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MnO_2/TiO_2 Catalyzed Synthesis of Coenzyme Pyridoxamine-5′-Phosphate Analogues : 3-deoxypyridoxamine-5′-phosphate

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The highly efficient-selective synthetic route of the pyridoxal-5′-phosphate (vitamin B_6, PLP) analogues: C3 substituted deoxy derivatives of pyridoxal (PL), pyridoxal-N-oxide (PLNO), pyridoxamine (PM), pyridoxamine-5'-phosphate (PMP) and pyridoxal-5′-phosphate (PLP) are developed via reduction and followed by selective oxidation in one pot using solid supported nanoparticles. The salient features of this strategy are: step economic two-fold conversion, more number of lewis acid sites and vacancies on the nanoparticle surface and good yields of 3-deoxypyridoxal and 3-deoxypyridoxamine-5′-phosphate.

Introduction

The chemistry of C3 substituted PMP, PLP, N-Oxide PLP analogues and homo-analogues of vitamin B_6 demonstrate similar kind of biological activities in the presence of different functional groups of the pyridine nucleotide, such as 3-deoxy-3-fluoropyridoxamine 5'-phosphate[1] (3-deoxy-3-fluoroPMP), 3-deoxy-3-fluoropyridoxal-5′-phosphate[2] (3-deoxy-3-fluoroPLP), 3-O-methylpyridoxal-5′-phosphate[3,4,5] (3-O-methylPLP), 3-O-methylpyridoxal-5′-phosphate N-Oxide[3] (3-O-methylPLP-NO), 1-deaza pyridoxal-5′-phosphate[6] (1-deazaPLP) and pyridoxal-5′-phosphate N-Oxide[7] (PLP-NO) etc. (Figure 1). The functional substituted groups open up unparalleled enzyme flexibility and bio-catalytic activity. The C3 substituted deoxy-PLP has received considerable interests in the past e.g., lysine 5,6-aminomutase[2,8], L-glutamate decarboxylase[9] and aspartate aminotransferase[1,10]. That might assist to trapped short lived transient cyclic azacyclopropyl carbonyl intermediate radical which has been escaped concealment for more than two decades[8].

As a result, there is an interest for the development of the synthetic facile route to modify C3 position in pyridine nucleotide and its derivatives. 3-deoxyPLP has been reported

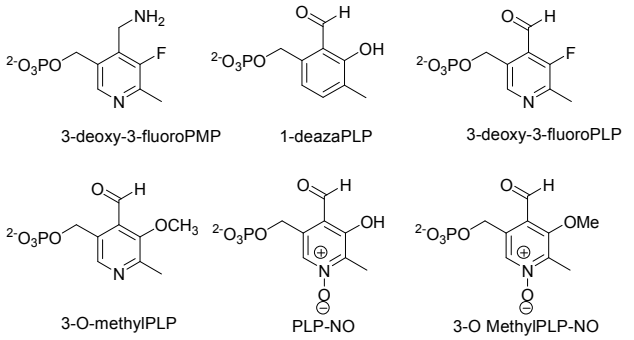

Figure 1 Representative of biologically active B_6 analogues

upon Schiff bases phosphorylation by Snell *et al.*[11] and thereafter, pyridoxamine phosphorylation has also been accounted by Stambolieva *et al.*[12,13]. Although both the above mentioned routes have various advantages, there have been also limitations in numerous occasions such as poor percentages of yield during esterification (11%), formation of different monohydric alcohol analogues[14], one equivalent of oxidized desired-compound is formed complying ratio of 1:6 with 30% yield[11] and phosphorylation of mixed amine compounds produces 20% of yield[12,13]. To the best of our knowledge, literature studies have revealed that the preparation of 3-deoxyPLP's derivatives and 3-deoxyPLP-NO are not known yet. In this account, to overcome above-mentioned issues, we introduce different chemical approach to improve the synthesis such as extensive reduction, over oxidation in one-pot, and new approaches using environment friendly catalyst, which gives birth of new mechanism in the field of nanoparticles (NPs). In the present study, we attempt to shed light on how MnO_2/TiO_2 heterogeneous catalysis facilitated the reaction to form the desired products selectively. The synthesis of fine chemicals, selective oxidation and minimize extensive reductions are most important in laboratory research. MnO_2/TiO_2 catalysts possess few advantages like easy removal, recyclable, economical, eco-

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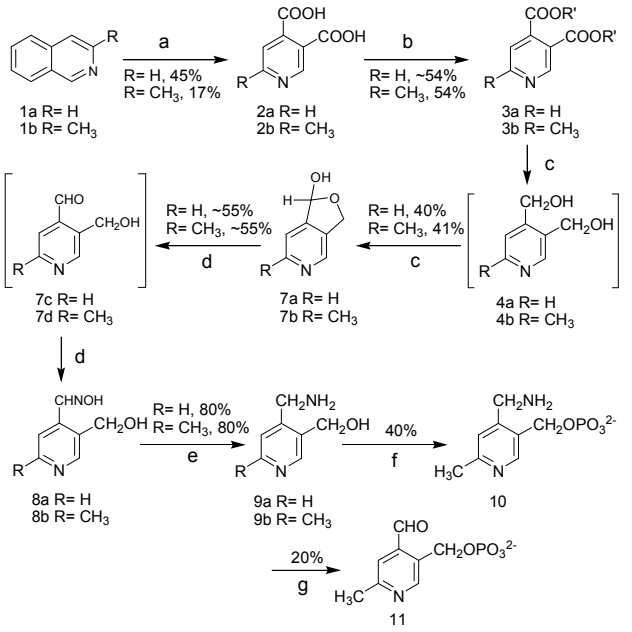
friendly, and highly efficient. Reagents on solid-support react differently, selectively than their unbound counterparts. Pure or supported metal oxide catalysts have been used in oxidation reaction[15,16,17,18]. Titania has been found to be a favourable material both as an active centre and a support, for volatile organic compounds (vocs) oxidation[19,20]. Manganese dioxide is also a versatile stoichiometric oxidation reagent for the direct oxidation of alcohols to aldehydes or ketones, In this regard Z. Chen and his co-workers synthesized mesoporous MnO_2 and studied their catalytic activity[21,22,23,24]. The role of support in catalysis is to increase the active phase dispersion and the catalyst specific activity[19,25, 26,27]. In this work, we have impregnated MnO_2 on TiO_2 NPs by incipient wetness technique followed by calcination in O_2 flow. The stoichiometric oxidation sites on MnO_2 can be converted into catalytic sites for the selective oxidation of alcohols. In particular, by using MnO_2 immobilized TiO_2 high conversion in the selective oxidation of alcohols has been achieved, which is a user friendly, green and effective catalytic system.

