$H_3PW_{12}O_{40}$: An Efficient and Green Catalyst for the Facile and Selective Oxidation of Sulfides to Sulfoxides, Applied to the Last Step of the Synthesis of Omeprazole

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ABSTRACT: *Omeprazole, (6-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl)-1H-benzimidazole is a well-established prescribed drug, exhibits proton pump inhibitor activity. In this work, a novel, facile, economical and selective oxidation approach using $H_3PW_{12}O_{40}$ as Keggin type heteropolyacids along with H_2O_2 in the last step of the conventional synthesis of this compound as well as its derivatives under environmental-benign conditions, is reported. This protocol can be well adopted for pilot plant scale giving a high pure pharmacopeia grade material. Our synthetic route involves the use of various heteropolyacids as heterogeneous catalysts. Due to the obtained results, it was concluded that Keggin type heteropolyacid , is an effective catalyst for this purpose. The optimized condition for the last step of this synthesis was applied to the synthesis of lansoprazole, pantoprazole, and rabeprazole.*

KEYWORDS: *Heteropolyacids; HPAs; Omeprazole; Sulfoxide; Oxidation; Hydrogen peroxide; Catalysis.*

INTRODUCTION

In the past few decades, compounds containing sulfoxide moiety have attracted much attention, due to their several biological properties [1]. Prominent examples are the sulfenyl-substituted benzimidazoles, which are proton pump inhibitors (PPIs) [2], a powerful class of antiulcer agents [3].

Several omeprazole derivatives [4] are commercially available and are prescribed for their proton pump inhibitor activity in the treatment of dyspepsia, peptic ulcer disease, gastro esophageal reflux disease, laryngopharyngeal reflux, and Zollinger–Ellison syndrome [4]. Several

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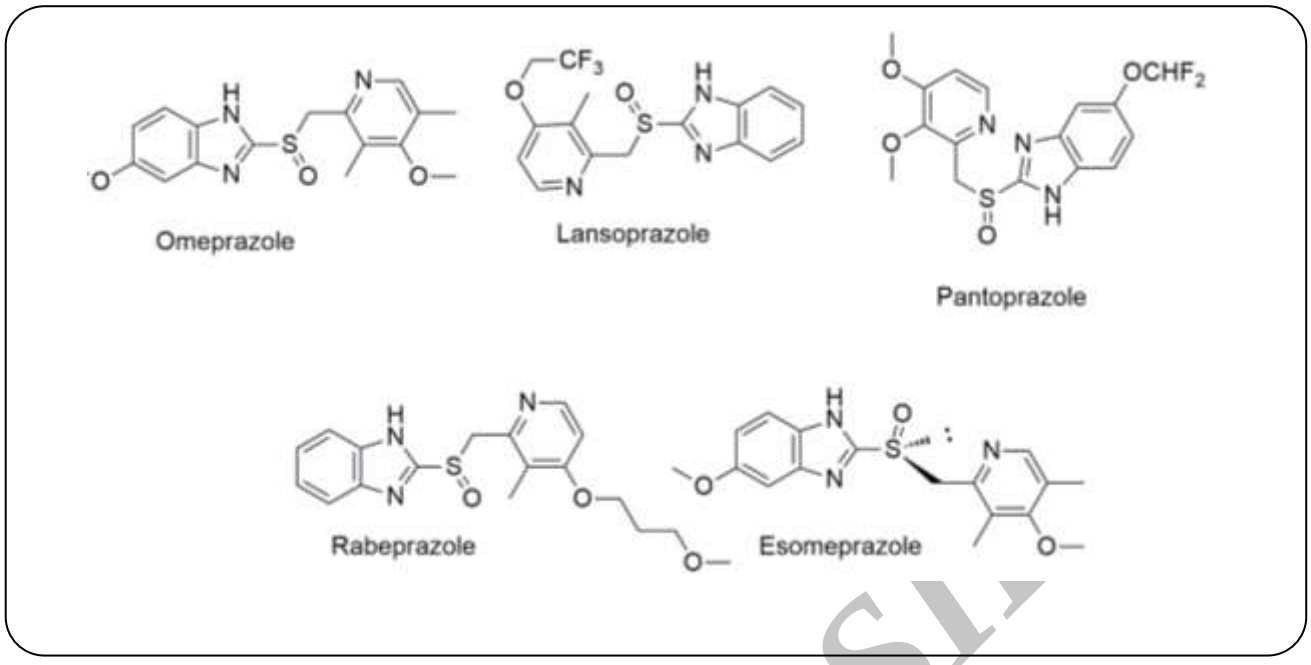


