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Oxidative aromatization of Hantzsch 1,4-dihydropyridines in the presence of mixed-addenda vanadomolybdophosphate heteropolyacid, $H_6PMo_9V_3O_{40}$

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Abstract—A variety of Hantzsch 1,4-dihydropyridines were oxidized to the corresponding pyridines in high yields in the presence of $H_6PMo_9V_3O_{40}$, a Keggin type heteropolyacid, in refluxing acetic acid. The heteropolyacid was found to be reusable.

1,4-Dihydropyridines (1,4-DHPs) are a class of model compounds of NADH coenzyme, and calcium channel antagonists (CCAs).[1] These compounds have been established as one of the first line drugs for treatment of hypertension because of their promising depressor effect and relatively good tolerability.[2] 1,4-Dihydropyridines have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process,[3] and their therapeutic functions for treatment of a variety of diseases,[4] such as cardiovascular disorders,[4a] cancer[4b] and AIDS.[4c] In the human body, these compounds are oxidized to pyridine derivatives by the action of cytochrome P-450 in the liver.[5] These oxidized compounds are largely devoid of the pharmacological activity of the parent compounds. The oxidation of 1,4-DHPs to the corresponding pyridine derivatives constitutes the principal metabolic route in biological systems,[1,3] as well as a facile access to the corresponding pyridine derivatives, which show anti-hypoxic and anti-ischemic activities,[6] from the easily available DHPs.[7] Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed.[8–10] Early works mostly used strong oxidants, such as HNO_3,[8b] $KMnO_4$,[8c] or CAN[8d] and I_2–MeOH.[8e] Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation[9] and catalytic aerobic oxidation using $RuCl_3$,[10a] Pd/C[10b] and activated carbon[10c] as the catalyst. Despite these intensive efforts, most of the reported oxidation procedures require long reaction times, utilize strong oxidants in large excess, afford products with only modest yields, and non-reusability of the catalyst. Therefore, the development of more effective methods for aromatization of 1,4-dihydropyridines is still necessary.

Recently, there has been considerable interest in the use of heteropolyacids as environmentally benign catalysts due to their unique properties such as high thermal stability, low cost, ease of preparation and ease of recyclability. Numerous chemical reactions can be carried out in the presence of heteropolyacids.[11]

Based on our previous studies on the use of heteropolyacids as catalyst for carrying out organic reactions[12–23] and continuing our interest in aromatization of Hantzsch 1,4-dihydropyridines,[24] we examined the possibility of using a mixed addenda heteropolyacid to effect the oxidative aromatization of Hantzsch 1,4-dihydropyridines (Scheme 1).

In order to get the best reaction condition the efficiency of a variety of solvents and heteropolyacids in the oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate as a model reaction was studied.

Keywords: Aromatization; Hantzsch 1,4-dihydropyridine; Mixed-addenda vanadomolybdophosphate; $H_6PMo_9V_3O_{40}$; Reusable catalyst.
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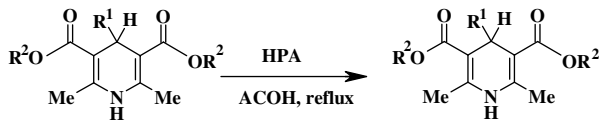

Scheme 1.

First we carried out the model reaction under solvent-free condition at room temperature. The reaction was not completed. The temperature of the reaction mixture started to rise but the reaction was not completed after 24 h. Then we decided to examine the effect of the solvent on the reaction. The results are summarized in Table 1.

One of the important factors affecting the oxidation capacity of plyanions is the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied orbital (LUMO). The heteropoly anions are easily reducible chemical species, thus the energy of the LUMO must be sufficiently low. The solvent molecules can stabilize these anions and place molecular orbitals at the appropriate level. Therefore both yields and reaction times can be affected by varying the solvent. By taking a look to the results of Table 1, we can see the highest yield of product has been obtained with acetic acid as solvent. In solutions, the acid properties of heteropolyacids have been characterized in terms of dissociation constants and Hammett acidity function.[25] As heteropolyacids have different dissociation constants and Hammett acidity in various solvents[25–28] and therefore, show different behaviors for dissociation of protons in different solvents.[26,27] In this area, in the less polar acetic acid, Keggin-type acids behave as 1–1 electrolytes.[25] From the conductivity study,[27] it was inferred that in polar nonaqueous solvents heteropolyacids are fully ionized, so the solvated protons are loosely bound to the anion as a whole rather than to a certain oxygen atom in the anion, in contrast to the crystalline acid.