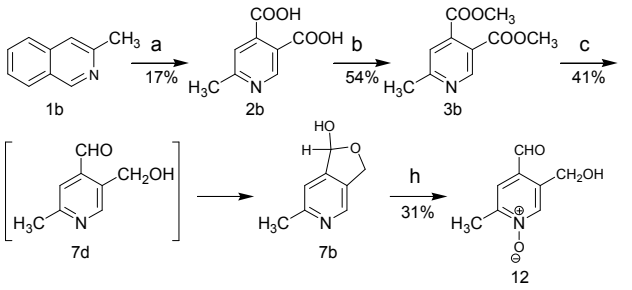
Herein, we report new method for the synthesis of 3-deoxypyridoxal reduction followed by selective oxidation in one-pot using known environmental friendly MnO_2/TiO_2 catalyst. The successful synthesis of novel 3-deoxy PLNO compound and execution of phosphorylated 3-deoxy PMP is afforded in good yield.

Results and Discussion

The synthesis of 3-deoxyPL and its derivatives are sought a flexible approach, outlined in Scheme 1. The pyridine nucleotide dicarboxylic acid core was obtained by oxidation, with excess O_3 through the glacial acetic acid with trace amount of water, at room temperature as per literature[28,29]. The obtained white precipitate was recrystallized to afford compound 2. The filtrate passed through O_3, obtained quantitative yield of desired dicarboxylic acid. By addition of methanol and conc H_2SO_4 to above dicarboxylic acid, heated to reflux for two days accomplished dicarboxylic ester 3 of 54% yield. Moreover, this modified strategy of oxidation followed by esterification gives 36% of yield, which is significantly improved over the previous study (11%) by Jones *et al*[14]. Reduction of di alkyl ester of 3 with lithium aluminium hydride was not promising by yield due to the over-extensive decomposition, and also produced different analogues of monohydric alcohol[30]. In continuation selective oxidation using MnO_2 is also not encouraged by yield[11]. After extensive studies on the reduction and oxidation (red-ox) in different conditions, we resolved this problem for the first time by introducing effective heterogeneous catalysis to the red-ox protocol.

Herein, this manuscript reports convergent and flexible behavior of MnO_2/TiO_2 nanoparticle for the improvement of the aforementioned synthesis. We performed blank reactions to check the activities in absence of $NaBH_4$ & TiO_2 under ethanol solution at room temperature and reflux conditions. No progress was observed in the reaction, using either $NaBH_4$ or TiO_2 NPs. However, the conversion in polar protic solvent was very low using catalysts like reduced TiO_2 (H-TiO_2), P25 TiO_2 and TiO_2 NPs along with $NaBH_4$ & MnO_2. Interestingly when the same reaction was carried out in the presence of a catalytic amount of 1%MnO_2/TiO_2 in room temperature using





Scheme 1 Reagents and conditions: (a) excess O_3, glacial CH_3COOH, H_2O, RT; (b) conc H_2SO_4, MeOH/EtOH, reflux, 2days; (c) $NaBH_4$, 1% MnO_2/TiO_2, EtOH, H_2O, MnO_2, pH-3.5; (d) $NH_2OH{\cdot}HCl$, NaOAc, H_2O; (e) 10% Pd/C, CH_3OH; (f) Mixture of P_2O_5 and H_3PO_4, HCl, EtOH, ether, aqueous NH_3, Amberlite CG-50; (g) $HC(O)COONa{\cdot}H_2O$, glacial CH_3COOH, Cupric acetate, Dowex 50X8 (h) mCPBA, THF, 0°C.

ethanol, the desired product (7b) was obtained in moderate yields (Table 1 entry 10). The incorporation of MnO_2 onto TiO_2 creates additional sites for adsorbing more borohydride ions, which leads to greater activity, compared to bare TiO_2. Because of MnO_2 is highly dispersed on the surface of TiO_2, Mn^{4+} may occupy the surface vacant site of TiO_2 and the oxygen anions will stay at the top of the occupied site as capping oxygen. Nanoscale metal oxides hold the potential of high surface-to-volume ratio of the active species, contribute more material productivity and act as an excellent selective catalysts than the respective bulk materials[19,31]. In the table 1 entry 10 conditions have been exploited for all the experiments.

