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CATALYTIC AROMATIZATION OF HANTZSCH 1, 4-DIHYDROPYRIDINES BY BIS (SALICYLALDEHYDE-1, 2-PHENYLENEDIIMINE) Mn (III) CHLORIDE USING UREA HYDROGEN PEROXIDE AS MILD AND EFFICIENT OXIDANT

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Abstract – A variety of Hantzsch 1,4-dihyropyridines were oxidized efficiently by a catalytic amount of bis(salicylaldehyde-1,2-phenylenediimine)Mn(III) chloride (Mn(III)-salophen **I)** in the presence of urea hydrogen peroxide adduct (UHP **II**) as convenient and mild oxidant to afford the related pyridine derivatives in high yields at room temperature.

INTRODUCTION

It has been recognized Hantzsch 1,4-dihydropyridines act as vital drugs in the treatment of angina and hypertension. Some of these compounds such as Amlodipine, Felodipine, Isradipine, Lacidipine, Nicardipine and Nimodipine are commercially available. Therapeutic success of these compounds is related to their efficiency to bind to calcium channels and consequently to decrease the passage of the transmembrance calcium current for the treatment of cardiovascular diseases.[1-4] In addition to biological application of 1,4-dihydropyridines, these compounds are used for preparation of pyridine derivatives in organic synthesis. Various reagents and methods have been introduced for this purpose, such as ferric or cupric nitrates on a solid support (clayfen or claycop),[5] ceric ammonium nitrate,[6] clay-supported cupric nitrate accompanied by ultrasound-promotion,[7] manganese dioxide or DDQ,[8] nitric oxide,[9] bismuth nitrate pentahydrate,[10] PCC, [11] tetrakis-pyridine cobalt(II) dichromate (TPCD),[12] nicotinium dichromate,[13] S-nitrosoglutathione,[14] N_2O_4 complex of 18-crown-6,[15] diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents,[16] $KMnO_4$,[17] CrO_3,[18] HNO_3,[19] HNO_2,[20] *tert*-butyl hydroperoxide,[21] silica gel supported ferric nitrate (silfen),[22] N_2O_3,[23] photochemical oxidation, [24] inorganic acidic salts and sodium nitrite or nitrate and catalytic oxidation.[25-27]

Amongst above methods, chemists today have been interested to resemble biotic systems

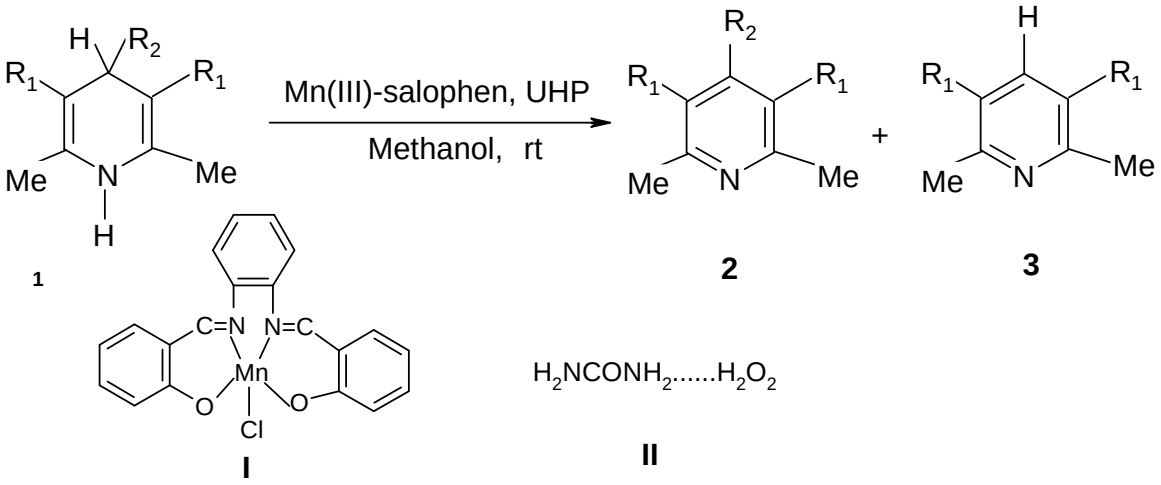
because of their high efficiency and mild conditions. In this direction, many efficient enzymatic model systems such as metal porphyrins[28-31] and metal-tetra dentate Schiff base complexes have been used for the oxidation of organic compounds[32-37] in the presence of PhIO, OCl^-, persulfates and periodate[38-42] as oxygen donating compounds. Although manganese Schiff base complexes have been used as biomimetic catalyst in several oxidation methods, development of their application in this category of reaction is important for chemists yet.

