Catalytic Method for Synthesis of Aspirin by a Green, Efficient and Recyclable Solid Acid Catalyst (Preyssler's Anion) at Room Temperature

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Synthesis of aspirin at room temperature *via* O-acetylation of salicylic acid in the presence of Preyssler type heteropolyacids has been investigated in order to contribute toward clean technology, which is the most important need of the society. All of the catalysts are recyclable and reusable.

Keywords: Preyssler; Catalyst; Heteropolyacid; Aspirin; Green catalyst.

INTRODUCTION

It is known that a number of aliphatic and aromatic alcohols react with a range of acids to give esters in a reaction catalyzed by acids.[1-6] Generally, in acid-catalyzed reactions, solid acid catalysts are suitable. Many research groups continue to explore the catalytic properties of strong solid acids in an attempt to eliminate environmental concerns caused by the use of liquid acids.[7,8]

Heteropolyacids (HPAs) are strong Bronsted acids composed of heteropolyanions and protons as the countercations and are used to replace environmentally harmful liquid acid catalysts.[9-11] These bulk compounds catalyze many reactions much more effectively than the conventional protonic acids, such as sulfuric acid and nitric acid, and they can even be better than BF_3 etherate. It has been proposed that such a high catalytic efficiency of these heteropolyacids is mainly due to specific properties of the heteropolyanion with weak basicity and great softness, in addition to the large molecular size of the heteropolyanion.

Among HPAs, Keggins-type HPAs have attracted much interest since they possess strong acidity. However, only a few reports have been published on the use of Preyssler's anion heteropolyacid.[12] In some cases there have been reports of no catalytic activity of Preyssler's anion.[13] For the first time the exact structure of this polyanion was found in 1985.[14] Structure of the anion $[NaP_5W_{30}O_{110}]^{14-}$ is a cyclic assembly of five $\{PW_6O_{22}\}$ groups. The unusual 5-fold symmetry of this anion is achieved by fusion of five $\{PW_6O_{22}\}$ groups. The central sodium ion lies not on the equator of the anion but in a plane roughly defined by oxygen atoms of the phosphate groups. The sodium cation is nonlabile on the NMR time scale and appears to be essential for the anion synthesis. The presence of the sodium cation reduces the overall anion symmetry from D_{5h} to C_{5v}. This anion is even more robust than $[P_8W_{48}O_{184}]$ (pH stability range 0-12). A top and side view of the Preyssler structure is shown schematically in Fig. 1.

Important advantages of this polyanion over the Keggin heteropolyacids are: a) more thermal stability, b) more hydrolytic stability (pH = 0-12), and c) larger number of protons. These properties are very important in catalytic processes especially in synthesis of drugs.

Aspirin is an important drug worldwide and conventionally is prepared by an acid-catalyzed process. The most widely employed catalysts for this reaction are concentrated sulfuric and phosphoric acids.[15] Both acids are strongly corrosive and must be handled with care. Recently, an alternative method was reported in which aspirin could be prepared using acetyl chloride-pyridine as the acetylating agent *via* esterification reaction at low tempera-

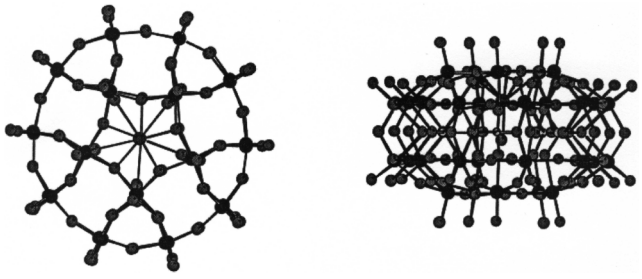

Fig. 1. Structure of Preyssler's catalyst (left: top view, right: side view).

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tures.[16] However the obnoxious and irritating odors of these reagents make them unsuitable for industrial scale operations. Keggin-type heteropolyacids and other derivatives have also been reported to be efficient catalysts for the esterification reactions.[17,18] It appears from the open literature that attention has been focused on obtaining maximum yield rather than maximum selectivity and greenness.

In continuation of our research on the synthesis and application of heteropolyanions in organic syntheses,[19-22] we now report the application of a novel and recyclable solid acid catalyst, Preyssler catalyst, with exclusive properties surpassing the Keggin heteropolyacids, for highly selective and rapid liquid-phase O-acetylation of salicylic acid in order to synthesize aspirin at room temperature. Recently we have been exploring the application of the Preyssler catalyst,[19,20] and the major aim described in this work is also the design and extension of the applications of the Preyssler catalyst.

RESULTS AND DISCUSSIONS

Highly selective acetylation of salicylic acid with acetic anhydride at room temperature has been carried out for the first time by an inexpensive, recyclable, and easily prepared Preyssler's anion. The performance of this polyanion in different forms was compared with Keggin types: $H_4[SiMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PW_{12}O_{40}]$ and $H_3[PMo_{12}O_{40}]$ and H_2SO_4.