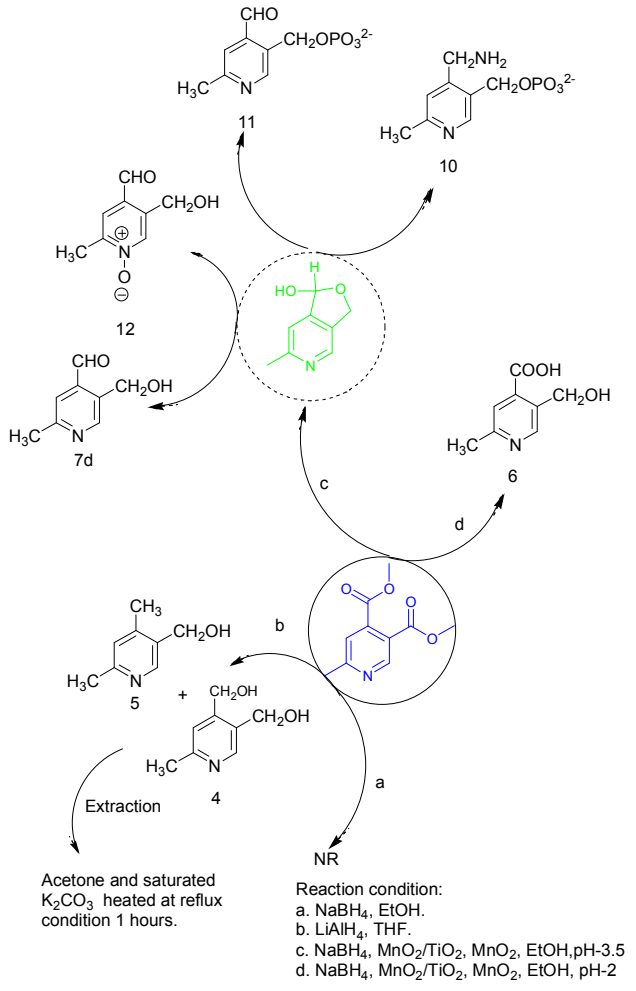
Table 1 Optimized reaction condition of 3-deoxypyridoxal derivatives[a] (Compounds 3 → 3-deoxypyridoxal)

Entry	Catalyst with NaBH4 (10mol %)	Solvent	Time (h)	Temp	Yield[b] (%)
1	-	EtOH	12 h	RT	NR
2	-	EtOH	12 h	Reflux	NR
3	NaBH4*	EtOH	12 h	RT	NR
4	NaBH4*	EtOH	12 h	Reflux	NR
5	TiO_2**	EtOH	12 h	RT	NR
6	TiO_2**	EtOH	24 h	Reflux	NR
7	TiO_2 P25	EtOH	12 h	RT	2(7a)
8	NPS TiO_2	EtOH	24 h	RT	5(7a)
9	Reduced TiO_2	EtOH	42 h	RT	-
10	1%MnO_2/TiO_2	EtOH	7 h	RT	40†,41††
11	1%MnO_2/TiO_2	MeOH	10 h	RT	37 (7a)
12	1%MnO_2/TiO_2	THF	10 h	RT	25 (7a)
13	1%MnO_2/TiO_2	CH_3CN	12 h	RT	12 (7a)
14	5%MnO_2/TiO_2	EtOH	24 h	RT	36 (7a)
15	10%MnO_2/TiO_2	EtOH	48 h	RT	28 (7a)
16	MnO_2	EtOH	32 h	Reflux	-

[a] Reaction condition: Pyridine dicarboxylic ester (1 mmol), MnO_2. [b] Isolated yield
* Without Catalyst, ** without $NaBH_4$, †7a, ††7b,

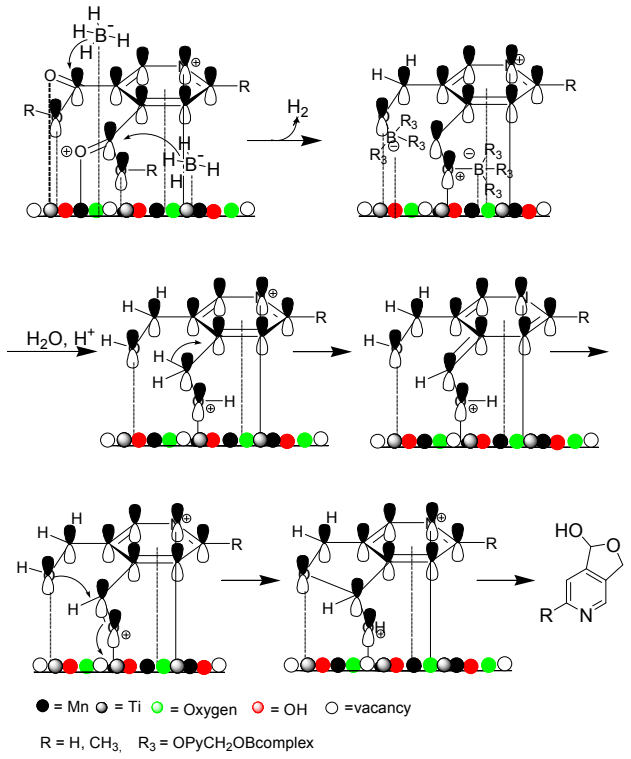
The reaction was monitored by thin layer chromatography (TLC), isolation was done by extensive recrystallization, and characterization was done using NMR spectroscopy. From proton NMR (*see supporting information*) the synthesized product 7b signaled three singlets at 8.46, 7.25, and 2.49 ppm with a 1:1:3 ratios, which were recognized as 6-H, 3-H, and 2-Me, respectively. Two doublets at 5.06 and 4.91 ppm were also identified, two protons for $–CH_2O-$ cyclic hemiacetal and one doublet at 6.29 ppm for hemiacetal of C–H. From ^{13}C NMR and ^{13}C DEPT-135NMR hemiacetal carbon was observed at 100.3 ppm, 5'C, and methyl carbon peaks were observed at 69.3 and 24.3 ppm respectively, and MALDI - TOF MS: m/z = 152.08 (152.07 calcd for $C_8H_9NO_2$, $M+H^+$). Encouraged by this result, under optimized conditions a variety of dicarboxylic esters were employed in this one-pot red-ox reaction. Dicarboxylic esters of pyridine bearing different R' groups such as Me, Et, Pr, iPr, and nBu were tested in all the cases the corresponding one-pot product was isolated in good yields. When pyridine moiety was replaced with benzene, oxidation products were not observed, only reduced products were detected in qualitative yield (Table 2 entry 16, 17). Because of pyridine nitrogen gets quaternized with catalyst surface to form lewis adduct and generate electron-sink pyridinium ion which influence 4' allylic carbon-hydrogen bond. That carbanion stabilize positive charge via electron delocalization through π-conjugation and generated highly selective oxidized product where nitrogen playing a vital role comparing with benzene carbon. MnO_2-doped (% : 1,5,10) TiO_2 & reduced TiO_2 catalysts were characterized by electron paramagnetic resonance (EPR) spectroscopy at 298 K produced an signal at g value 2.002 (*SI figure-1*). Which is characteristic of manganese exists in several oxidation states out of them only Mn^{2+}, Mn^{4+} possesses paramagnetic nature at either low or high spin. The FT-IR spectrum of catalysts is depicted in supporting information (figure-2). The intensity of the band near ~1630 cm^{-1} decrease with the increase percentage of MnO_2 on TiO_2 because of large numbers surface hydroxyl group might be physically diminishing on the nanoparticle. XRD technique was used to characterize the synthesized nanoparticles. MnO_2 and reduced TiO_2 were found to be amorphous in nature. XRD remains silent towards the detection of Mn species in the synthesized composites, anatase phase of TiO_2 with relatively dominance than rutile and Mn species (*SI figure-3*).

