Biomimetic aromatization of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by a new polystyrene-bound manganese porphyrin

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Abstract: Efficient oxidation of Hantzsch 1,4-dihydropyridines with sodium periodate catalyzed by a polystyrene-bound manganese(III) porphyrin is reported. This catalyst shows high activity in the oxidation of various 1,4-dihydropyridines at room temperature. This heterogeneous catalyst can be reused five times without significant loss of its activity.

Key words: biomimetic oxidation, supported metalloporphyrin, periodate, 1,4-dihydropyridine.

Résumé : On a effectué l'oxydation efficace des 1,4-dihydropyridines de Hantzsch par le biais d'une réaction avec du periodate de potassium catalysée par une porphyrine de manganèse(III) liée à du polystyrène. Ce catalyseur présente une grande activité pour l'oxydation, à la température ambiante, de diverses 1,4-dihydropyridines. Ce catalyseur hétérogène peut être réutilisé jusqu'à cinq fois dans perte significative de son activité.

Mots clés : oxydation biomimétique, métalloporphyrine déposée sur un support, periodate, 1,4-dihydropyridine.

[Traduit par la Rédaction]

Introduction

In the last two decades, metalloporphyrins have been successfully used as models for the cytochrome P-450 enzyme with respect to the oxidation of organic compounds such as hydrocarbons (1–3). Development in this area is based on different strategies with the aim of designing selective, stable, and high turnover catalytic systems (4). 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 to understand the mechanism of the cytochrome P-450 monooxygenation enzyme (5–10). Great efforts have been made toward the chemical modification of the metalloporphyrin microenvironment in the studies of the cytochrome P-450 model. One method is to immobilize the metalloporphyrins onto solid supports. Such immobilization not only modifies the metalloporphyrin microenvironment, but also increases the catalytic activity of metalloporphyrins, so one can prepare the catalysts, which are easier to handle and easily separate from reaction medium. Among the metalloporphyrin microenvironment models, polystyrene derivatives are often utilized because they can provide a suitable microenvironment for the "accommodation" of the porphyrin catalytic center.

Amlodepine besylate, nifedepine, and related dihydropyridines are Ca^{2+} channel blockers and are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension cardiac arrhythmias (11). In the human body, it has been observed that these compounds undergo oxidation to form pyridine derivatives by the action of cytochrome P-450 in the liver. This observation led us to investigate the ability of this biomimetic catalyst to act in the oxidation of 1,4-dihydropyridines. These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds (12, 13).

Recently, we reported on the oxidation of 1,4-dihydropyridines with tetra-*n*-butylammonium periodate catalyzed by homogeneous Mn(TPP)Cl (14). In this paper, we report on the efficient oxidation of 1,4-dihydropyridines with sodium periodate at room temperature catalyzed by a Mn(TPyP) supported on chloromethylated polystyrene (CMP) (Scheme 1).

Results and discussion

The manganese(III) tetrapyridylporphyrin supported on polystyrene (Mn(TPyP)–CMP) is easily prepared from commercially available porphyrin and chloromethylated polystyrene (Fig. 1).

The high catalytic activity of this heterogeneous catalyst in the alkene epoxidation and alkane hydroxylation and oxidation of alcohols (15, 16) prompted us to investigate its ability in the oxidation of 1,4-dihydropyridines with sodium periodate at mild reaction conditions. The oxidation of 1,4-dihydropyridines by Mn(TPyP)–CMP and sodium periodate yielded the corresponding pyridine derivative in CH_3CN–

Received 6 July 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 3 February 2006.

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 doi:10.1139/V05-255

Scheme 1.

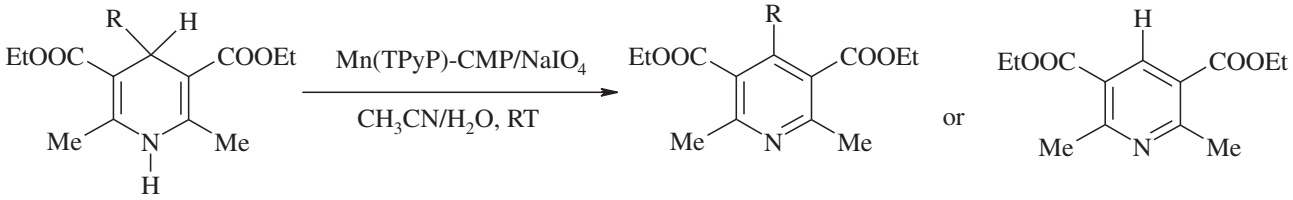
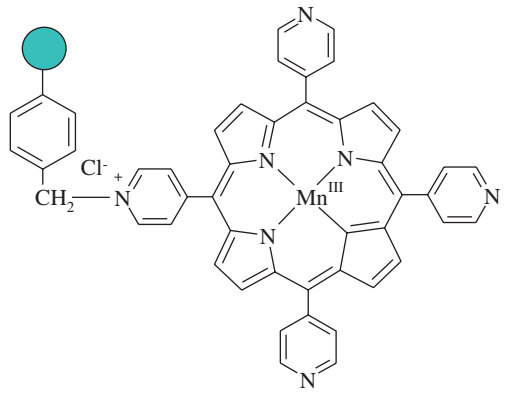


Fig 1. The catalyst used in this study.



