasr-Esfahan, M.; Tangestani, S.; Mirkhani, V. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3276.
34. Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.
35. *Metalloporphyrins in Catalytic Oxidations*; Sheldon, R. A., Ed.; Marcel Dekker: New York, 1994.
36. Meunier, B.; Robert, A.; Pratviel, G.; Bernadou, J. In *The Porphyrins Handbook*; Kadish, K., Smith, K. M., Guilard, R., Eds.; Academic Press: New York, London, 2000; Vol. 4.
37. Sheldon, R. A. In *Biomimetic Oxidations Catalyzed by Transition Metal Complexes*; Meunier, B., Ed.; Imperial College Press: London, 2000.
38. Coon, M. J.; White, R. E. In *Dioxygen Binding and Activation by Metal Centers*; Spiro, T. G., Ed.; Wiley: New York, 1980.
39. Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786.
40. Bortolini, O.; Meunier, B. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1967.
41. Meunier, B.; Guilmet, E.; De Carvalho, M. E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668.
42. Mohajer, D.; Tangestaninejad, S. *J. Chem. Soc., Chem. Commun.* **1993**, 240.
43. Mohajer, D.; Tangestaninejad, S. *Tetrahedron Lett.* **1994**, *35*, 945.
44. Linares, M. L.; Sanchez, N.; Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J. *Synthesis* **2001**, *3*, 382.
45. Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Kargar, H.; Komeili-Isfahani, H. *Catal. Commun.* **2005**, *6*, 688.
46. Ortiz de Montellano, P. R.; Beilan, H. S.; Kunze, K. L. *J. Biol. Chem.* **1981**, *256*, 6708.
47. Adler, A. D.; Long, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476.
48. Adler, A. D.; Long, F. R.; Kampas, F.; Kim, J. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2443.
49. Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827.