Two-fold conversion was achieved which indicates more number of lewis acid sites were presented on TiO_2. Benefit of immobilizing MnO_2 on TiO_2 is to consume less amount of MnO_2 in the oxidation process. The rate of selective oxidation products 7 enhances in acidic medium (pH 3.5) at room temperature. The oxidizing property of compound 4 have enhanced at selective 4' carbon atom when the pH in between 1.5 to 2, resulted corresponding carboxylic acid at 4' carbon (Scheme 2) because of charge on the pyridinium nitrogen depends on pH and acidity of active site[6].



Scheme 2 Reaction of dimethyl 2-methyl-4,5-pyridinedicarboxylic ester

The mechanism of the hydrogenation of the ester indicates that the process is influenced by the hydride transfer from borohydride ion. The reduction of di ester proceeded via hydride transfer from the donor, BH_4^- ion to electrophilic carbon to form aldehyde, upon the expulsion of ethoxy species, as evident from the steps involved in the mechanism. The aldehyde will be reduced further into the corresponding alcohol upon transfer of one more hydride ion to the electrophilic carbon and followed by hydrolysis. It is reasonable to assume that the B–H bond became weaker during adsorption of $[BH_4]^-$ ions on the metal surface. It is predicted that the surface positive charge of the metal oxides facilitated the interaction between the metal oxide surface and the donor species BH_4^-. The main reason for the less activity of TiO_2 could be less concentration of hydroxyl groups, less surface area and less acidity. Earlier reports proved the reduction of metal during the $NaBH_4$ treatment, indicates the strong reduction ability of $NaBH_4$ for creating strong metal support interaction[16] (SMSI) effects observed from blank reaction as proposed Scheme 3.



Scheme 3 Plausible mechanism for the synthesis of 7

We can suggest that the Ti^{4+} and Mn^{4+} active centers are surrounded by BH_4^- ions because of a high electrostatic interaction between them, which causes an easier removal of H^- ions. On the other hand, absorbed H_2O on Ti & Mn active centers causes a weakening of H-OH bonds, favoring the liberation of H_2[32]. This confirms the role of $NaBH_4$ as an electron donor in the presence of TiO_2. Less conversion was observed, when the reaction was carried out with MnO_2 (Table 1 entry 16). It has been shown that the content of manganese loading on TiO_2 has an effect on the catalytic activity in the selective oxidation[33]. Maximum activity was obtained for the Mn/Ti-1 catalyst. The results are summarized in Table 2 (3a and 3b as a fixed substrates with different ester derivatives). Unwanted side products were observed, when the ratio of Mn increased from 5 to 10.

Abad.[34] and Sun Hua-yin[35] coworkers proposed reaction mechanism for the aerobic oxidation of alcohols. According to their studies, activation of oxygen molecules takes place at the oxygen defect sites on the surface of the support. Correlated to the reports the positive manganese and titanium ions play

Table 2. Synthesis of 3-deoxy pyridoxal derivatives (Compounds 3 → 3-Deoxy pyridoxal)

Entry	R	R′	Time (h)	Yield[b] (%)
1	H	H	12 h	NR
2	H	CH_3	7 h	40(7a)
3	H	CH_3CH_2	7 h	~40(7a)
4	H	$CH_3CH_2CH_2$	7 h	~38(7a)
5	H	CH_3CHCH_3	12 h	~36(7a)
6	H	$CH_3CH_2CH_2CH_2$	12 h	~31(7a)
7	H	OC(O)-	12 h	NR
8	CH_3	H	12 h	NR
9	CH_3	CH_3	7 h	41(7b)
10	CH_3	CH_3CH_2	7 h	41(7b)
11	CH_3	$CH_3CH_2CH_2$	7 h	~38(7b)
12	CH_3	CH_3CHCH_3	12 h	~36(7b)
13	CH_3	$CH_3CH_2CH_2CH_2$	12 h	~33(7b)
14	CH_3	OC(O)-	12 h	NR
15*	H	H	12 h	NR
16*	H	CH_3	2 h	70[#]
17*	H	OC(O)-	3 h	75[##]

* Benzene moiety [#](1,2-benzenedimethanol) [##](2-hydroxymethyl benzoic acid)
[b] Isolated yield

an important role in the rate determining step involving the hydride shift from the alcohol to lewis acid sites. Therefore, the presence of more oxygen vacancies and lewis acid sites is considered to be the key point in relation to the excellent activities of the MnO_2/TiO_2 catalyst for the aerobic oxidation of alcohols.