In the present paper, we report a new role of Mn (III) - salophen (**I**) as biomimetic catalyst for the oxidation of 1,4-dihyropyridines to the corresponding pyridine derivatives using urea hydrogen peroxide(**II**) as single oxygen donating compound. We have chosen urea hydrogen peroxide adduct(**II**) because it has been used as an odorless, safe, non-toxic and easy to use white crystalline powder which releases hydrogen peroxide locally on application in many reports. Over the past few years, several papers have been published on the use of urea hydrogen peroxide adduct(**II**) in the oxidation reactions such as Baeyer-Villiger oxidation of ketones,[43] oxidation of sulfides to sulfones,[44] oxidation of aromatic aldehyde,[45] epoxidation of alkenes.[46] Recently we reported oxidation of imines to oxaziridines and nitrones using UHP(**II**) / maleic anhydride system.[47] In these application, urea-hydrogen peroxide(**II**) alone or in combination with carboxylic acid or anhydride as catalyst (rarely inorganic complex as co-catalyst) has acted as mild and efficient oxidant.[48]

RESULTS AND DISCUSSION

Metal Schiff base complexes have been used widely as efficient catalysts for oxidation of various substrates with hydrogen peroxide. During the search for a good mediator or catalyst that can transfer active oxygen of UHP(**II**) to 1,4-dihydropyridines oxidation systems, we found Mn(III)- salophen(**I**) suitably catalyses oxidative aromatization of 1, 4-dihydropyridines in the presence of UHP(**II**) as oxidant (Scheme 1). Therefore, general factors in the catalytic system such as solvent, exigency of an axial ligand, amount of the catalyst, oxidant and temperature were investigated by a typical reaction on **1c** Among the methanol, acetonitrile, chloroform, dichloromethane and carbon tetrachloride, we found methanol as the best solvent. Very low aromatization in the absence of imidazole as axial ligand revealed necessity of it for the efficient catalytic conversion. Various molar ratios of the catalyst to the substrate, 1/50, 1/25, 1/15 and 1/10 were used and based on the completion time of the reaction, 300 min, 180 min, 90 min and 50 min , we recognized 1/10 molar ratio as optimum. With this optimum amount of the catalyst to the substrate,

different molar ratio of the oxidant, UHP(**II**) to the substrate 2/1, 4/1 and 6/1 were used. With 2/1 molar ratio, the reaction was not completed even with prolonged time. The 4/1 molar ratio completed the conversion in 180 min but the 6/1 molar ratio resulted maximum conversion in minimum reaction time. In some reactions containing UHP(**II**), 0 ^{0}C has reported the proper temperature but we did not observe considerable change between 0 ^{0}C and room temperature in the progress of reaction. After optimization of these factors, a variety of 1, 4-dihydropyridines were subjected to the catalytic oxidative aromatization (Scheme1, Table 1).



Scheme 1

The aromatization reactions were carried out under the optimized conditions at room temperature with good to excellent yields. The results were summarized in Table 2. As shown in Table 2 the oxidation of 1,4-dihydropyridines(**1**) (Entries 5, 6) bearing secondary or tertiary alkyl substituent (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gives only dealkylated pyridine derivative(**3**). This is in agreement with the observation made by other employing different oxidative conditions.[49] However, aryl- substituted 1, 4-dihydropyridines(**1**) (Entries 4, 7-12 and 15) furnished the corresponding pyridine derivatives (**2**) (Table 2).

Based on these evidences and other reported mechanism, [48] the shown mechanism in Scheme 2 is proposed for the oxidation of 1,4- dihydropyridines in our reaction conditions.

In Scheme 2 Mn (III)-salophen(**I)** is converted to [Mn^V (O)-salophen](**4**) by released H_2O_2 from UHP(**II**), which is the oxidant that affords a hydroperoxy manganese species(**3**). Also hydroperoxy manganese can be assumed as the active species without the presence of oxo-compound(**4**), [48] but necessity of axial ligand

for convenient progress of the reaction support(**4**) as an important oxidant in our reactions. In the next stage, 1, 4- dihydropyridines(**1**) approaches to oxidant species(**4**) and 1, 4- dihydropyridine- Mn^{III}- salophen

Table 1. 1, 4-Dihydropyridines (**1**) and their corresponding pyridine derivatives (**2** or **3**).

