

A green catalytic procedure for oxidation of pyridines catalyzed by a lacunary polyoxometalate in water at room temperature†

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A green and reusable catalytic procedure for oxidation of pyridines to *N*-oxides was developed. High yields of heterocyclic *N*-oxides were obtained when catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in water at room temperature. The catalyst used in the system could be recovered and reused several times without obvious loss of activity.

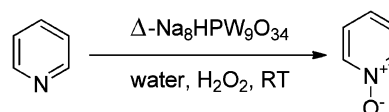
Pyridine *N*-oxides are versatile and important synthetic intermediates, which are used widely in fields of biology and chemistry. Heterocyclic *N*-oxides are used as protecting groups, auxiliary agents, oxidants, catalysts, surrogates for heterocyclic boronic acids and ligands in metal complexes.^{1–5} In addition, recently pyridine *N*-oxide derivatives have been reported to represent a new class of anti-HIV compounds.⁶ They are usually prepared by non-catalytic oxidation of pyridines using strong oxidants, such as H_2SO_5 ,⁷ dioxiranes⁸ and magnesium monophtalate.⁹ High activity was also observed in the oxidation of pyridines in the presence of peracetic acid or acetic acid.^{10–12} However, the byproduct of the oxidation in the presence of them is acetic acid, which is corrosive to the equipment and the environment. Besides, peracetic acid used as an oxidant is also more dangerous during reaction because of its explosive nature. Aqueous hydrogen peroxide, as a cheap and clean oxidant with active catalysts, has been developed to minimize waste production and meet the requirements of green chemistry. Use of homogeneous catalysts with hydrogen peroxide for catalytic oxidation of pyridines received much attention in recent years, such as $\text{AcOH}/\text{H}_2\text{O}_2$,¹³ $\text{MeReO}_3/\text{H}_2\text{O}_2$,¹⁴ trifluoroacetic anhydride ($\text{TFAA}/\text{H}_2\text{O}_2$)¹⁵ and $\text{Tf}_2\text{O}/\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}$.¹⁶ In order to make the catalysts reusable expediently, several heterogeneous catalysts like perfluoroketone–silicate,¹⁷ TS-1¹⁸ and $\text{V}_x\text{Si}_{4x}\text{O}_{6.4x}$ ¹⁹ were also

demonstrated for the oxidation of pyridines. However, for these recovered catalytic systems, high reaction temperature and poisonous organic solvents are usually required. So the design of a new recyclable, effective and mild catalytic system for the oxidation of pyridine is necessary.

Polyoxometalates, as effective catalysts for oxidation reactions with hydrogen peroxide, have drawn wide attention in the past years, such as olefin epoxidation,^{20–25} alcohol oxidation^{26–29} and water oxidation.³⁰ But the report on oxidation of pyridines using polyoxometalates with hydrogen peroxide is less,^{5,31} and high reaction temperature and poisonous organic solvent were necessary for these procedures. Recently, a vanadium-substituted polyoxometalate of $\text{K}_6[\text{PW}_9\text{V}_3\text{O}_{40}] \cdot 4\text{H}_2\text{O}$, as an effective and recyclable catalyst for the oxidation of pyridines, has been reported.³² To expand the applications of the green system for oxidation of pyridines and avoid using metal-substituted polyoxometalates, a green and reusable synthetic procedure for oxidation of pyridines catalyzed by a lacunary polyoxometalate is developed in this paper.

Heterocyclic *N*-oxides were obtained by oxidation of pyridines in water at room temperature when catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ (see Scheme 1). The catalyst after reaction could be recovered and reused several times without obvious loss of activity.

Firstly, 4-picoline was used as a model substrate to check the feasibility of oxidation in several different systems. As shown in Table 1, a high yield of 4-picoline-*N*-oxide was obtained when catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in water at room temperature (97%). The control experiment was carried out to reveal that the oxidation of 4-picoline was hardly processed without



Scheme 1

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Table 1 Synthesis of 4-picoline-*N*-oxide in different systems^a

Entry	Catalyst	Solvent	Yield ^b (%)
1	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Water	97
2	No	Water	5
3	$\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$	Water	68
4	$\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$	Water	9
5	$\text{H}_3\text{PW}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$	Water	82
6	$\text{H}_4\text{SiW}_{12}\text{O}_{40} \cdot x\text{H}_2\text{O}$	Water	73
7	$\text{K}_8[\gamma\text{-SiW}_{10}\text{O}_{36}] \cdot 13\text{H}_2\text{O}$	Water	85
8	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Ethyl acetate	83
9	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Chloroform	72
10	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Acetonitrile	54
11	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Ethanol	55
12	$\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$	Acetone	28


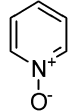

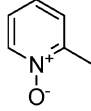
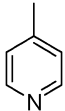
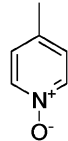