After successful synthesis of compound 7, our attention was extended to synthesize different analogues of pyridoxal derivatives. The formation of 3-deoxy PL-NO is performed in the presence of per acid, and 3-deoxy PLP-NO is formed upon phosphorylation. Furthermore compound 7 was tested under hydroxylamine hydrochloride followed by hydrogenation with 10% Pd/C-H_2 gas to achieved 3-deoxy PM with 80%, yield and then selective mono-phosphorylation using P_2O_5 85% H_3PO_4 to afford 3-deoxy PMP in good yield (40%). Finally 3-deoxy PLP was formed by the oxidation of the crude products from 3-deoxy PMP[12].

Conclusions

In summary, we have described a simple step economic, efficient and green method to develop 3-deoxypyridoxal derivatives followed by red-ox, two-fold conversion in one-pot

using eco-friendly and flexible MnO_2/TiO_2 catalysis. These heterogeneous catalysts exhibit new and unique high selective approach to obtain synthetically useful scale of 3-deoxypyridoxal (41%) in comparison with Snell *et al.*. The functionality of this cyclic five membered core intermediate 7 has immense capability to work as a coenzyme and explore to produce synthetic equivalent 3-deoxyPLNO, 3-deoxyPM, 3-deoxyPMP and 3-deoxyPLP respectively which are valuable synthons for organic enzymatic reactions. In addition to this 5'-hydroxy methyl phosphate 10 anticipate more promising, by yield in contrast to Stambolieva *et al.*.[13]

Experimental Section

General information

The reagent 3-methylisoquinoline was purchased from Sigma-Aldrich, and other chemical, high performance liquid chromatography (HPLC) grade solvents and deuterated solvent were obtained from Alfa-Aesar, Acros, JT baker and Sigma-Aldrich respectively, used without further purification. Air and moisture sensitive reaction were carried out under argon atmosphere with HPLC grade solvents. The cation exchange chromatography was done under oxygen free water (two cycles of freeze - pump - thaw). The reactions were monitored in an analytical thin-layer chromatography (TLC) and performed using ALOX-25 UV_{254} and DURASIL-25 UV_{254} glass plate indicator. Spots on TLC were identified using either UV light (254 nm), Basic $KMnO_4$, DNP staining solutions, Iodine vapor chamber, or Ninhydrin spray. The products were purified by cation exchange chromatography (phosphorylated analogues) and flash chromatography was performed using Amberlite CG-50 (H^+ form), Dowex 50X8 (H^+ form) and silica gel 60 (high purity grade, 70 - 230 mesh) respectively. ^1H and ^{13}C NMR spectra were recorded using Bruker NMR 300 MHz, NMR 400 MHz, and NMR 600 MHz spectrometers respectively and ^{31}P were performed on Bruker 300 MHz instrument at 121 MHz. Mass spectra were recorded on MALDI - TOF mass spectrometer. The deuterated solvent, DMSO-d_6, $CDCl_3$, CD_3OD- d_4 or D_2O were used as a standard, using TMS as internal and 85% H_3PO_4 as external reference.

Preparation of TiO_2 NPs

TiO_2 NPs were synthesized by sol-gel-hydrothermal method. 4.5 mL of TTIP was dissolved in 20.5 mL anhy. EtOH. 25 mL of EtOH was mixed with 25 mL distilled water. Above TTIP solution was added dropwise into the aq. EtOH. White gel was observed during the addition of TTIP indicating the formation of $Ti(OH)_4$. The solution containing gel was stirred at RT for 4-5 h for complete hydrolysis. Then the gel was transferred into a Teflon lined autoclave and heated at 120 ˚C for 10 h. Then the gel was centrifuged and washed with ethanol in order to minimize hydrogen bonding. This gel was dried at 100 ˚C for 10 h. The white powder was grinded and used as catalyst in our reactions. This was labelled as T.

MnO_2 immobilization on TiO_2

MnO_2 immobilized TiO_2 was synthesized by wet impregnation method. Respective amounts of $MnSO_4$ were dissolved in 50 mL distilled water and 500 mg of TiO_2 was dispersed into the solution and stirred for 24 h. The solid was centrifuged and washed with excess of water to remove inorganic salts. Then the sample was dried at 100 ˚C for 10 h. The sample was grinded and heated at 400 ˚C for 2h in O_2 flow. Light yellow powder was obtained which was labelled as Mn/Ti-X (X=1, 5, 10).

Reduced TiO_2

$Ti(OH)_4$ was heated in argon/hydrogen atmosphere at 300˚C for 30 min. Black powder was obtained.

