Catalytic oxidation of 1,4-dihydropyridins by tetrabutylammonium periodate in the presence of manganese amino acid Schiff base

Gholam Reza Karimipour*, Masoud Nasr-Esfahani and Ghasem Valipour

Department of Chemistry, Yasouj University, Yasouj 75914-353, Iran

The amino acid Schiff base manganese complex (Tryp–Mn); **1,** was prepared with L-tryptophan, salicylaldehyde and $Mn(OAc)_2.4H_2O$ in methanol. In the presence of **1**, 1,4-dihydropyridines (1,4-DHPs) were oxidised by *n*-Bu_4NIO_4 to the corresponding pyridine derivatives in high yields. Imidazole was used as an additive to improve the catalytic oxidation.

Keywords: amino acid Schiff base, 1,4-dihydropyridine, tetrabutylammonium periodate, oxidation

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are the analogues of NADH coenzymes known as Ca^{2+} channel blockers.[1] They have received most attention because of their relevant applications in various cardiovascular diseases and hypertension, and of their pharmacological activity in antioxidant protective effects.[2] 4-substituted-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl esters have anti-hypoxic and anti-ischemic behaviours. Moreover, Hantzsch 1,4-DHPs are important agents for organic synthesis. For example, various novel dihydroindolizine-based compounds were synthesised using 2-formyl-1,4-DHP by the Michael addition/intramolecular amino-nitrile cyclisation method.[3]

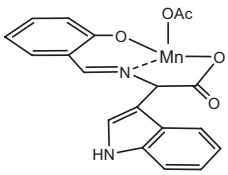
The oxidation of 1,4-DHPs is also one of the ubiquitous issues in organic chemistry. Various methods were employed for this purpose including oxidation with ferric nitrate on a solid support,[4] ceric ammonium nitrate,[5] Claycop,[6] pyridinium chlorochromate,[7] nitric acid,[8] nitric oxide and N-methyl-N-nitrosotoluene-P-sulfonamide.[9] Recently, periodate has been used extensively in oxidation of 1,4-DHPs in the presence of metalloporphyrin catalysts.[10-13]

We now report the room temperature oxidation of 1,4-DHPs with tetrabutylammonium periodate (*n*-Bu_4NIO_4) to their corresponding pyridine derivatives catalysed by a L-tryptophan-base manganese(III) complex (Tryp–Mn); **1** (Fig. 1) in CH_2Cl_2.

Results and discussion

The ligand and manganese(III) complex (Tryp–Mn) (**1**) were synthesised according to Wong *et al.* (Scheme 1).[14] The IR spectrum (KBr) of **1** was compared with that of the free ligand to determine the changes that might have taken place during the complexation. The results show that vibration absorption bands appear at 1616 cm^{-1}($\upsilon_{as\ COO}$), 1410 cm^{-1} ($\upsilon_{s\ COO}$), 1635 ($\upsilon_{C=N}$) and 1249 cm^{-1} (υ_{Ph-O}) for the amino acid Schiff base ligand.

The metal ion coordination caused a dramatic change in COO, C=N and Ph-O vibrations, leading to changes of their characteristic frequencies to 1600, 1376, 1625 and 1236 cm^{-1} respectively. Moreover, bands at 548 cm^{-1} and 441 cm^{-1} appear in the complex and are attributed to the Mn–N and Mn–O stretching vibrations, respectively. These structural data are nicely consistent with the results obtained by Wong *et al*.[14]



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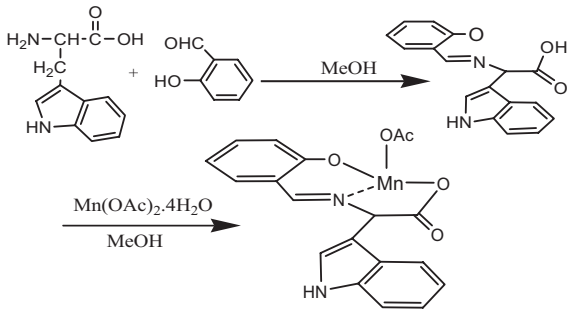
* Correspondent. E-mail:ghkar@mail.yu.ac.ir