H_2O (1:1) as solvent, whereas trace amounts of the product was detected when the identical reaction was carried out in the absence of periodate. The effects of other oxidants were also studied in the oxidation of 4-phenyl derivatives of 1,4-dihydropyridines. The obtained results showed that $NaIO_4$ is more effective than H_2O_2, NaOCl, *t*-BuOOH, and urea-hydrogen peroxide adduct (UHP) (Table 1). To choose the reaction media, different solvents were investigated in the oxidation of 4-phenyl derivatives of 1,4-dihydropyridines. As shown in Table 2, among the studied solvents, the 1:1 mixture of CH_3CN–H_2O was chosen as solvent because a higher amount of pyridine derivative was observed. The blank experiment, in the absence of catalyst, showed that the presence of catalyst is crucial in oxidation reactions. In biomimetic systems using metalloporphyrins as catalyst, addition of an axial base is necessary to obtain high catalytic activity. One observation is that this catalytic system shows higher catalytic activity in the absence of imidazole. When imidazole is added as axial ligand to this catalytic system, the reaction times become longer in the oxidation of 1,4-dihydropyridines. For instance, the oxidation of 4-phenyl and 4-nitrophenyl derivatives was completed in 60 and 90 min, respectively; but addition of imidazole as co-catalyst led to longer reaction times of 90 and 150 min for 4-phenyl and 4-nitrophenyl derivatives, respectively. These observations show that the 1,4-dihydropyridines can play the axial ligand role. The Mn(TPyP)–CMP–$NaIO_4$ catalytic system can be used for oxidizing a wide variety of 1,4-dihydropyridine derivatives to their corresponding pyridine derivatives giving excellent yields at room temperature. All reactions were completed during the appropriate time (until no starting material is detected by TLC) and gave only the corresponding pyridine derivatives. The results are summarized in Table 3. As shown in Table 3, the oxidation of the 4-isopropyl derivative accompanied by expulsion of this substituent gave the dealkylated pyridine derivative (Table 3, entry 12), which was previously reported by Ortiz de Montellano et al. (17) in the oxidation of 1,4-dihydropyrines by cytochrome P-450. This approach shows that this synthetic model behaves in the same way as cytochrome P-450.

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

Oxidant	Solvent	Yield (%)[a]
$NaIO_4$	CH_3CN–H_2O	97
H_2O_2	CH_3CN	40
H_2O_2–urea	CH_3CN	32
NaOCl	CH_3CN	17
t-BuOOH	CH_3CN	10

[a]Isolated yields.

Table 2. Effect of solvent oxidation of 4-phenyl derivatives of 1,4-dihydropyridines.

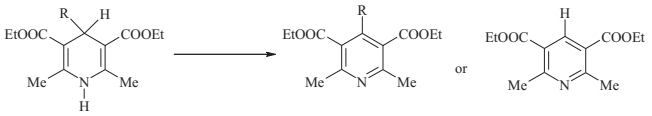
Solvent	Yield (%)[a] after 60 min
CH_3CN–H_2O	97
CH_3COCH_3–H_2O	75
CH_3OH–H_2O	58
CH_3CH_2OH–H_2O	42
$CHCl_3$–H_2O	15
CH_2Cl_2–H_2O	33
CCl_4–H_2O	8

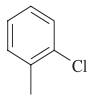
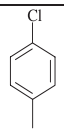
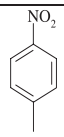
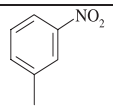
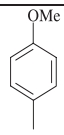
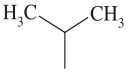
[a]Isolated yields.

We also studied recycling of the used Mn(TPyP)–CMP in the repeated oxidation reactions. After the first run, the polymer was recovered by filtration followed by washing with water and acetonitrile and then reused. The catalyst was reused five consecutive times without loss of its activity. No manganese was detectable in the filtrates by atomic absorption spectrometry.

From a synthetic point of view, the oxidation of Hantzsch 1,4-dihydropyridines is an old reaction in synthetic organic chemistry. In recent years, several new methods have been reported for dehydrogenation of Hantzsch 1,4-dihydropyridines with ferric or cupric nitrates on a solid support: ceric ammonium nitrate, pyridinium chlorochromate, *t*-BuOOH, photochemical oxidation, NO gas, inorganic acidic salts – $NaNO_3$ – wet SiO_2, and $NaHSO_4$–$NaNO_2$ (18). Most of the reported procedures suffer from disadvantages such as producing by-products that are difficult to remove from the desired product, using the reagents that are either highly toxic or present serious environmental problems (or both such as NO), and nonreusability of heterogeneous catalysts. The comparison of our reported system with the previously re-

Table 3. Oxidation of Hantzsch 1,4-dihydropyridines with $NaIO_4$ catalyzed by Mn(TPyP)–CMP.



Row	R	Time (min)
1	H	60
2	CH_3	60
3		60
4		120
5		90
6		90
7		130
8		120
9		140
10		140
11		60
12		60[a]
13		90
14		70

Note: All products were identified by comparison with authentic samples (IR, ^{1}H NMR, and mp).

[a]The product is dealkylated.

ported systems shows that the Mn(TPyP)–CMP–$NaIO_4$ catalytic system has the following advantages: mild reaction conditions, robustness of the catalyst, nontoxicity of reagents, and reusability of the catalyst without loss of its activity.

Experimental

All materials were commercial reagent grade. The tetrapyridylporphyrin ligand (TPyP) was purchased from the Fluka Chemical Company (Dubai, UAE), and metalated and supported according to literature procedures (19, 14). All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures (20). ^{1}H NMR spectra were obtained with a Bruker AW80 (80 MHz) spectrometer.

General procedure for oxidation of 1,4-dihydropyridines with $NaIO_4$ catalyzed by Mn(TPyP)–CMP

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) and MnTPyP–CMP (20 μmol) in CH_3CN (10 mL). The progress of the reaction was monitored 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 the solvent. Further purification was followed using a silica gel plate. IR and ^{1}H NMR spectral data confirmed the identities of the products.

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