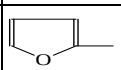
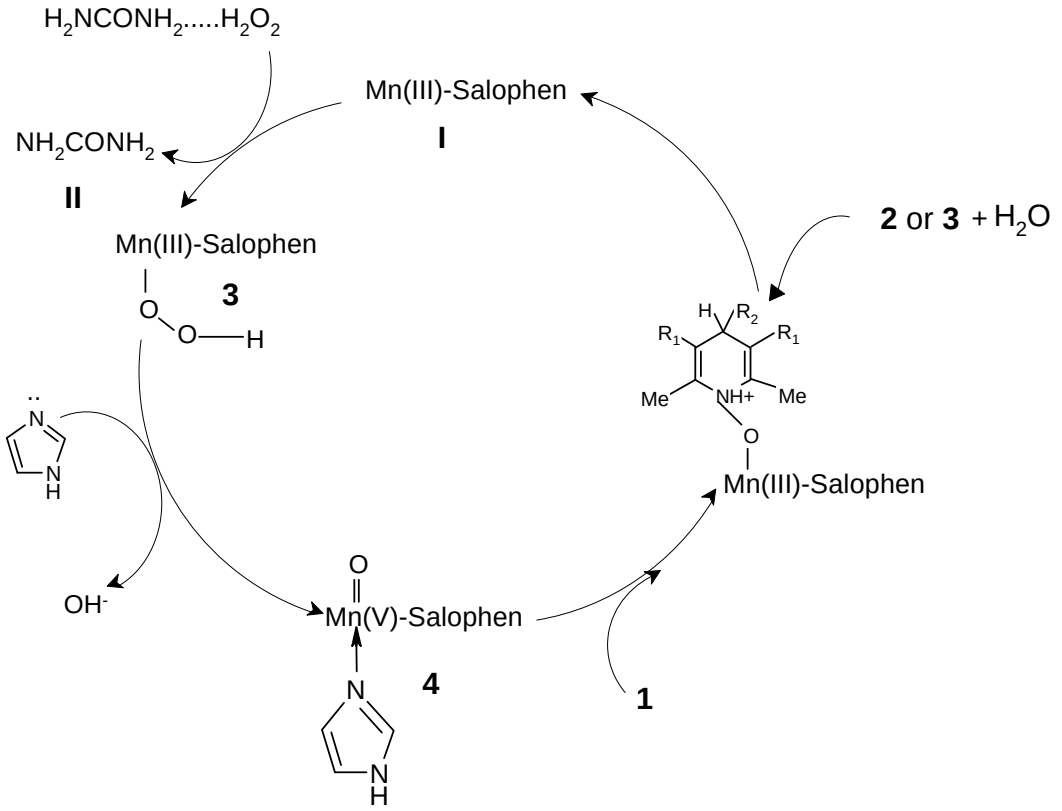
1,2,3	**R_1**	**R_2**	**1,2,3**	**R_1**	**R_2**
a	COOEt	H	**i**	COOEt	4-MeO-C_6H_4-
b	COOEt	Me	**j**	COOEt	4-Cl-C_6H_4-
c	COOEt	Et	**k**	COOEt	
d	COOEt	Ph	**l**	COOEt	4-Br-C_6H_4-
e	COOEt	*i*-Pr	**m**	COMe	H
f	COOEt	*t*-Bu	**n**	COMe	Me
g	COOEt	3-NO_2-C_6H_4-	**o**	COMe	Ph
h	COOEt	2-MeO-C_6H_4-			

Table 2. Oxidation of 1,4-dihydropyridines (**1**) to their corresponding pyridine derivatives (**2** or **3**) by Mn (III)-salophen (**I**) using UHP (**II**) in methanol at room temperature.

Entry	Substrate	Product	Time (min)	Yield [a,b] (%)	Ref.
1	**1a**	**3a**	10	93	25-26
2	**1b**	**2b**	40	92	25-26
3	**1c**	**2c**	50	91	25-26
4	**1d**	**2d**	15	90	25-26
5	**1e**	**3e**	60	94	25-26
6	**1f**	**3f**	40	94	25-27
7	**1g**	**2g**	90	90	25-26
8	**1h**	**2h**	20	88	25-26
9	**1i**	**2i**	45	89	25-26
10	**1j**	**2j**	60	92	25
11	**1k**	**2k**	20	92	25-27
12	**1l**	**2l**	60	91	26-27
13	**1m**	**2m**	40	87	25-27
14	**1n**	**2n**	40	90	25, 27
15	**1o**	**2o**	30	91	25, 27

[a] Isolated yields. [b]0.1 mmol (**I**): 0.5 mmol imidazole: 6 mmol (**II**): 1 mmol substrate

complex is formed that releases pyridine derivative (**2** or **3**), water and regenerated Mn (III)-salophen (**I**). In conclusion, we described a facile, mild and biomimetic oxidation of 1, 4- dihydripyridines(**1**) to relative



Scheme 2

pyridine derivatives using catalytic amounts of Mn (III) - salophen (**I)** as biotic model catalyst in the presence of UHP (**II**) as stable, safe and non-toxic oxidant. Several advantages of this method including high yields of products, relatively short reaction times, inexpensive (catalytic amount of Mn (III) - salophen (**I**) and ease of preparation of catalyst which make this reaction convenient and efficient in organic synthesis.

EXPERIMENTAL

Chemicals were purchased from Aldrich, Fluka and Merck. UHP (**II**) was synthesized according to previous report. Mn (III)-salophen (**I**) was prepared as previous described method.[50] 1,4- Dihydropyridines (**1**) were prepared according to literature.[20] The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with those in the literatures.[25-27] IR spectra were recorded on FT-IR JASCO-680 and the ^{1}H-NMR spectra were obtained on a Brucker instrument 300 MHz model.

General procedure for aromatization of 1,4- dihydropyridines (1)

To a solution of 1 mmol of 1,4- dihydropyridine (**1**) in 15 mL of methanol, 6 mmol of UHP(**II**), 0.1 mmol of Mn(III)-salophen (**I**) and 0.5 mmol of imidazole were added at rt. Completion of aromatization reaction was followed by TLC (n-hexane: ethyl acetate, 8:2). After completion of the reaction, the solvent was evaporated under vacuum at rt and then 10 mL of CH_2Cl_2 was added and filtered on silica gel. Dichloromethane was removed by water bath to afford corresponding pyridine derivative.

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