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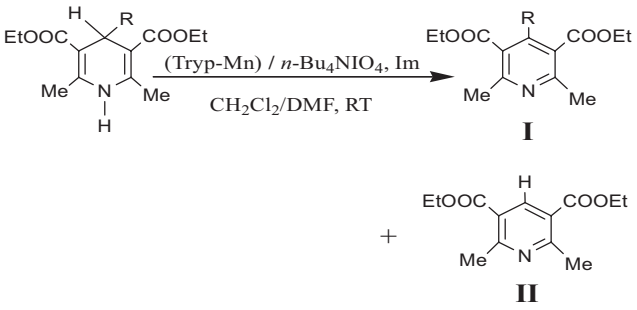
Scheme 1 Synthesis of the Schiff base ligand and the Tryp–Mn complex (**1**).

Oxidative dehydrogenation of 1,4-DHPs

Tetrabuthylammonium periodate (*n*-Bu_4NIO_4), soluble in chlorinated organic solvents, is used as a neutral weak oxidant for sulfides, α-bromoketones and α-hydroxycarboxylic acids.[15] However, it can serve as a potent monooxygen donor by combining with metalloporphyrin catalysts, simulating the function of P-450.[16]

As a continuation of our studies on the oxidative decarboxylation of diphenylacetic acid[17] and epoxidation of alkenes with periodates,[18] we now report the oxidation of Hantzsch 1,4-DHPs to the corresponding pyridine derivatives by *n*-Bu_4NIO_4 in the presence of **1** as catalyst. By control experiments employing different solvents and their selected mixtures, CH_2Cl_2/DMF (90/10) was chosen as the expedient solvent due to the facile solvation of starting materials, oxidant and **1** in this mixed solvent. DMF is necessary because CH_2Cl_2 has very little capability to solve the complex. We first confirmed that the oxidative dehydrogenation of 1,4-DHPs does not proceed by *n*-Bu_4NIO_4 alone. Furthermore, the reactions are not affected even if performed in the presence of the simple $Mn(OAc)_3.2H_2O$ and $Mn(OAc)_2.4H_2O$ salts. The efficiency of **1** as catalyst was then tested by changing its concentration in the reaction mixture. We found that the yields reach in a maximum value when the **1**/DHP ratio was 1/2.

It is notable that the catalytic activity of **1** increased during the reactions. It seems that the produced pyridine derivatives act as axial ligands for the catalyst, leading to acceleration of the oxidation during the course of the reactions. This hypothesis was confirmed by adding a nitrogenous donor such as imidazole into the reaction mixture. We found that the oxidation rate was 1.3 times that of no imidazole. Nitrogenous ligands such as imidazoles and pyridines are reported to improve selectivity, reactivity and turnover number of metalloporphyrin-mediated reactions, leading to weakening of the M–O bond in the oxidised form of the porphyrin catalysts by donating electron density into the M–O antibonding orbitals, which can account for the improved reactivity.[19]



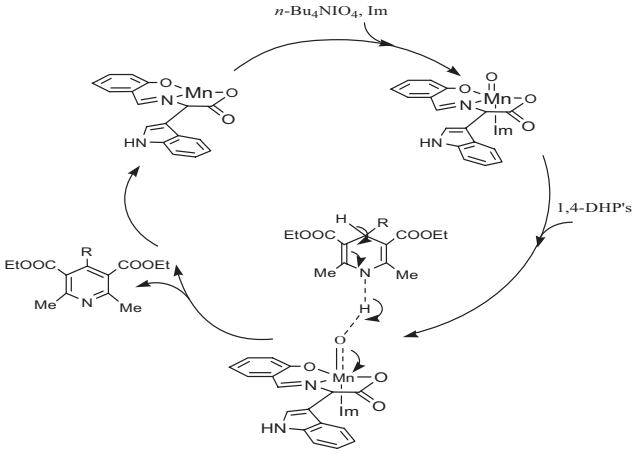
Scheme 2

When acetic acid was added as the additive into the oxidation systems, formation of the pyridine products is completely retarded. It seems that the nitrogenous ligand is bound to the Mn centre during the course of the reactions.

