Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

Organic Salts of Polyoxometalates: Novel and Efficient Catalysts for the Synthesis of Pyridine N-oxide Derivatives

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Organic Salts of Polyoxometalates: Novel and Efficient Catalysts for the Synthesis of Pyridine N-oxide Derivatives

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Catalytic N-oxidation of pyridine derivatives to related N-oxides were performed in the peresence of three organic salts of polyoxometalates including two heteropolyanion (THA)$_{7.7}$H$_{6.3}$[NaP$_5$W$_{30}$O$_{110}$], 1, and (THPA)$_{7.5}$ H$_{6.5}$[NaP$_5$W$_{30}$O$_{110}$], 2, and one isopolyanion [TBA]$_2$[W$_6$O$_{19}$] (3) with W as central metal atom. Catalyst (3) showed the best catalytic activity. The highly selective oxidation gave good to excellent yields of the related N-oxides along with decarboxylation at 2-position of pyridine ring. The effect of some operative variables, such as temperature, various solvents, and the reaction time was studied. The reaction conditions were optimized.

1. INTRODUCTION

Pyridine N-oxides belong to a vast class of heterocyclic N-oxides, many of which are biologically active.[1,2] Recently, pyridine N-oxide derivatives represented a new class of anti-HIV compounds, for which some members exclusively act through inhibition of HIV reverse transcriptase, and thus characteristically behave as non-nucleoside reverse transcriptase inhibitors.[3] Interestingly, in the nanotechnology field, it has been shown that nanoshampoo including carboxylic acid pyridine N-oxide is a very powerful hair growth stimulator with a high level of safety.[4] Pyridine N-oxides are also useful as protecting groups, auxiliary agents, oxidants, ligands in metal complexes, and catalysts.[5] Many researchers have studied the N-oxidation of pyridines using various oxidants and catalysts.[6–10] Pyridine N-oxides are usually prepared by oxidation of pyridines using peracids such as meta-chloroperbenzoic acid and peracetic acid, from the esters of N-hydroxy-2-thiopyridone, by

ring transformation of isoxazoles and through cycloaddition reactions.[11–17] The shortcomings of these methods are the requirement of high temperature or catalyst loading, longer reaction times, expensive and highly toxic catalysts, specific conditions and tedious work up procedures. Hence, a practical and more efficient method using inexpensive and environment friendly catalyst is still of interest. 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. Our previous work was devoted to study the catalytic performance of H$_{14}$[NaP$_5$W$_{30}$O$_{110}$], so called Preyssler acid, in order to obtain pyridine N-oxides from pyridine derivatives.[18] Therefore, it is of great interest to know what occurs if in Preyssler acid, organic groups are replaced instead of some acidic protons. We also investigated the catalytic performance of an isopolytungstate. As part of research project and in continuation of our researches on polyoxometalates,[19,20] the present work screens the performance of the organic salts of polyoxometalates as: tetrahexyl ammonium (THA) and tetraheptyl ammonium (THPA) with Preyssler, **1** and **2**, and tetrabutylammonium (TBA) hexatungestate (**3**), in N-oxidation of pyridine derivatives. To the best of our knowledge, there is not any report concerning the catalytic behavior of the studied polyoxometalates in this work in the oxidation of pyridines.

2. EXPERIMENTAL

2.1. Chemicals and Apparatus

All compounds were known, and their physical and spectroscopic data were compared with those of authentic samples and found to be identical. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The TG curves were recorded using TGA-1500 instrument. GC-Mass analysis was performed on a GC-Mass model: 5973 network mass selective dedector,

TABLE 1
N-oxidation of pyridine derivatives using H_2O_2 and polyoxometalate catalysts with various solvents[a]

