Asian Journal of Chemistry Vol. 22, No. 6 (2010), 4249-4254

Biomimetic Catalytic Oxidation of Hantsch 1,4-Dihydropyridines Using [*Bis*-(salicylaldehye)-4-methyl-1,2-phenylenediimine]-Mn(III) Chloride/Sodium Periodate Under Mild Conditions

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[*Bis*(salicylaldehye)-4-methyl-1,2-phenylenediimine]Mn(III) chloride [Mn(III)-BSMP] as biomimetic catalyst was synthesized and identified by spectral and analytical data. A variety of Hantzsch 1,4-dihyropyridines were subjected by a catalytic amount of this catalyst in the presence of sodium periodate as convenient and mild oxidant to afford the related pyridine derivatives in good to high yields at room temperature. The effects of some operational parameters such as amount of catalyst, the type of oxidant, necessity of axial ligand and solvent effect were investigated.

Key Words: Oxidation, Schiff base, Pyridines, Catalytic.

INTRODUCTION

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. The 1,4-dihydropyridine based drugs are oxidatively transformed into the related pyridines by the action of cytochrome P-450 in the liver[1,2]. Furthermore the aromatization of readily accessible 1,4-dihydropyridines is known as the easiest method to obtain pyridine derivatives. It is evident that the aromatization of 1,4-dihydropyridines has been obtained by using various oxidants such as bismuth nitrate *penta*-hydrate[3] PCC[4], *tetrakis*-pyridine cobalt(II) dichromate (TPCD)[5], nicotinium dichromate[6], S-nitrosoglutathion[7], N_2O_4 complex of 18-crown-6[8], diphenylpicrylhydrazyl and benzoyl peroxide as free radical oxidizing agents[9], $KMnO_4$[10], CrO_3[11], *tert*-butyl hydroperoxide[12], silica gel supported ferric nitrate (silfen)[13], photochemical oxidation[14], inorganic acidic salts and sodium nitrite or nitrate and catalytic oxidation[15-18] Dess-Martin periodinane[19], silver carbonate on silica gel and celite[20], microwave-assisted with $FeCl_3{\cdot}SiO_2$[21], bismuth(III) chloride supported onto wet HZSM-5 zeolite[22], selenium dioxide[23], iodobenzene diacetate[24], iodoxy benzoic acid (IBA)[25], iodine/alkali hydroxide[26], the one-pot synthesis and aromatization in refluxing water[27], Co(II) catalyzed auto oxidation[28] and biomimetic catalyzed oxidation[29]. Schiff base complexes similar to metalloporphyrins have been successfully applied as models mimicking the cytochrome P-450 enzyme with respect to the oxidation of organic compounds[30,31]. In this view different strategies have been developed with the aim of designing

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selective and stable catalytic systems with high turnover[32]. It was found that when Schiff base complexes and metalloporphyrins were used as catalysts, organic compounds could be oxidized by oxygen donors[33-37] such as PhIO, ClO^-, H_2O_2, ROOH or IO_4^-. Although manganese Schiff base complexes have been used as biomimetic catalyst in several oxidation methods, but development of their application in this category of reaction is important for chemists yet. In continuation of our recently studies in oxidation reaction[38-42], herein the biomimetic catalytic oxidation of a variety of 1,4-dihydropyridines using [Mn(III)-BSMP]/sodium periodate under mild conditions is reported.

EXPERIMENTAL

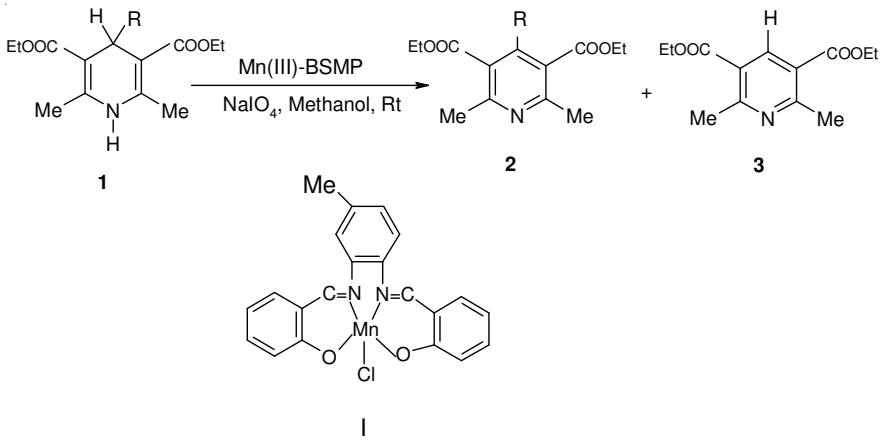
All chemicals were commercial reagent grade from the Fluka Chemical Company. All Hantzsch 1,4-dihydropyridines were synthesized by the reported procedures[43]. Tetradentate ligand, *bis*(salicylaldehyde)-4-mthyl-1,2-phenylenediimine was synthesized according to previous report and identified by spectral and physical data[44]. ^{1}H NMR spectra were obtained with a Bruker (250 MHz) spectrometer. IR spectra were recorded on JASCO-680 FT-IR. Melting points were recorded on Barnstead Electrothermal.