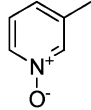

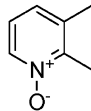

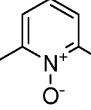

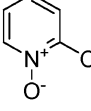

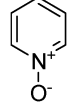

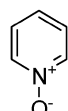
^a Reaction conditions: 0.03 mmol catalyst; 3 ml solvent; 4 mmol substrate; 20 mmol (30% aq.) H_2O_2 ; reaction temperature: room temperature (about 298 K); reaction time: 24 h. Assignments of products were analyzed using ^1H NMR and ^{13}C NMR. ^b Isolated yields.

catalyst (5%). The oxidation proceeded sluggishly using $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ or $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ under the same conditions, indicating the special catalytic activity of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$. In addition, some Keggin-type polyoxometalates (entries 5–7) were also used and it was found that $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ exhibited the highest activity among all the examined catalysts, indicating the special activity of this lacunary polyoxometalate. Interestingly, sodium tungstate shows some activity in the system. The reason may be attributed to the formation of tungsten-peroxo intermediate when sodium tungstate was treated with hydrogen peroxide. Even so, the activity of sodium tungstate is much less than that of lacunary polyoxometalate of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$. Compared with the reported polyoxometalate catalysts used for pyridine oxidation,^{31,32} the catalyst $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in this paper is easily prepared without metal-substitutes and shows better catalytic activity.

The effect of solvents on the activity of the catalyst was also investigated. The activity of the catalyst in water was much higher than that in other organic solvents. Even synthesis of *N*-oxide was carried out in organic solvents, the results were also different. The yields of 4-picoline-*N*-oxide in acetonitrile, ethanol and acetone were less than 55% (entries 10–12). But in ethyl acetate and chloroform, the yields of the products were much higher (entries 8 and 9). These results should be attributed to the solubility of the catalyst in these solvents. The polyoxometalate of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ is an inorganic salt that was soluble in the aqueous phase during the reaction. The organic solvents, such as ethanol, acetonitrile or acetone, are insoluble in aqueous solution, which made the catalyst partly precipitate from the aqueous phase. So no significant activity was observed in these solvents. In contrast, the hydrophobic solvents, such as ethyl acetate and chloroform, had no effect on the catalyst dissolved in the aqueous phase. So, moderate yields were obtained in these two solvents. The solubility of the catalyst in the system played an important role in the oxidation. Based on the above results, it is noteworthy that this catalytic system using $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in water is more effective than other systems.

The catalytic system was investigated for being used in synthesis of other *N*-oxides by oxidation of pyridine derivatives.

Table 2 Catalytic oxidation of pyridines to *N*-oxides in water at room temperature^a

Entry	Substrate	Product	Time (h)	Yield ^b (%)
1			16	96
2			16	90
3			24	97
4			24	96
5			24	94
6			24	93
7			24	26
8 ^c			16	96
9 ^d			16	95

^a Reaction conditions: 0.03 mmol $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$; 3 ml water; 4 mmol substrate; 20 mmol (30% aq.) H_2O_2 ; reaction temperature: room temperature (about 298 K). Assignments of products were analyzed using ^1H NMR and ^{13}C NMR. ^b Isolated yields. ^c The catalyst of cycle 1. ^d The catalyst of cycle 2.

The results are shown in Table 2. Most of the substrates were successfully oxidized to their corresponding *N*-oxides in high yields at room temperature in water. Selectivities to the *N*-oxides were $\geq 99\%$. In pyridine oxidation, a yield of 96% was obtained within 16 h when catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in this system. The substrates of picolines were also examined. It was found that 2-picoline, 3-picoline and 4-picoline were converted to the corresponding *N*-oxides in excellent yields in an appropriate reaction time (entries 2–4). Di-substituted pyridine derivatives of 2,6-lutidine and 2,3-lutidine were also successfully

oxidized in this catalytic system with high yields (entries 5 and 6). An electron-deficient substrate (2-chloropyridine) was hardly reactive as expected.

The catalyst used in this system could be recovered and reused. During reaction, the catalyst was soluble in aqueous solution forming a homogeneous system. After reaction, the solution was concentrated by evaporation. Because the catalyst is insoluble in anhydrous ethanol, the polyoxometalate was recovered as a deposit from the mixture after the addition of anhydrous ethyl alcohol. The recovered catalyst was washed with anhydrous ethyl alcohol and ether, which was then used for the next oxidation. The reuse performance of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in the oxidation of pyridine is also shown in Table 2 (entries 8 and 9). After three consecutive reuse, the yield of pyridine-*N*-oxide obtained using the recovered catalyst was nearly the same as that obtained from the first reaction (95%), indicating that this is a green and reusable catalytic system for synthesis of pyridine *N*-oxides.