In all cases, the heteropolyacids with Preyssler structures show higher activity in esterification reactions compared with Keggin type heteropolyacids and H_2SO_4. The yields of O-acetylation of salicylic acid into aspirin with various heteropolyacids are given in Table 1. In the presence of H_{14}-P_5, salicylic acid was converted to aspirin with acetic anhydride in 78% yield with 100% selectivity at room temperature in 10 minutes (entry 1). $H_{14}P_5$-Mo has lower activity than H_{14}-P_5. It leads to 69% aspirin with 100% selectivity after 10 minutes (entry 2).

Catalytic activity of Keggin heteropolyacids such as $H_4[SiMo_{12}O_{40}]$, $H_4[SiW_{12}O_{40}]$, $H_3[PW_{12}O_{40}]$ and $H_3[PMo_{12}O_{40}]$, was less than Preyssler's anion. They lead to 57, 61, 59 and 47%, respectively, with 90-95% selectivity (entries 3-6). The yield of aspirin in the presence of silica-supported Preyssler increased from 19% to 73% with an increase in catalyst loading from 10% to 50% (entries 7-11). It is clear that esterification yield depends on the nature of the acid. A heteropolyacid with tungsten atom shows higher acidity than a molybdenum analogue.[18] When tungsten is replaced by molybdenum, the negative charge on the oxygen atoms increases which leads to a decrease in acidity.[18,23]

Table 1. Yields of aspirin in *O*-acetylation of salicylic acid with various heteropolyacid catalysts at room temperature

Entry	Time (min)	Catalyst	%Yield
1	10	$H_{14}[NaP_5W_{30}O_{110}]$	78
2	10	$H_{14}[NaP_5W_{29}MoO_{110}]$	69
3	15	$H_4[SiMo_{12}O_{40}]$	57
4	15	$H_4[SiW_{12}O_{40}]$	61
5	15	$H_3[PW_{12}O_{40}]$	59
6	15	$H_3[PMo_{12}O_{40}]$	47
7	10	$H_{14}[NaP_5W_{30}O_{110}]/SiO_2$(%10)	20
8	10	$H_{14}[NaP_5W_{30}O_{110}]/SiO_2$(%20)	35
9	10	$H_{14}[NaP_5W_{30}O_{110}]/SiO_2$(%30)	62
10	10	$H_{14}[NaP_5W_{30}O_{110}]/SiO_2$(%40)	68
11	10	$H_{14}[NaP_5W_{30}O_{110}]/SiO_2$(%50)	73

In homogeneous conditions higher activity of Preyssler is attributed to the higher number of acidic protons. The results point out that the catalytic effectiveness may be enhanced as the number of tungsten atoms (or the number of protons) is increased. Both possibilities are logical. The large anion with the larger number of tungsten atoms also provides many "sites" on the oval-shaped molecule that are likely to render the catalyst effective.

It is also interesting to consider that, like the Keggin types, by replacing one of the tungsten atoms of H_{14}–P_5 with molybdenum in H_{14}–P_5Mo, the yield of aspirin decreases. By replacing tungsten with molybdenum, symmetry is also decreased, and this distortion may affect the nature of polyacid and acidity of a heteropolyacid. However, the results show that among all of the heteropolyacid catalysts, H_{14}–P_5 shows the highest yield.

Compared with mineral acids, such as H_2SO_4, H_{14}–P_5 is more active and shows a higher selectivity and a minimizing of side reactions. Fig. 2 gives the yield of aspirin in esterification obtained under the same conditions and over H_2SO_4 and H_{14}–P_5. It can be seen from the Figure that the activity of H_{14}–P_5 is higher than that of sulfuric acid. In order to achieve heterogeneous catalysis, the esterification was carried out by $H_{14}P_5/SiO_2$ with different loadings. Catalyst loading was varied from 10% to 50%. As illustrated in Table 1, the yield of aspirin increased with an increase in catalyst loading from 10% to 50%. It is attributed to the increase in the total number of available active catalytic sites for the reaction. For heterogeneous catalyzed reactions, it

is not very good to use more than 50% (w/w) catalyst loading, and hence it can be concluded that the optimal catalyst loading based on the current findings was 50% (w/w). In all cases, the supported polyacid is less active than that of the non-supported.

Oxide supports such as SiO_2 have a large surface area and a peculiar pore structure. In the process of adsorption, surface hydroxyl groups play a very important role in adsorbing different ions from solution. On the other hand, although SiO_2-supported HPAs are more stable, the interaction of HPA and the OH surface groups can bring about the decrease of acidity and redox property of HPAs.[22] On the basis of the obtained results, we can suggest that there is a direct interaction between Preyssler and the surface of support. So it is reasonable to assume that the adsorption of Preyssler on support could be ascribed to an acid-base reaction.

It is well known that heteropolyacid is an acid with higher acid strength. In view of the difference in softness or hardness of hydroxyl of various supports and HPAs, the reaction between heteropolyanion and hydroxyl on the support may proceed according to a two-step ligand exchange mechanism (hard-hard reaction) or coordination of protonated surface hydroxyl with heteropolyanion in solution to form an outer sphere surface complex instead of exchange reaction (hard-soft reaction).

