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Biomimetic oxidation of Hantzsch 1,4-dihydropyridines with tetra-*n*-butylammonium periodate catalyzed by tetraphenylporphyrinatomanganese(III) chloride [Mn(TPP)Cl]

Masoud Nasr-Esfahani,[a] Majid Moghadam,[a,*] Shahram Tangestaninejad[b] and Valiollah Mirkhani[b]

[a]*Department of Chemistry, Yasouj University, Yasouj 75914-353, Iran*
[b]*Department of Chemistry, Isfahan University, Isfahan 81746-73441, Iran*

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Abstract—Efficient oxidation of Hantzsch 1,4-dihydropyridines to their corresponding pyridine derivatives with $(Bu_4N)IO_4$ catalyzed by tetraphenylporphyrinatomanganese(III) chloride [Mn(TPP)Cl] is reported. This catalytic system shows high efficiency in the oxidation of 1,4-dihydropyridines at room temperature in the presence of imidazole.

1. Introduction

Synthetic metalloporphyrins are well known for their ability to carry out a wide range of oxidation reactions. These catalysts have attracted much attention because their structures are similar to cytochrome P-450, a natural catalyst which oxidizes foreign organic compounds and metabolizes drugs in our bodies.[1] It was found that when metalloporphyrins were used as catalysts, organic compounds could be oxidized by oxygen donors such as PhIO, ClO^-, H_2O_2, ROOH or IO_4^-.[2–11] The high efficiency of some of these systems makes them potentially useful for preparative oxidations in organic synthesis.

Hantzsch 1,4-dihydropyridines are widely used as calcium channel blockers for the treatment of cardiovascular disorder including angina, hypertension and cardiac arrhythmias.[12] In the human body, these compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver.[13] These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds.

In this paper, we report the room temperature oxidation of 1,4-dihydropyridines with tetra-*n*-butylammonium periodate to their corresponding pyridine derivatives catalyzed by Mn(TPP)Cl (Fig. 1) in the presence of imidazole in CH_2Cl_2 as solvent (Scheme 1).

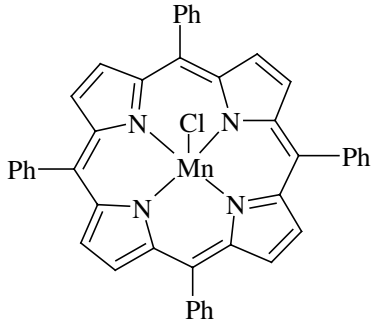

Figure 1. Structure of Mn(TPP)Cl catalyst.

2. Results and discussion

2.1. Oxidation of 1,4-dihydropyridine with $(Bu_4N)IO_4$ catalyzed by Mn(TPP)Cl in the presence of imidazole

Initially, in order to show the periodate anion activation by manganese(III) porphyrin complex, the catalytic oxidation of 4-phenyl derivative of 1,4-dihydropyridine with $(Bu_4N)IO_4$ in the presence of imidazole and in the CH_2Cl_2 was investigated. The obtained results showed that this catalyst is an efficient catalyst in the

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* Corresponding author. Tel.: +98 913 3108960; fax: +98 741 2223048; e-mail: moghadamm@mail.yu.ac.ir