The above synthesized catalysts were examined by EPR. EPR of MnO_2 immobilized TiO_2 catalysts showed the presence of the paramagnetic species. Mn exists with variable oxidation states, Mn^0 (d^7), Mn^+ (d^6), Mn^{2+} (d^5), Mn^{3+} (d^4), Mn^{4+} (d^3). Certain ions (Mn^{2+}, Mn^{4+}) remain paramagnetic at low and high spin and then could be detected with the EPR technique. Whereas (Mn^{3+}) EPR silent, because it is paramagnetic at high spin and diamagnetic at low spin as per the reported literature.

2-Methyl-4,5-pyridinedicarboxylic acid (2b) 9 gm (62.8 mmol) of 3-methylisoquinoline, 120 ml of glacial acetic acid and few drop of water was added under atmospheric pressure in a 250 ml two-neck round bottom flask. The reaction mixture was stirred for 15 min at room temperature and then purged in 0.5 mmol ozone per liter of gas. The reaction temperature (20°C to 25°C) was maintained during the course of reaction. White suspension was formed after 6 hours, then 3 ml of water was added and the reaction was continued for 10 hours again. The result was promising in our view, compare to the previously reported article[16]. After completion of the reaction, fine white precipitate was separated by filtration after washing with cold water. Then resulted solid was recrystallized with boiling water and nice crystalline pure product was formed. White solid 1.93 gm (17%); ^1H NMR (300 MHz, D_2O): δ = 9.07 (s, 1H, 6-H), 7.82 (s, 1H, 3-H), 2.82 (s, 3H, 2-Me) ppm; ^{13}C NMR (300 MHz, D_2O): δ = 171.3, 165.3, 157.6, 155.0, 143.1, 124.9, 20.3 ppm; MALDI - TOF MS: m/z = 183.05 (183.05 calcd for $C_8H_8NO_4$, $M+H^+$).

Dimethyl 2-Methyl-4,5-pyridinedicarboxylic acid (3b) 3 gm of dicarboxylic acid (16.5 mmol), was dissolved in 90 ml anhydrous methanol and 3.5 ml of concentrated H_2SO_4 in a round bottom flask. The resulting mixture was heated to reflux for 48 hours. After cooling, excess of methanol was added to the solution and followed by evaporation of alcohol solution. The left-red-gum was dissolved using ethyl acetate and neutralize with 25% NH_4OH. The organic extracts were dried over Na_2SO_4 and concentrated solid was found. The desired product was recrystallized with ethanol and nice crystalline white pure product was formed. 1.87gm (54%); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1H, 6-H), 7.55 (s, 1H, 3-H), 3.85 (s, 6H, OMe's), 2.58 (s, 3H, 2-Me) ppm; ^{13}C NMR (300 MHz, DMSO): δ = 166.8, 165.4, 163.4, 149.8, 140.7, 121.6, 53.2, 24.3 ppm;

MALDI - TOF MS: m/z = 210.07 (210.07 calcd for $C_{10}H_{11}NO_4$, $M+H^+$).

2-Methyl-4,5-dihydroxymethylpyridine (3-Deoxy pyridoxine) (4b) To solution of lithium aluminium hydride (379 mg, 10 mmol) in dry THF (20 ml) was added methyl 2-methyl-4,5-pyridinedicarboxylate (1.0 gm, 4.15 mmol) under N_2 atmosphere at 0°C, stirred for 10 min. The reaction mixture was stirred at room temperature for 17h, and filtrated concentrated under reduced pressure. Then the resulting solid was redissolved in the mixture of acetone (30 ml) and saturated solution of K_2CO_3 (30 ml) and it was heated at reflux condition 1 hours. Organic phase was extracted from the reaction mixture after cooling at room temperature and dried over anhydrous $MgSO_4$. And the solvents were removed under reduced pressure. The crude product was passed through column silica and eluted with 10-15 % methanol in $CHCl_3$. The oily residue was recrystallized with ethyl acetate. White solid, 0.37gm (51%); ^{1}H NMR (300 MHz, DMSO): δ = 8.28 (s, 1H, 6-H), 7.29 (s, 1H, 3-H), 5.29 (b, 1H, 4'COH), 5.17 (b, 1H, 5'COH), 4.57 (s, 2H, 4'CH_2), 4.46 (s, 2H, 5'CH_2), 2.43 (s, 3H, 2-Me) ppm; ^{13}C NMR (300 MHz, CD_3OD): δ = 159.0, 152.1, 148.5, 132.6, 122.4, 61.3, 60.5, 23.8 ^{13}C DEPT-135NMR (75.46 MHz, CD_3OD): δ = 148.5, 122.4, 61.3, 60.5, 23.9 ppm; MALDI - TOF MS: m/z = 154.05 (154.08 calcd for $C_8H_{11}NO_2$, $M+H^+$).

2-nor-4,5-dihydroxymethylpyridine (4a) methyl 2-nor-4,5-pyridinedicarboxylate (1.0 gm, 5.1 mmol), lithium aluminium hydride (379mg, 10mmol) in dry THF (20 ml), under N_2 atmosphere at 0°C, stirred for 10 min, at room temperature for 17h. White solid, 0.37gm (53%); ^{1}H NMR (300 MHz, DMSO): δ = 8.44 (d, 1H, 2H,6-H), 7.43 (d, 1H, 3-H), 4.60 (s, 2H, 4/CH_2), 4.51 (s, 2H, 5/CH_2) ppm; ^{13}C NMR (300 MHz, DMSO) 149.2, 148.4, 147.7, 133.5, 120.4, 58.8, 58.4 ppm; MALDI - TOF MS: m/z = 140.06 (140.06 calcd for $C_7H_9NO_2$, $M+H^+$).

