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Rapid and efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by manganese (III) Schiff base complexes

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Abstract—Rapid and efficient oxidation of Hantzsch 1,4-dihydropyridine with sodium periodate is reported. The Mn(III)-salophen/$NaIO_4$ catalytic system converts 1,4-dihydropyridines to their corresponding pyridine derivatives at room temperature in a 1:1, CH_3CN/H_2O mixture. The ability of various Schiff base complexes in the oxidation of 1,4-dihydropyridine was also investigated.
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1. Introduction

The heme-containing monooxygenases cytochrome P-450 is known to play a key role in the oxidative metabolism of drugs and other environmental products, allowing their elimination from living organisms.[1] Therefore, numerous studies have been performed on the mimic of this enzyme.[2,3] Iron and manganese porphyrins proved to be able to catalyze oxidation reactions using various single oxygen atom donors such as PhIO, ClO^-, H_2O_2, ROOH or IO_4^-.[4–13] The high efficiency of some of these systems makes them potentially useful for preparative oxidations in organic synthesis. Recently, mono- and binuclear transition metal complexes derived from ligands other than porphyrins have also been employed as catalysts. The use of metal Schiff base complexes, that is, metal salen and metal salophen to catalyze the oxidation of organic compounds by single oxygen atom donors has received much attention. Manganese, chromium, nickel, and cobalt Schiff base complexes have been used for these transformations.[14–23]

Hantzsch 1,4-dihydropyridines are widely used as calcium channel blockers for the treatment of cardiovascular disorder including angina, hypertension, and cardiac arrhythmias.[24] These compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver.[25]

In this paper, we report the rapid and efficient oxidation of 1,4-dihydropyridines with sodium periodate to their corresponding pyridine derivatives at room temperature in a 1:1, CH_3CN/H_2O mixture (Scheme 1).

We have chosen the salophen ligand because it is similar to porphyrin, and the electronic and steric nature of the metal complex can be tuned by introducing electron-withdrawing and electron-releasing substituents and bulky groups in the ligand.

2. Results and discussion

2.1. Oxidation of 1,4-dihydropyridine derivatives with different metal–Schiff base complexes

Initially, in order to show the periodate anion activation by metal Schiff base complexes, we decided to investigate the activity of various Schiff base complexes of Fe, Mn, Co, and Ni as metal ions. The obtained results

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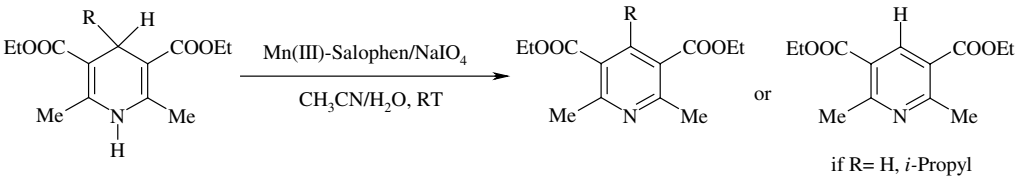


Scheme 1.

on catalytic oxidation of 4-phenyl derivative of 1,4-dihydropyridine with sodium periodate in the presence of different Schiff base complexes (Fig. 1) are shown in Table 1. These results indicated that the nature of the metal ion has an important role on the catalytic activity of Schiff base complexes. The iron, cobalt, and nickel complexes give a small amount of the corresponding pyridine derivative in the oxidation of 4-phenyl derivative of 1,4-dihydropyridine. In the case of nickel and cobalt, these metal ions are not capable of forming the high oxidation state oxo species, and in the case of iron it is not clear why Fe Schiff bases show lower activity than manganese complexes in the oxidation reactions. However, the use of manganese (III) complexes give a higher oxidation product in the oxidation of 4-phenyl derivative of 1,4-dihydropyridine.

In comparing the influence of Schiff base ligands on catalytic activity, the hindered Schiff base ligand, salophen, exhibits a significant greater catalytic power than that of the unhindered Schiff base ligand, salen. On the other hand, the presence of electron-withdrawing substituents on the Schiff base complexes decreases the catalytic activity.