Because of large negative charge of polyoxoanions, all of the HOMOs and LUMOs of them have very high energy levels. Heteropolyanions are reducible easily and it is necessary in oxidative catalytic reactions. The LUMO must be sufficiently low to accept the electrons in oxidative catalytic reactions. The solvent molecules can place these molecular orbitals at the appropriate level. It is suggested that the solvent effects are dominated by the electrostatic component-the interactions of the polarized polyanions with the charge distribution of the solvent, to place the molecular orbitals at the appropriate level and or to lower the activation energy. In this research, with respect to the Table 1 it seems likely that this effect is higher for the acetic acid.

The effect of a variety of heteropolyacids including $H_3PW_{12}O_{40}$, $H_6P_2W_{18}O_{6\ 2}$, $H_5PMo_{10}V_2O_{40}$, $H_4PMo_{11}VO_{40}$ and $H_3PMo_{12}O_{40}$ in the oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(A) and 2,6-dimethyl-4-ethyl-1,4-dihydropyridine-3,5-dicarboxylate(B) in refluxing acetic acid was also explored. The results are shown in Table 2. Among Keggin type heteropolyacids $H_6PMo_9V_3O_{40}$ gave the best results in terms of yields and times. It is difficult to clarify the different activity between these anions clearly. Obviously there is a complex relationship between the activity and structure of polyanions. Transition metal cations have an important effect on the properties of these compounds when they substitute molybdenum cations in the Keggin units or when they are present as counter cations. The case of vanadium, which can occupy both anionic and cationic positions, is more complex. The introduction of vanadium (V) into the Keggin framework is beneficial for redox catalysis,[29] shifting its reactivity from acid to redox-dominated. One of the difficulties encountered in interpreting data obtained from reactions of vanadomolybdophosphate anions is that in solution, a mixture of heteropoly anions are usually present. In addition positional isomers of the polyvanadium anions are also apparent. Another complication inherent in the study of multi electron

Table 1. The effect of the solvent on the oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate, (entry 5, Table 3) in the presence of catalytic amount of $H_6PMo_9V_3O_{40}$

Solvent	Dichloromethane	Chloroform	Ethanol	Water	Acetonitrile	Acetic acid
Time (min)	70	70	70	70	70	70
Yield (%)[a]	20	20	25	35	40	96

[a] Yields were analyzed by GC.

Table 2. Oxidation of 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate(A) (entry 1, Table 3) and 2,6-dimethyl-4-ethyl-1,4-dihydropyridine-3,5-dicarboxylate(B) (entry 5, Table 3), using a catalytic amount of different heteropolyacids (1 mol%) in refluxing acetic acid

Entry	Heteropolyacid	Time (min)		Yield (%)[a]	
		A	B	A	B
1	$H_3PW_{12}O_{40}$	240	240	10	12
2	$H_6P_2W_{18}O_{62}$	240	240	15	15
3	$H_3PMo_{12}O_{40}$	225	80	95	96
4	$H_4PMo_{11}VO_{40}$	80	130	95	98
5	$H_5PMo_{10}V_2O_{40}$	80	35	80	98
6	$H_6PMo_9V_3O_{40}$	70	20	96	99

[a] Yields were analyzed by GC.

oxidations by polyvanadium-containing anions is the capacity of these oxidants to be reduced by one or more electrons (reduction of each V(V) ion to V(IV)).[30,31]

Considering the real oxidant in these reactions one can tell, redox chemistry of polyoxometalates is extremely diverse.[32,33]

According to Pope,[32,34] polyoxometalates, regarding their redox abilities, can be divided into two groups-mono-oxo, (type I) and, *cis*-dioxo, (type II). This classification is based on the number of terminal oxygen atoms attached to each addenda atom, for example, molybdenum or tungsten, in the polyanion. Examples of type I polyanions are the Keggins, the Wells–Dawsons and their derivatives that have one terminal oxygen atom M=O per each addenda atom. Type II polyanions can be represented by the Dexter–Silverton anion which has two terminal oxygens in cis positions on each addenda atom.

In type I octahedral MO_6, the lowest unoccupied molecular orbital (LUMO) is a nonbonding metal-centered orbital, whereas the LUMO for type II octahedral is antibonding with respect o the terminal M=O bonds. Consequently, type I polyoxometalates are reduced easily and frequently reversibly to form mixed-valence species, heteropoly blues, which can act as an oxidant. In contrast, type II polyoxometalates are reduced with more difficultly and irreversibly to complexes with yet unknown structures.[32,34] For this reason, only type I heteropoly compounds, by and large the Keggins, are of interest for oxidation catalysis.