5-Hydroxymethyl-2-Methyl-4-pyridinecarboxaldehyde hemiacetal (3-Deoxy pyridoxal) (7b) Sodium borohydride (0.94 gm, 24.9 mmol) and 1% MnO_2/TiO_2 (40mol%, 133 mg) were suspended in 30 ml ethanol under nitrogen blanket and stirred for 15 minutes. Solution of dimethyl 2-methyl-4,5-pyridinedicarboxylate (1.0 gm, 4.15 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 3 h, after that water and freshly prepared manganese dioxide were added and maintained the pH–3.5, stirred at room temperature for 4 hours. The catalyst and desired unreacted materials was filtered off and washed with water. The pH of the reaction mixture was adjusted to 7.5 by adding $NaHCO_3$ followed by extraction with ethyl acetate. The extract was dried over $MgSO_4$, and solvents were removed under reduced pressure to provide the desired product in good yield after recrystallization with acetone. White solid, 0.29gm (41%); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 (s, 1H, 6-H), 7.25 (s, 1H, 3-H), 6.94 (d, J = 7.6 Hz, OH), 6.29 (d, J = 5.7 Hz, CH of hemiacetal form), 5.06 (d,1H, J = 12.8 Hz, CH_2O), 4.91 (d, 1H, J = 12.9 Hz, CH_2O), 2.49 (s, 3H, 2-Me) ppm; 13C NMR (400 MHz, DMSO-d_6): δ = 157.0, 149.6, 142.8, 133.0, 117.3, 100.3, 69.3, 24.3 ppm; ^{13}C DEPT-135NMR (75.46 MHz, DMSO-d_6): δ = 142.8, 117.3, 100.3, 69.3, 24.3 ppm; MALDI - TOF MS: m/z = 152.08 (152.07 calcd for $C_8H_9NO_2$, $M+H^+$).

5-Hydroxymethyl-2-nor-4-pyridinecarboxaldehyde hemiacetal (7a) Sodium borohydride (1.16 gm, 30.72 mmol) and 1% MnO_2/TiO_2 (40mol%, 164 mg) were suspended in 35 ml ethanol, Solution of dimethyl 2-methyl-4,5-pyridinedicarboxylate (1 gm, 5.12 mmol) was added at 0°C. The manganese dioxide was added and maintained the pH–3.5. White solid, 0.28gm (40%); ^{1}H NMR (300 MHz, DMSO) δ = 8.52 (d, 2H, 2-H &6-H), 7.45 (d, 1H, 3-H), 6.96 (d, J = 7.6 Hz, OH), 6.33 (d, J = 7.8 Hz, CH of hemiacetal form), 5.10 (d,1H, J = 12.4 Hz, CH_2O), 4.95 (d, 1H, J = 13.4 Hz, CHO) ppm; ^{13}C NMR (300 MHz, DMSO): δ =148.4, 148.2, 143.4, 135.5, 117.9, 100.0, 69.0 ppm; MALDI - TOF MS: m/z = 138.05 (138.05 calcd for $C_7H_7NO_2$, $M+H^+$).

3-deoxy pyridoxal N-oxide (12) A solution of mCPBA (70%, 755.8 mg, 4.38 mmol) in 30 mL THF was added to a solution of 7b (471 mg, 3.12 mmol) in THF at 0-5°C over a period of 90 min. The mixture was stirred for another 30 min at 0-5°C and then left to stand overnight at room temperature. the resultant solution was quenched by Na_2CO_3(aq), thoroughly washed with deionized water, dried over anhydrous Na_2SO_4 and collected 0.161 gm (31%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (s, 1H, 6-H), 7.77 (s, 1H, 3-H), 5.31 (s, 2H, CH_2O), 2.55 (s, 3H, 2-Me) ppm; 13C NMR (300 MHz, $CDCl_3$): δ = 202.2, 141.7, 134.1, 122.0, 103.5, 67.0, 18.3 ppm; MALDI - TOF MS: m/z = 168.06 (168.06 calcd for $C_8H_9NO_2$, $M+H^+$).

5-Hydroxymethyl-2-Methyl-4-pyridinecarboxaldehyde oximes (3-Deoxy pyridoxal oxime) (8b) To a Mixture of sodium acetate monohydrate (492 mg, 6mmol) and hydroxylamine hydrochloride (416.9 mg, 6mmol) in 25 ml of water, a suspension of pyridinecarboxaldehyde hemiacetal (605 mg, 4 mmol) was added. The mixture was stirred at 100°C for 90 minutes. Then the resulting mixture was cooled at room temperature and condensed to 15 ml. The resulting solution was kept in refrigerator overnight and gave precipitates, which were collected by filtration. Solid, 0.36gm (55%); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.76 (s, 1H, NOH), 8.45 (s, 1H, 4'-CH), 8.33 (s, 1H, 6-H), 7.45 (s, 1H, 3-H), 5.26 (s, 1H OH), 4.58 (d, 2H, J = 4.4 Hz, CH_2O), 2.45 (s, 3H, 2-Me) ppm; ^{13}C NMR (300 MHz, DMSO-d_6): δ = 157.4, 149.6, 146.1, 138.7, 131.7, 119.0, 59.4, 24.1 ppm; MALDI - TOF MS: m/z = 167.09 (167.09 calcd for $C_8H_{10}N_2O_2$, $M+H^+$).