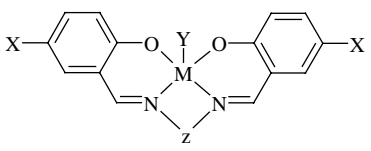
Table 1. Oxidation of 4-phenyl derivative of 1,4-dihydropyridines by various metal Schiff base complexes with sodium periodate

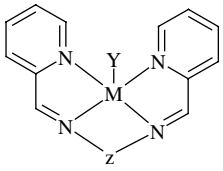
Schiff base	Yield[a] (%) after 5 min
1	97
2	35
3	6
4	7
5	6
6	15
7	10
8	30
9	5
10	20
11	10

[a] Isolated yields.

2.2. Effect of solvent on the oxidation of 4-phenyl derivative of 1,4-dihydropyridine

Among the 1:1 mixture of methanol, ethanol, acetone, acetonitrile (single-phase systems), chloroform, and carbon tetrachloride (two-phase systems with Bu_4NBr as the phase transfer catalyst) with water, the 1:1 acetonitrile/water mixture was chosen as the reaction

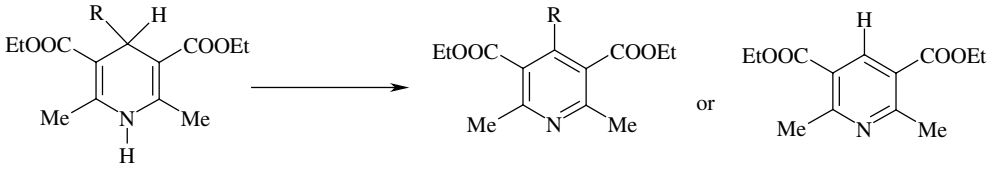


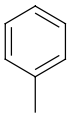
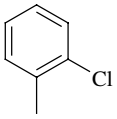
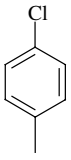
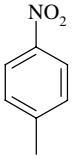
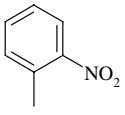
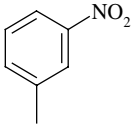
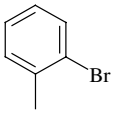
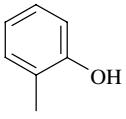
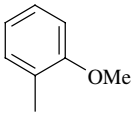
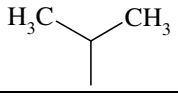


	M	z	X	Y
1	Mn	C_6H_4	H	Cl
2	Mn	C_6H_4	NO_2	Cl
3	Fe	C_6H_4	H	Cl
4	Co	C_6H_4	H	-
5	Ni	C_6H_4	H	-
6	Mn	$(CH_2)_2$	H	Cl
7	Fe	$(CH_2)_2$	H	Cl
8	Mn	C_6H_4	H	Cl
9	Fe	C_6H_4	H	Cl
10	Mn	$(CH_2)_2$	H	Cl
11	Fe	$(CH_2)_2$	H	Cl

Figure 1. Transition metal Schiff base complexes used in this study.

Table 2. Oxidation of Hantzsch 1,4-dihydropyridines with $NaIO_4$ catalyzed by Mn(III)-salophen



Row	R	Time (min)	Yield[a] (%)
1	H	5	97
2	CH_3	5	97
3		5	98
4		15	96
5		5	97
6		15	96
7		15	95
8		15	96
9		20	94
10		15	95
11		15	97
12		15	97[b]

[a] Isolated yields; All products were identified by comparison with authentic samples (IR, ^1H NMR, mp).
[b] This product is a dealkylated pyridine derivative.

medium, because the metal Schiff base complexes are highly soluble in this solvent and higher pyridine derivative yields were observed.