Synthesis of [*bis*(salicylaldehye)-4-methyl-1,2-phenylenediimine]Mn(III) chloride catalyst [Mn(III)-BSMP]: Ligand, *bis*(salicylaldehyde)-4-methyl-1,2-phenylenediimine was synthesized according to previous report[42] by condensing of 2 mmol (0.122 g) of salicylaldehyde and 1 mmol of 4-methyl 1,2-phenylenediimine) in ethanolic solution. The catalyst was prepared similar to previously reported method *via* addition of 20 mL ethanolic solution of $MnCl_2 \cdot 4H_2O$ (1 mmol, 0.198 g) to synthesized ligand (1 mmol, 0.375 g) in 20 mL ethanol. The reaction mixture was severely stirred for 0.5 h and then was treated by air bubbling for 6 h. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated and dark brown precipitate of Mn(III)-BSMP was filtered. IR (KBr, ν_{max}, cm^{-1}): 3413 (m), 1605 (vs, C=N), 1535 (vs), 1439 (m), 1373 (m), 1316 (s), 1192 (m), 1125 (m), 1054 (m), 923 (m), 821 (m), 762 (m), 618 (m), 559 (m), 456 (m). UV-Vis (CH_2Cl_2, λ_{max}): 210, 250, 334 and 430 nm.m.p. ºC: 322-324 (dec.). Analytical data, $C_{27}H_{36}N_2O_3ClMn$, [Mn(III)-BSMP]. H_2O: C, 63.40 (cal. 61.54); H, 6.80 (cal. 6.89); N, 5.40 (cal. 5.32).

General procedure for oxidation of 1,4-dihydropyridines with $NaIO_4$ catalyzed by [Mn(III)-BSMP]: All 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), Mn(III)-BSMP (1/15 mol) and imidazole (2/15 mmol) in methanol (20 mL). The progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was filtered on silica gel and the pyridine derivative was extracted with CH_2Cl_2 or diethyl ether (2 mL × 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.

RESULTS AND DISCUSSION

From a synthetic point of view, the oxidation of Hantzsch 1,4-dihydropyridines to pyridine derivatives is an old method in organic chemistry. In recent years, several new methods have been reported for the oxidation of Hantzsch 1,4-dihydropyridines. 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 present serious environmental problems. Therefore introducing the new methods for this aim is in demand yet. [Mn(III)-BSMP] is easily prepared from condensing of salicylaldehyde and 4-methyl-1,2-phenylenediamine to produce the tetradentate ligand and then reaction of it with $MnCl_2$ under air bubbling. The good catalytic activity of this catalyst in a test on oxidation reaction prompted us to investigate its ability in the oxidation of a variety of 1,4-dihydropyridines with sodium periodate as oxidant at mild reaction conditions (**Scheme-I**). Various molar ratios of catalyst to substrate, 1/50, 1/30, 1/15 and 1/10 were used in oxidation of 4-phenyl-1,4-dihydropyridine and finally 1/15 molar ratio was chosen as optimum amount. The effects of other oxidants were also investigated in the oxidation of 4-phenyl-1,4-dihydropyridine as typical substrate. The obtained results showed that $NaIO_4$ is more effective than other oxidants such as H_2O_2 and urea hydrogen peroxide adduct (UHP) (Table-1). With optimum amount of catalyst to substrate, different molar ratio of the oxidant ($NaIO_4$) to substrate 1/1, 2/1, 3/1 and 4/1 were used. The 2/1 molar ratio was recognized as optimal amount for conversion in minimum reaction time and higher amount did not affect notably on the progress of the reaction.



Scheme-I

To find the suitable solvent, several solvents were investigated in the oxidation of 4-phenyl-1,4-dihydropyridine for example. As shown in Table-1, among the used solvents, aqueous acetonitrile was chosen as the best solvent because higher amount of pyridine derivative was observed. The controlled reaction, in the absence of catalyst

or oxidant showed that both catalyst and oxidant has crucial role in the oxidation reactions. In biomimetic systems using metal-Schiff base complexes as catalyst, addition of an axial base such as imidazole is necessary to obtain high catalytic activity. When imidazole is added as axial ligand to this catalytic system, the reaction times become shorter in the oxidation of 1,4- dihydropyridines.