5-Hydroxymethyl-2-nor-4-pyridinecarboxaldehyde oximes (8a) Sodium acetate monohydrate (492 mg, 6mmol), hydroxylamine hydrochloride (416.9 mg, 6mmol) in 25 ml of water, and suspension of 2-nor-pyridinecarboxaldehyde hemiacetal (548 mg, 4 mmol) was stirred at 100°C for 90 minutes. The filtrated solid, 0.33gm (55%); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.81 (s, 1H, NOH), 8.60 (s, 1H, 4'-CH), 8.49 (d, 1H, 2-H), 8.38 (s, 1H, 6-H), 7.60 (d, 1H, 3-H), 5.36 (t, 1H OH), 4.58 (d, 2H, J = 4.4 Hz, CH2O) ppm; ^{13}C NMR (300 MHz,

DMSO-d_6) δ = 149.7, 148.7, 145.6, 138.1, 134.1, 119.5, 59.0 ppm; MALDI - TOF MS: m/z = 153.06 (153.06 calcd for $C_7H_8N_2O_2$, $M+H^+$).

4-Aminomethyl-2-Methyl-5-hydroxymethylpyridine (3-Deoxy pyridoxamine) (9b) 3-Deoxy pyridoxal oxime (202 mg, 1.2mmol) was dissolved in 20 ml of methanol and then 75 mg 10% Pd/C was added to the previous mixture. The resulting mixture was hydrogenated for 2 hours. The catalyst was filtered off and the filtrate was removed under reduced pressure. The crude product was recrystallized with MeOH / Ether and the pure product was collected. Solid, 148mg (80%); ^{1}H NMR (CD_3OD): δ 8.34 (s, 1H, 6-H), 7.35 (s, 1H, 3-H), 4.65 (s, 2H, 5-CH_2), 3.95 (s, 2H, 4-CH_2), 2.53 (s, 3H, 2-Me). ^{13}C NMR (CD_3OD): δ 159.4, 153.1, 149.5, 133.8, 124.2, 61.1, 43.4, 24.0 ppm ^{13}C DEPT-135NMR (75.46 MHz, CD_3OD): δ 149.5, 124.2, 61.1, 43.4, 24.0 ppm MALDI - TOF MS: m/z = 153.09 (153.09 calcd for $C_8H_{12}N_2O$, $M+H^+$).

4-Aminomethyl-2-nor-5-hydroxymethylpyridine (3-Deoxy pyridoxamine) (9a) 3-Deoxy pyridoxal oxime (199.4 mg, 1.2mmol) was dissolved in 20 ml of methanol and then 75 mg 10% Pd/C was added to the previous mixture. The crude product was recrystallized with MeOH / Ether and the pure product was collected. Solid, 132mg (80%); ^{1}H NMR ($CDCl_3$): δ 8.49 (s, 1H, 6-H), 8.45 (d, J = 4.89, 1H, 2-H), 7.35 (d, J = 4.89, 1H, 3-H), 4.66 (s, 2H, 5'CH_2), 3.93 (s, 2H, 4'CH_2). ^{13}C NMR ($CDCl_3$): δ 150.3, 149.8, 148.8, 136.1, 123.9, 61.3, 44.4 ppm MALDI - TOF MS: m/z = 139.08 (139.08 calcd for $C_7H_{10}N_2O$, $M+H^+$).

3-Deoxypyridoxamine-5'-phosphate (10) 3-Deoxy pyridoxamine (20 mg, 0.13 mmol) was added in homogeneous mixture of PPA (prepared from 93 mg, 0.328 mmol, phosphorus pentoxide and 0.1 ml, 1.72 mmol, 85% phosphoric acid) under nitrogen atmosphere. This mixture was stirred at room temperature until evolution of HCl gas, and then heated at 65°C for 2.5 hours. The resulting syrup cooled at room temperature and 2.5 ml of EtOH followed by 7 ml of ether slowly was added to the syrup, which yielded a white precipitate and the precipitate was kept at 6°C for 1 hours. The precipitate was successively washed with EtOH and dried under vacuum. The crude product was hydrolysed with 1N HCl (3 ml) at steam bath temperature for 2.5 hours. The pH of solution was adjusted to 6.0-7.0 using 25% aqueous ammonia and then loaded on cation exchange column (Amberlite CG-50 in H^+ form). Subsequently, it was eluted with water. The frictions were evaporate under vacuum at 35°C and lyophilized. 12mg (40%); ^{1}H NMR (600 MHz, D_2O): δ 8.49 (s, 1H, 6-H), 7.41 (s, 1H, 3-H), 4.95 (d, 2H, 5-CH_2 J=5.94 Hz), 4.34 (s, 2H, 4-CH_2), 2.59 (s, 3H, 2-Me). ^{13}C NMR (600 MHz, D_2O): δ 159.2, 149.2, 142.6, 130.6, 125.4, 62.0, 39.9, 22.7 ppm. ^{31}P NMR (121.4 MHz, D_2O with respect to external standard 85% H_3PO_4) δ 4.14 (t, J=5.7) ppm MALDI - TOF MS: m/z = 231.05 (231.05 calcd for $C_8H_{11}N_2O_4P^{2-}$, $M+H^+$).

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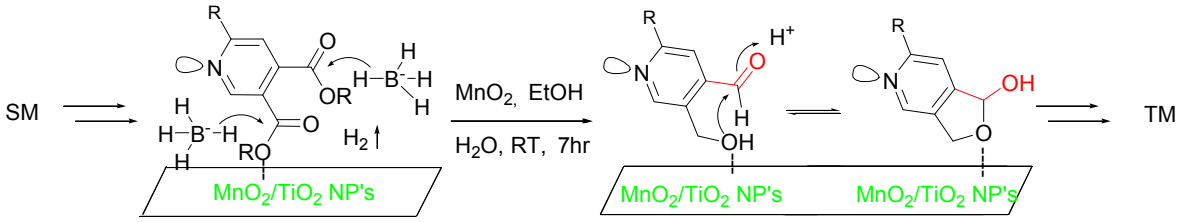
Graphical Abstract



SM = Starting Materials TM = Target Molecule