The fresh catalyst, recovered catalysts and the catalyst treated with hydrogen peroxide were characterized with FT-IR spectra. As shown in Fig. 1, the IR spectrum of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}\cdot 19\text{H}_2\text{O}$ (Fig. 1a) exhibited characteristic peaks at 1171–994 and 896–742 cm^{-1} , which were attributed to $\nu(\text{P-O})$ and $\nu(\text{W-O})$, respectively.³³ There were obvious differences in the IR spectra between the fresh catalyst and the catalyst of cycle 1, indicating that the structure of the catalyst after first reaction was changed. However, when the catalyst was recycled again, we found that the IR spectrum of cycle 2 catalyst was similar to that of the cycle 1 catalyst (Fig. 1b and c), indicating that the structure of the catalyst would not change from the first cycle. An obvious peak at 840 cm^{-1} appeared in the spectrum of the catalyst treated with hydrogen peroxide (Fig. 1d), which was attributed to $\nu(\text{O-O})$.²⁰ Compared with the activity of the used catalyst and the characterizations of IR spectra, we supposed the possible mechanism of pyridine oxidation using the catalyst $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}\cdot 19\text{H}_2\text{O}$ in water with hydrogen peroxide (shown in Fig. 2). When the catalyst was treated with hydrogen peroxide, the structure of the catalyst changed to a mixture of polytungstophosphate species. With the effect of H_2O_2 , they could

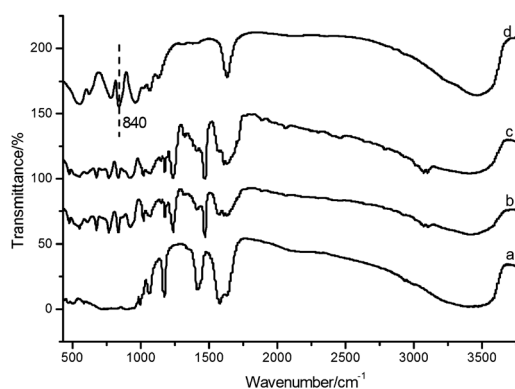


Fig. 1 IR spectra of the catalyst before and after oxidation reaction: (a) the fresh catalyst; (b) the catalyst of cycle 1; (c) the catalyst of cycle 2; (d) the catalyst treated with H_2O_2 .

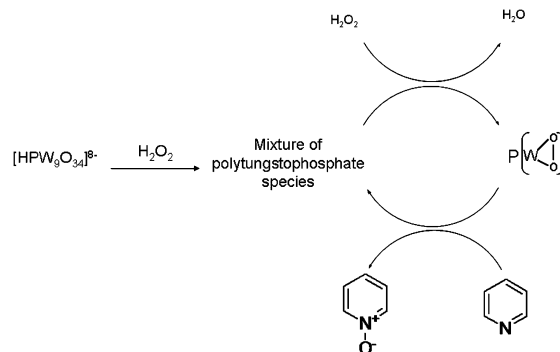


Fig. 2 Possible mechanism for oxidation of pyridines catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ in water.

be transferred to each other and finally became the true active peroxy tungstophosphate species. The intermediate is quite active and might be responsible for the oxidation of pyridines to the corresponding *N*-oxides. When the oxidation catalyzed by the active complexes was completed, the catalyst changed back to the mixture of polytungstophosphate species.

In conclusion, an effective and green synthetic procedure for pyridine *N*-oxides catalyzed by $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}$ was developed. In the system, reactions were carried out in water at room temperature using hydrogen peroxide as an oxidant. This system is an environmentally friendly and reusable oxidation system for pyridine oxidation.

Experimental section

Preparation of catalyst $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}\cdot 19\text{H}_2\text{O}$ ³³

First 30 g of $\text{Na}_2\text{WO}_4\cdot 2\text{H}_2\text{O}$ was dissolved in 37 ml of distilled water with stirring. Then 0.75 ml of 85% H_3PO_4 , followed by 5.5 ml of glacial acetic acid were added to the stirring solution. After a few seconds, the solution became cloudy and after about 1 min a heavy white precipitate had formed. The solid was collected and first dried under aspiration for 24 h, and then the aspirated solid was left in air for 24 h. After that, the solid was dried at 140 °C for about 1.5 h. The yield of $\Delta\text{-Na}_8\text{HPW}_9\text{O}_{34}\cdot 19\text{H}_2\text{O}$ was about 80%. IR spectrum (KBr, cm^{-1}): 1171, 1057, 994, 947, 896, 818, 742, 653, 624, 588, 507, 470, 417.

Catalytic reaction

Catalyst (0.03 mmol), H_2O (3 ml), substrate (4 mmol), and H_2O_2 (20 mmol, 30% aq.) were charged in the reaction flask, which was firstly bathed in cold water (about 283 K). The mixture was then stirred at room temperature for 16–24 h. The reaction was detected by TLC. After reaction, the system was concentrated by evaporation, and the catalyst precipitated from the mixture after the addition of anhydrous ethyl alcohol. The recovered catalyst obtained by filtration was washed with anhydrous ethyl alcohol and diethyl ether, which was then used for the next oxidation after drying. The filtrate was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 , and the pure products were obtained by

evaporation or column chromatography. The products were analyzed using ^1H NMR and ^{13}C NMR.

Acknowledgements

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