2.3. Effect of axial ligand on the oxidation of 4-phenyl derivative of 1,4-dihydropyridine

In biomimetic systems using metalloporphyrins and Schiff base complexes as catalyst, addition of an axial base is necessary to obtain high catalytic activity. One comment is that, this catalytic system shows a higher catalytic activity in the absence of imidazole. When imidazole is added as axial ligand to this catalytic system, the reaction times become higher in the oxidation of 1,4-dihydropyridines. For instance, the oxidation of 4-phenyl and 4-nitrophenyl derivatives was completed in 5 and 15 min, respectively. Addition of imidazole as co-catalyst led to longer reaction times which are 15 and 20 min for 4-phenyl and 4-nitrophenyl derivatives. These observations show that the 1,4-dihydropyridines can play the axial ligand role.

2.4. Oxidation of 1,4-dihydropyridine derivatives with sodium periodate catalyzed by Mn(III)-salophen

The Mn(III)-salophen/$NaIO_4$ catalytic system can be used for oxidizing a wide variety of 1,4-dihydropyridine derivatives to their corresponding pyridine derivatives in excellent yields at room temperature. All reactions were completed during the appropriate time and gave only the corresponding pyridine derivative. The results are summarized in Table 2. As shown in Table 2, oxidation of 4-isopropyl derivative was accompanied by expulsion of this substituent and gave a dealkylated pyridine derivative (entry 12), which was previously reported by Ortiz de Montellano in the oxidation of 1,4-dihydropyrines by cytochrome P-450.[26] This approach shows that this synthetic model behaves as cytochrome P-450.

In the absence of manganese (III)-salophen catalyst, $NaIO_4$ has poor ability to oxidize 1,4-dihydropyridines to their corresponding pyridine derivatives at room temperature (6–10% yields).

In the catalytic oxidation of 1,4-dihydropyridines, we examined different oxidants such as NaOCl, $NaIO_4$, H_2O_2, *tert*-butylhydroperoxide, and urea–H_2O_2 (UHP) in the oxidation of 1,4-dihydropyridines. The results are summarized in Table 3. When NaOCl, *tert*-butylhydroperoxide, and urea–H_2O_2 (UHP) are used as oxygen sources in acetonitrile or dicholoromethane, Mn(salophen) shows poor ability in the oxidation of 1,4-dihydropyridines and in comparison with $NaIO_4$, H_2O_2 showed lower activity. When sodium periodate is used as the oxygen source, a higher yield is observed.

Table 3. Effect of various oxidants on the oxidation of 4-phenyl derivative of 1,4-dihydropyridines

Oxidant	Solvent	Yield (%)[a] after 5 min
$NaIO_4$	CH_3CN/H_2O	97
H_2O_2	CH_3CN	87
H_2O_2/urea	CH_3CN	44
NaOCl	CH_3CN	31
t-BuOOH	CH_3CN	23

[a] Isolated yields.

3. Conclusions

Mn(III)salophen/$NaIO_4$ catalytic system have the following advantages in the oxidation of Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives: (i) understanding the action of cytochrome P-450 in the oxidation of Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives, (ii) short reaction time, (iii) high efficiency for oxidation of Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives, (iv) mild reaction conditions, and (v) ease of preparation of the catalyst.

Therefore, the present method could be a useful addition to the available methods in organic synthesis.

4. Experimental

Schiff base complexes **1**–**11** (Fig. 1) were prepared as described by Boucher[27] or by the more recently modified methods.[14,28,29] All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures.[30] ^1H NMR spectra were obtained with a Brucker AW80 (80 MHz) spectrometer.

4.1. General procedure for oxidation of Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives

All reactions were carried out at room temperature in a 25 mL flask equipped with a magnetic stirring bar. A solution of sodium periodate (2 mmol in 5 mL H_2O) was added to a mixture of Hantzsch 1,4-dihydropyridine (1 mmol), Mn-salophen (0.067 mmol) in CH_3CN (5 mL). Progress of the reaction was monitored by TLC. After the reaction was completed, the reaction products were extracted with CH_2Cl_2 (20 mL) and purified by a silica gel plate or a silica gel column (eluent: CCl_4–Et_2O). The identities of products were confirmed by mp, IR, and ^1H NMR spectral data.

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