TABLE-1
OXIDANT EFFECT IN VARIOUS SOLVENTS ON CATALYTIC OXIDATION OF 4-PHENYL-1,4-DIHYDROPYRIDINE AS TYPICAL SUBSTRATE WITHIN 105 min

Oxidant	Solvent	Yield (%)
$NaIO_4$	Aqueous methanol (30 %)	85
$NaIO_4$	Methanol	65
$NaIO_4$	Aqueous acetonitrile	95
$NaIO_4$	Acetonitrile	40
H_2O_2	Aqueous methanol (30%)	60
H_2O_2	Methanol	45
H_2O_2	Acetonitrile	40
H_2O_2	Aqueous acetonitrile	70
UHP	Aqueous methanol (30%)	72
UHP	Methanol	55
UHP	Aqueous acetonitrile (30 %)	60
UHP	Acetonitrile	45
$NaIO_4$	Aqueous chloroform (30 %)	25
$NaIO_4$	Aqueous dichloromethane (30 %)	25
$NaIO_4$	Aqueous carbon tetrachloride (30 %)	15

UHP = Urea hydrogen peroxide adduct.

For instance, the oxidation of 4-phenyl-1,4-dihydropyridine was completed in 150 min but addition of imidazole as co-catalyst led to shorter reaction times of 105 min for 4-phenyl-1,4-dihydropyridine. These observations show that the oxidation reaction proceeds *via* oxo-intermediate because generally axial ligand stabilizes this intermediate in such catalytic systems. Although it is observed from above controlled reaction that addition of imidazole as axial ligand reduces the reaction time only to 0.76 times the time required when imidazole is not present in reaction mixture. This observation can be ascribed to this fact that in addition to imidazole, 1,4-dihydropyridines themselves can play the axial ligand role during the reaction. Therefore the role of axial ligand in this type of reaction is less than similar reaction reported in literature.

The [Mn(III)-BSMP] (I)/$NaIO_4$ catalytic system can be used for oxidation of a wide variety of 1,4-dihydropyridine derivatives to their corresponding pyridine derivatives giving good to excellent yields at room temperature. All the reactions were completed as monitored by TLC and gave only the corresponding pyridine derivatives. The results are summarized in Table-2. As shown in Table-2, the oxidation of substrates bearing the alkyl group (alkyl moieties may be responsible for generating stable carbocations) at the 4-position gave the dealkylated pyridine derivative (Table-2,

entries 5 and 6), which was previously reported[12,45,46], however, aryl-substituted-1,4-dihydropyridines furnished the corresponding pyridine derivatives. This method shows that this system behaves in the same way as in biological system[45]. Based on literature survey[45,47], our rationalization about the reaction mechanism is so that [Mn(III)-BSMP] is converted to oxo-intermediate [Mn(V)(O)-BSMP] as the direct oxidant by oxygen transfer from periodate to it. Although periodate can be assumed as the active oxidant species without the presence of oxo-intermediate but blank experiment did not show effective progress of the reaction by it alone. In next stage, 1,4-dihydropyridines (**1**) approaches to oxo-intermediate and [1,4- dihydropyridine-Mn(III)-BSMP] adduct is formed that releases pyridine derivative (**2** or **3** in **Scheme-I**), water and regenerated [Mn(III)-BSMP] that enter into another oxidation reaction cycle.

TABLE-2
CATALYTIC OXIDATION OF 1,4-DIHYDROPYRIDINE DERIVATIVES TO THEIR CORRESPONDING PYRIDINE DERIVATIVES USING [Mn(III)-BSMP] (I)/$NaIO_4$ IN AQUEOUS ACETONITRILE AT ROOM TEMPERATURE

Entry	Substrate (R)	Product[a]	Time (min)	Yield[b] (%)	m.p. (°C) [lit.[15-18]]
1	1a (H)	**3**	30	90	69-71[68-69]
2	1b (Et)	**2b**	25	91	Oil [Oil]
3	1c (Me)	**2c**	30	90	Oil [Oil]
4	1d (Ph)	**2d**	105	95	61-63[63-65]
5	1e (i-Pr)	**3**	95	84	68-70[68-69]
6	1f (Ph-CH_2)	**3**	60	86	67-69[68-69]
7	1g (3-NO_2-C_6H_4)	**2g**	210	70	62-64[61-62]
8	1h (2-pyridil)	**2h**	60	90	57-59[57-58]
9	1i (4-MeO-C_6H_4)	**2i**	40	90	49-52[50-51]
10	1j (4-Cl-C_6H_4)	**2j**	135	85	65-66[63-65]
11	1k (2-Furyl)	**2k**	240	80	Oil [Oil]
12	1l (2-MeO-C_6H_4)	**2l**	165	75	58-60[61-62]

a: Products were compared to the spectral data reported in literature. b: Isolated yields.

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(*Received*: 19 May 2009; *Accepted*: 4 February 2010) AJC-8396