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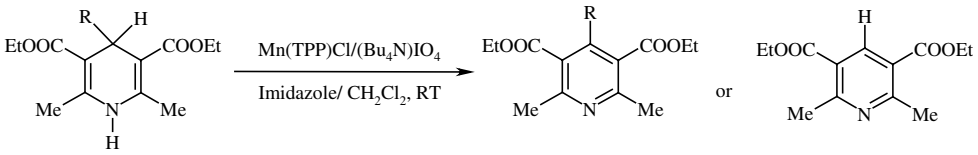
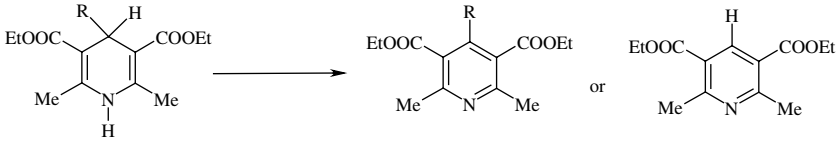
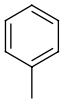
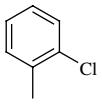
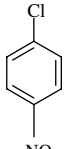
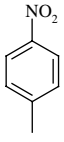
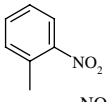
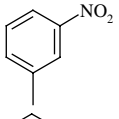
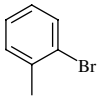
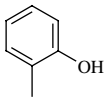
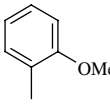
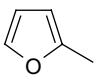
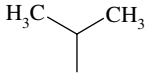


Scheme 1.

oxidation of 4-phenyl derivative of 1,4-dihydropyridine with $(Bu_4N)IO_4$ at room temperature. The manganese(III) porphyrin/$(Bu_4N)IO_4$ catalytic system can be used for oxidizing a wide variety of 1,4-dihydropyridine derivatives bearing an alkyl or an aryl group to their corresponding pyridine derivatives in excellent yields

Table 1. Oxidation of Hantzsch 1,4-dihydropyridines with $(Bu_4N)IO_4$ catalyzed by imidazole modified Mn(TPP)Cl in CH_2Cl_2



Row	R	Time (min)	Yield[a] (%)
1	H	60	98
2	CH_3	60	97
3		65	96
4		80	95
5		60	97
6		75	95
7		80	94
8		80	95
9		90	91
10		80	92
11		80	96
12		60	95
13		60	97

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

at room temperature in the presence of imidazole as axial ligand. As shown in Table 1, oxidation of 4-isopropyl derivative (alkyl moiety may be responsible for generating stable carbocation) was accompanied by expulsion of this substituent and gave dealkylated pyridine derivative (entry 13). All reactions were completed during the appropriate time and gave only the corresponding pyridine derivative. The results are summarized in Table 1.

In the absence of Mn(TPP)Cl catalyst, $(Bu_4N)IO_4$ has poor ability to oxidize 1,4-dihydropyridines at room temperature (6–10% yields).

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

Among methanol, acetone, acetonitrile, chloroform and dichloromethane, CH_2Cl_2 was chosen as the reaction medium, because manganese(III) porphyrin complex, 1,4-dihydropyridine derivatives and oxidant 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

One important aspect of this catalytic system is the modification of the oxidation rate by addition of a small amount of imidazole to the reaction mixture. The formation of their corresponding pyridine derivatives in the absence of axial ligand is slow and the yields are always below 10%, whereas the amount of product reaches 97% in the catalyzed reaction with the imidazole as the axial base.

The effect of different axial ligands upon the oxidation rate decreased in the order: imidazole = 1-methylimidazole > 4-*t*-butylpyridine > pyridine.

3. Experimental

Tetraphenylporphyrin was prepared and metallated according to reported procedure.[14] All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures.[15] ^{1}H NMR spectra were obtained with a Brucker AW80 (80 MHz) spectrometer.

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

All of the reactions were carried out at room temperature in a 25 mL flask equipped with a magnetic stirring bar. To a solution of Hantzsch 1,4-dihydropyridine (1 mmol), Mn(TPP)Cl (0.02 mmol) and imidazole (0.067 mmol) in CH_2Cl_2 (10 mL) was added tetra-*n*-butylammonium periodate (2 mmol). Progress of the reaction was monitored by TLC. After the reaction was completed, the product was purified by silica gel plate or silica gel column (eluent: CCl_4–Et_2O). The identities of products were confirmed by mp, IR and ^{1}H NMR spectral data.

4. Conclusions

Mn(III) porphyrin/IO_4^- catalytic system has 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 and (iv) mild reaction conditions. Therefore, the present method could be a useful addition to the available methods in organic synthesis.

Acknowledgments

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