REUSABILITY OF PREYSSLER CATALYST

The major problem, limiting the utility of homogeneously catalyzed processes, is a well-known difficulty in catalyst recovery and recycling. The recycling of HPA catalysts is the key issue to their application. In both homogeneous and heterogeneous conditions Preyssler catalyst can be easily recovered and recycled. IR spectrum of the recovered solid catalyst indicated that the catalyst can be recovered without structural degradation. The recovered solids were reused as catalyst for new reactions. The recovery had only slightly decreased its catalytic activity and yield (2-5%), pointing to the stability and retention capability of this useful polyanion.

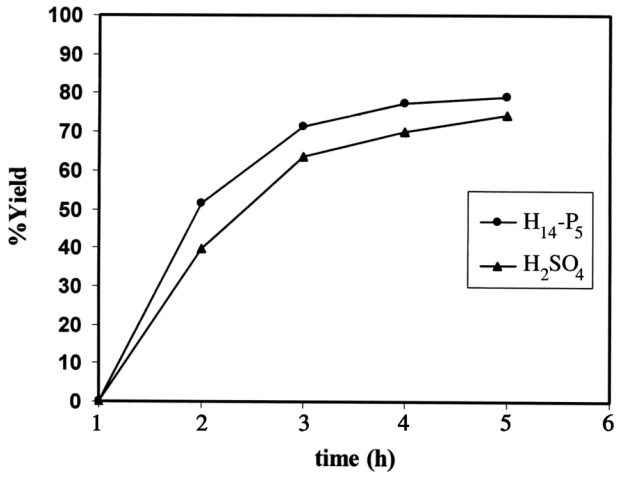

Fig. 2. Yield of aspirin as a function of time in the presence of $H_{14}[NaP_5W_{30}O_{110}]$ and H_2SO_4.

EXPERIMENTAL SECTION

Materials

Acetic anhydride, salicylic acid, sodium tungstate dihydrate, molybdotungstate dihydrate, orthophosphoric acid, sulfuric acid, ethyl acetate, potassium chloride and silica gel were commercially available.

Instruments

^{1}H-NMR spectra were recorded on an FT-NMR Bruker 100 MHz Aspect 3000 spectrometer. IR spectra were obtained with a Buck 500 scientific spectrometer (KBr pellets).

Catalyst Preparation

Keggin type heteropolyacids were acquired from commercial sources. Potassium salt of Preyssler's anion was prepared according to the procedure developed in our laboratory.[20] The free acid was prepared by passage of a solution of the potassium salt in water through a column of Dowex 50wx8 in the H^+ form and evaporation of the elute to dryness under vacuum.[20] Molybdenum substituted Preyssler heteropolyanion, H_{14}–P_5Mo, was prepared as follows: 2.8 g (0.169 mol) $Na_2WO_4.2H_2O$ and 2 g (0.008 mol) $Na_2MoO_4.2H_2O$ were dissolved in 35 mL of water and mixed at 60 °C for 30 min. Then this solution was cooled to room temperature, and 25 mL of concentrated phosphoric acid was added. The resulting yellow solution was refluxed for 18 h. The solution was brought to room temperature, diluted with water and then during stirring, 10 g of KCl was added. The mixture was stirred and then heated up to dryness. The product was dissolved in warm water and upon cooling to room temperature yellow crystals formed. The acidic form of molybdenum substituted heteropolyacid

was obtained as described above for the unsubstituted analogue.

Supported heteropolyacid catalysts were prepared by impregnating a support in the form of powder (SiO_2) with an aqueous solution of the heteropolyacid with different concentrations. Samples were dried at 120-140 °C, and the catalysts were calcined at 300 °C in a furnace prior to use.

General Procedure

The homogeneous process was performed by adding acetic anhydride (5 mL) to a solution of H_{14}–P_5 (0.2 g) and salicylic acid (2 g) at room temperature with stirring. The heterogeneous reactions were performed by contacting salicylic acid (2 g), acetic anhydride (5 mL) with 0.05 g of 10-50% H_{14}–P_5/SiO_2 at room temperature for the mentioned time with intense stirring. At the end of reaction, the mixture was diluted with 50 mL of water, and the crude product was precipitated in an ice bath. The crude product was removed and after the usual work up, the resulting solid was washed with cold water and recrystallized in ethyl acetate. The product was characterized by comparison of its spectroscopic (IR, ^{1}H-NMR, Mass) data, and melting point with that of an authentic sample. The product yield was determined quantitatively.

CONCLUSIONS

Preyssler catalyst is an effective solid acid catalyst for preparation of aspirin. Among various forms of Preyssler catalyst used, the H_{14}-P_5 shows higher activity than the other forms of Preyssler, as well as Keggin types and sulfuric acid. This method demonstrates the applicability of Preyssler's anion for some reactions that require a solid catalyst, with strong acidic properties, highly thermal stability and functionality over a wide range of pH. In addition, simple experimental setup and procedure makes this method a useful addition to the present methodologies.

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