Entry	Pyridine	Product	Time (h)	Solvent	% Yield with catalysts (**3/2/1**)
1			1	Solvent-free	95/trace/trace
			5	PhCH₃	70/72/88
			5	CH₃CN	74/46/40
			5	THF	72/85/75
2			1	Solvent-free	93/trace/trace
			5	PhCH₃	71/70/86
			5	CH₃CN	75/32/36
			5	THF	73/84/72
3			1	Solvent-free	90/trace/trace
			6	PhCH₃	78/80/77
			6	CH₃CN	82/28/33
			5	THF	78/85/91
4			1	Solvent-free	88/trace/trace
			5.30	PhCH₃	75/81/87
			6	CH₃CN	80/25/27
			5	THF	73/82/74
5			1	Solvent-free	96/trace/trace
			4	PhCH₃	88/84/97
			4.30	CH₃CN	78/trace/trace
			4	THF	68/86/75
6			1	Solvent-free	92/trace/trace
			4.30	PhCH₃	82/80/88
			4.30	CH₃CN	84/26/18
			5	THF	72/89/78
7			1	Solvent-free	55/trace/trace
			5	PhCH₃	48/trace/trace
			5	CH₃CN	46/15/12
			5.30	THF	52/27/16
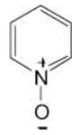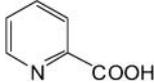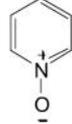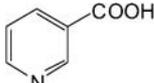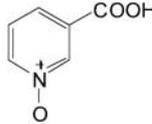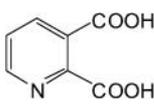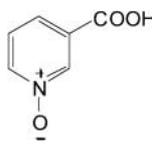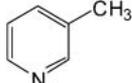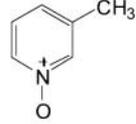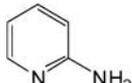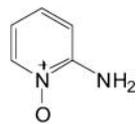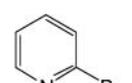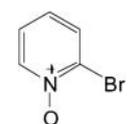
[a]Reaction conditions: pyridine (5 mmol), hydrogen peroxide (7.5 mL), catalyst (0.05 mol), solvent (10 mL), reflux, neat (90°C).

GC 6890 egilent. Mass spectra were obtained with a Massens POEKTRO METER CH-7A VARIAN MAT BREMEN spectrometer.

2.2. General Procedure for the Prepration of Pyridine N-oxides

A mixture of pyridine derivative (5 mmol), aqueous hydrogen peroxide 15% (7.5 ml), and appropriate catalyst (0.05 mmol) was heated under solvent free conditions at 90°C or in different solvents at reflux temperature.The reaction was monitored by TLC. After completion of the reaction, the precipitate was filtered off, washed with water and diethyl ether, and air dried to give pure pyridine N-oxides (Table 1).

2.3. Synthesis of Polyoxometalate Catalysts

2.3.1. Synthesis of (TBA)₂[W₆O₁₉]

This catalyst was prepared according to the literature. [21] A mixture of sodium tungstate dihydate (Na₂WO₄.2H₂O,99%) (100 mmol, 33g), acetic anhydride (40 ml), and DMF (30 ml) was heated at 100°C for 3 hours to obtain a white cream. Then a solution of acetic anhydride (20 ml) and HCl (18 ml, 12N) in DMF (50 ml) was added with stirring, and the resulting mixture is filtered off to eliminate the undissolved white solid. A solution of tetrabutylammonium bromide (47 mmol, 15 g) in methanol (50 ml) was added with rapid stirring to give a white precipitate. This suspension is stirred for 5 min and the product is filtered. Recrystalyzation from a minimum amount of hot DMSO gives colorless diamond-shaped crystals.

2.3.2. Synthesis of $H_{14}[NaP_5W_{30}O_{110}]$

$H_{14}[NaP_5W_{30}O_{110}]$ was prepared by passage of a solution of the potassium salt[22] in water through a column (50 cm × 1 cm) of Dowex 50w × 8 in the H+ form and evaporation of the elute to dryness under vacuum.