The total number of accepted electrons on reduction of type I polyoxometalates can be quite high. As the anion structure retains upon this process, the additional negative charge is compensated for by protonation of the anion from solvent. Thus, the reduction is frequently pH-dependent. This can be represented by Eq. 1. Also, this point shows the importance of solvent in these reactions (Table 1).

$$[XM_{12}^{6+}O_{40}]^{x-8} + pe^- + qH^+ \rightarrow Hq[XM_{12-p}^{6+}Mp^{5+}O_{40}]^{x+q-p-8} \quad (1)$$

where $q \leqslant p$.[32,33]

Redox properties of the mixed-addenda anions $[PMo_{12-n}V_nO_{40}]$ have been studied in considerable detail, especially in connection with their application for catalytic oxidation.[35–37] These anions are remarkable because they posses not only a fairly high oxidation potential (ca. 0.7 V)but also their reduced forms are very easily reoxidised by oxygen (air) in solution. These redox reactions can be represented by Eqs. 2 and 3.

$$[PMo_{12-n}V_nO_{40}] + Red + mH^+ \rightarrow H_m[PMo_{12-n}V_nO_{40}] + Ox \quad (2)$$

$$H_m[PMo_{12-n}V_nO_{40}] + (m/4)O_2 \rightarrow [PMo_{12-n}V_nO_{40}] + (m/2)H_2O \quad (3)$$

Electron-transfer reactions of Keggin polyoxometalates in solution can be viewed as the outer-sphere electron transfers,[38–41] which is in line with their very low solvation energies as well as their weakness as ligands.

In our reactions, the heteropolyacid, oxidizes the substrate and then, in a separate step, is reoxidised by O_2. Either step can be rate-determining to control the overall reaction rate.

In order to establish the scope of this novel oxidation protocol, we tested a variety 1,4-DHPs under the optimized reaction conditions.[46] As shown in Table 3 both electron donating and electron withdrawing substituents on the precursors afforded the corresponding pyridines in good to excellent yields. In the presence of more amount of the catalyst the corresponding products of 1,4-dihydropyridines containing electron-withdrawing groups were obtained in shorter reaction times (Table 3, entries 10 and 12).

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical.[3b,10a,42,43] Yields were obtained using GC analysis. The reusability of the catalyst was also studied. After completing the model

Table 3. Oxidation of Hantzsch 1,4-dihydropyridines in the presence of catalytic amount of $H_6PMo_9V_3O_{40}$ in refluxing acetic acid

Entry	R^1	R^2	Time (min)	Yield (%)[a]	mp (°C)	
					Found[b]	Reported
1	H-	Et	30	98	68–70	69–70[29]
2	Me-	Et	70	97	Oil	Oil[3b]
3	Et-	Et	20	99	Oil	Oil[3b]
4	Isopropyl-	Et	15	94	70–72	70–71[10a]
5	ph	Et	70	96	60–62	61–62[3b]
6	4-Me-ph	Et	75	98	72–73	72–73[9h]
7	4-MeO-ph	Et	50	97	50	50[10a]
8	4-Cl-ph	Et	300	80	64–66	65–66[30]
9	3-NO_2-ph	Et	720	100	62–63	61–63[29]
10	3-NO_2-ph[c]	Et	240	80	62–63	61–63[29]
11	2-NO_2-ph	Me	240	80	104–105	104–105[9d]
12	2-NO_2-ph[c]	Me	120	100	104–105	104–105[9d]

[a] Yields were analyzed by GC.
[b] Products exhibited physical properties in accordance with the assigned structures.
[c] The reactions were carried out in the presence of 2 mol% of the catalyst.

reaction, the catalyst was removed and washed with diethyl ether and subjected to a second run of the reaction process with the same substrate. The results of the first experiment and subsequent were maintaining more than 90% yield.

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46. *Aromatization of Hantzsch 1,4-dihydropyridines: general procedure:* All the dihydropyridines were prepared according to the literature procedure, using the appropriate aldehydes, ammonia, and ethyl acetoacetate.[44] Hantzsch 1,4-dihydropyridine (1 mmol) in acetic acid (3 mL) was treated with a catalytic amount of heteropolyacid (1 mol%) under refluxing condition. The progress of the reaction was monitored by TLC using petroleum ether: ethyl acetate as eluent. After completion of the reaction the catalyst was filtered off and diethylether (5 mL) was added to the mixture. The obtained solution was washed with 5% $NaHCO_3$ (10 mL) and brine (10 mL) successively and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude products. Further purification was obtained by flash chromatography. Heteropolyacids were prepared according to the literature.[45]