The coordinated nitrogenous bases (*i.e.* imidazole and/or produced pyridines) aid the possible electronic changes in the Mn centre in the proposed catalytic cycle shown in Scheme 3, leading to facile formation of the pyridine products. Addition of *n*-Bu_4NIO_4 and imidazole into the reaction mixture caused the generation of an imidazolated, high-valent, manganese oxo complex.

The oxidation was preceded by an electrophilic attack of oxo ligand to the N–H hydrogen atom, followed by a concomitant elimination of the hydrogen atom on the 4-position of the 1,4-DHPs as shown in Scheme 3.

It is important to note that dealkylation of 4-alkyl substituted 1,4-DHPs can be explained by this simple catalytic cycle. So, the elimination of the R groups on 4-position of 1,4-DHPs could lead the formation of dealkylated pyridine derivatives (Scheme 2).

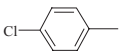
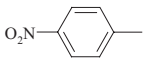
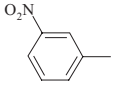
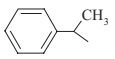
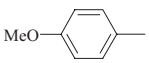


Scheme 3 A simple proposed catalytic cycle for oxidation of 1,4-DHPs by the *n*-Bu_4NIO_4/Tryp–Mn/Im system.

Initially, in order to show the periodate anion activation by **1**, the catalytic oxidation of 4-phenyl derivative of 1,4-dihydropyridine with *n*-Bu_4NIO_4 in the presence of imidazole was investigated. The obtained results showed that this complex is an efficient catalyst in the oxidation of 4-phenyl derivative of 1,4-dihydropyridine with *n*-Bu_4NIO_4 at room temperature.

The Tryp–Mn/*n*-Bu_4NIO_4 catalytic system can be used for oxidising a wide variety of 1,4-dihydropyridine derivatives bearing an alkyl or aryl group to their corresponding pyridine derivatives in good to excellent yields at room temperature in the presence of imidazole as axial ligand. As shown in Table 1, oxidation of a 4-(1-methyl-1-phenyl) derivative (alkyl moiety may be responsible for generating stable carbocation) was

Table 1 Oxidation of Hantzsch 1, 4-dihydropyridines with *n*-Bu_4NIO_4 catalysed by Tryp–Mn (**1**)[a]

Entry	R	Time/min	Yield/%[c]
1	H	10	92
2	CH_3	15	95
3		120	94
4		45	92
5		20	91
6		25	93
7		70	95
8		180[b]	93
9		70	92
10		50	94
11		48	95

[a]All products were identified by comparison with authentic samples (IR, ^{1}H NMR, m.p.).
[b]The product is a dealkylated pyridine derivative.
[c]Isolated yields.

accompanied by expulsion of this substituent to give the dealkylated pyridine derivative (entry 8). All reactions were completed during the appropriate time and gave only the corresponding pyridine derivative. In the absence of Tryp–Mn catalyst, *n*-Bu_4NIO_4 has poor ability to oxidise 1,4-dihydropyridines at room temperature (7–12% yields; not shown).

Experimental

L-tryptophan, salicylaldehyde, $Mn(OAc)_2.4H_2O$ and *n*-Bu_4NIO_4 were obtained from Aldrich and were used without further purification. All Hantzsch 1,4-dihydropyridines were synthesised by the reported procedures.[20] IR and NMR spectra were measured on Shimadzu IR-435 and Brucker AW DPX 250 spectrometers, respectively. The Schiff base ligand and Tryp–Mn **1** were synthesised in a manner similar to that described by Wong *et al*.[14] However, the complex synthesis was achieved under Argon.

General procedure

In a 10 ml round bottom flask were added in order: 1,4-DHP (0.5 mmol), Tryp–Mn **1** (0.001 mmol) imidazole (0.05 mmol) in CH_2Cl_2/DMF (90/10). The reaction mixture was stirred until the complete dissolution of chemicals. Tetrabutylammonium periodate (0.55 mmol) was then added to began the oxidation. The mixture was stirred thoroughly for the required time at ambient temperature in air. The products were separated by a simple flash chromatography and analysed.

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