2.3.3. Synthesis of catalysts 1 and 2

To a stirred aqueous solution of $H_{14}[NaP_5W_{30}O_{110}]$.25.5 H_2O was added a solution of THABr or THPABr dropwise (molar ratio: 1:14). The mixture was stirred for about 6h, which led the formation of an viscous solid and an oil for THA and THPA, respectively. The separated compounds were purified in a mixture of water and acetonitrile. Recrystalization was performed in water and acetonitrile. The number of THA and THPA cations were determined via TG analysis.[23]

3. RESULTS AND DISCUSSION

The catalytic oxidation of tertiary amines to the corresponding N-oxides by organic salts of polyoxometalate catalysts and hydrogen peroxide as oxidant was carried out in three different solvents at reflux and under solvent free conditions at 90°C. Acetonitrile, toluene, and tetrahydrofuran were examined as solvents. Among these solvents, tetrahydrofuran was the solvent of choice for reactions catalyzed by 1 and 2. Water miscible solvents like methanol and ethanol were poor solvents at room and reflux temperatures in the presence of organic salts of 1 and 2. For 3, solvent free conditions were excellent toward the organic solvents. One of the important factors affecting the behavior of POMs is the energy gap between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The POMs are easily reducible chemical species, and thus the energy of the LUMO must be sufficiently low to accept the incoming electron in catalytic reactions. The solvent molecules stabilize POMs and place these molecular orbitals at the appropriate level. The effects of COOH position, catalyst type and reaction time have been studied.

3.1. Effect of Position of the COOH Group

The effect of the COOH position in oxidation of pyridine carboxylic acids has been examined in the presence of organic salts of polyoxometalates catalysts. Our studies showed that for product type, the position of COOH group with respect to nitrogen is a very important factor. In general, the observed selectivity was 100%. Interestingly, the GC-mass results, mass and melting points of pyridine N-oxides showed, pyridine-2-carboxylic acid, and pyridine-2,3-dicarboxylic acid can be oxidized along with decarboxylation to give decarboxylated pyridine N-oxides, while pyridine-3-carboxylic acid is oxidized to the related N-oxide without any decarboxylation. The higher efficiency for decarboxylation in 2-position with respect to nitrogen for pyridine-2-carboxylic acid, and pyridine- 2,3-dicarboxylic acid can, most probably, be explained in the following way: the carboxylate anion forming in the transition state is very close to the pyridine nitrogen, causing, to some extent, a repulsion between the identical negative charges, resulting in the planar carboxylate anion being in a perpendicular position with respect to the pyridine ring, which is therefore subjected to a better carboxylate anion elimination. Pyridine-2- carboxylic acid afforded the pyridine N-oxide exclusively, with excellent yield and 100% selectivity. Also N-oxidation of pyridine-3-carboxylic acid and pyridine-2,3-dicarboxylic acid proceeded with good yields. An interesting observation in our system was high yield of 2- pyridine N-oxide in oxidation of pyridine-2-carboxylic acid. To establish the generality of method, we selected three other pyridines with amino, methyl and bromo moities. The catalytic oxidation of these pyridines have examined in the presence of both Preyssler salts catalyst and tetrabutylammonium hexatungestate isopolyanion. The results are presented in Table 1. These results show good to excellent activity for them.

3.2. Effect of the Reaction Time

For all substrates in the presence of three solvents and under solvent free conditions, the effect of reaction times on yield of pyridine N-oxides was studied (Table 1). The results showed that for 3, the maximum of yield can be obtained after one hour under solvent free conditions, while for 1 and 2 the maximum of yields can be obtained after 4–6 hours.

3.3. Effect of the Catalyst Type

All of these three catalysts are the strongly crystalline materials that are soluble in most of organic solvents, such as acetonitrile, CH_2Cl_2, and THF, and all of them are stable to air and moisture. As we can see in Table 1, tetrabutylammonium hexatungestate 3 shows the best catalytic activity.

The good performance of catalytic activity of 3 can be attributed to the double role of it as solvent and catalyst, so it can affect not only the yield, but also acceleration of reaction.

4. CONCLUSION

In summary, the present study demonstrates the catalytic activity of some organic salts of polyoxometalates such as $(THA)_{7.7}H_{6.3}[NaP_5W_{30}O_{110}]$, $(THPA)_{7.5} H_{6.5}[NaP_5W_{30}O_{110}]$, and $(TBA)_2[W_6O_{19}]$ in N-oxidations of pyridine derivatives. The significance of this study with inexpensive and easily prepared catalysts fundamentally lies in the fact that their use would lead to an alternative technology for the other system and amines, which are of interest for the pharmaceutical industry and nanotechnology, with advantages from the point of view of the environmental care.

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