Fig. 1: The structure of commonly used proton pump inhibitors.

attempts have been made to synthesize pro-drugs of the proton pump inhibitors. The synthesis of *N*-acyloxyalkyl [5–7], *N*-carboxyalkyl [8], *N*-alkoxycarbonyloxyalkyl [8,9], *N*-alkoxycarbonyl, *N*-(aminoethyl) and *N*-alkoxyalkyl benzimidazole sulfoxides [5] has been successfully, accomplished and reported. Omeprazole structure which is shown in Fig. 1, is similar to thestructures of the other commonly used PPIs, such as lansoprazole, rabeprazole, esomeprazole and pantoprazole, which all bear a benzimidazole moiety, in their structures.

A conventional strategy to synthesize sulfoxides, is the oxidation of the corresponding sulfides [10-12]. This conversion appears to be an easy and classical approach in organic synthesis, however several details should be considered for obtaining desirable results. It has been found that selection of suitable oxidant and solvent play a key role, circumventing, the formation of known problematic side-products. Specifically, the over-oxidation of sulfides to sulfones [13-17] should be avoided, due to the separation problems. Furthermore, since the chemists are encouraged to choose their chemical routes considering the green chemistry principles, an outstanding step forward would occur which is undesirable, especially for the synthesis of prescribed drugs and commercially available compounds which should be produced in large scale [18].

Heteropolyacids with special structural features have witnessed considerable attention in organic reactions as oxidants and catalysts showing actively, in a range of milligram to kilogram scale [19]. Being strong acid as well as suitable oxidant [20-22] and along with being stable in air and humid have distanced these compounds as selective oxidant as well as superior alternative catalysts compared to the more sensitive catalytic counterparts. In addition, they have all advantages of a heterogeneous catalyst with the merits of being easily, separated, recovered and reused [23].

The conventional oxidant being used in the last stage of ongoing production of the best-selling drug in 1997, omeprazole is H_2O_2 [24]. However other oxidants such as m-chloroperbenzoic acid (m-CPBA), t-BuOOH [25] and potassium peroxymonosulfate [26] can be used in the oxidation of sulfide (5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole) to the corresponding sulfoxides, 6-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1H-benzimidazole. Utilization of these oxidants showed several back draws such as tedious work-up procedure, requirement of expensive reagents and obtaining low yields.

The selective oxidation of sulfides to sulfoxides using divergent heteropolyacids [27-29] together with diverse oxidant has been already reported.

In continuation of our efforts, manipulating heteropolyacids as catalyst and oxidant [19,22,30,31] in the present communication, we wish to report the selective oxidation of sulfide functionality to sulfoxide moiety in the last step of the synthesis of omeprazole using H_2O_2 as oxidant and different HPAs as co-oxidant and catalysts. Our methodology, involves, the use of the combination of hydrogen peroxide with various heteropolyacids as commercially available or readily accessible a green co-oxidants and catalysts. They were actually examined in the in the final step of the synthesis of the first known drug to inhibit gastric acid secretion, so-called, omeperazole.

EXPERIMENTAL SECTION

Analysis

HPLC instrument (Varian pro star with a model 330). MZ- Analytical column (4.6 mm_150 mm), orbit, 100-C8 5µm. The IR spectra were taken by KBr disks using a Shimadzu FTIR-8400. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. The ^{1}H-NMR was run on a Bruker DPX, 300 MHZ and chemical shifts are expressed as δ (ppm) with tetramethyl silane (TMS) as internal standard.

Material

All chemicals, reagents, and solvents were purchased from either Merck or Sigma-Aldrich with the highest purity and used without further purification.

Synthesis of (5-methoxy-2-[(4-nitro-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole)

A solution of 5-methoxy-2-mercaptobenzimidazole (2.78, 0.015mol) and sodium hydroxide (1.2g, 0.03 mol) in methanol (20 ml)/H_2O (2 ml) was prepared. The mixture was stirred at room temperature for 10 minutes. 2-chloromethyl-3,5-dimethyl-4-nitropyridine (3 g, 0.015 mol) was added to this mixture which was refluxed for 3 h. The progress of reaction was monitored by TLC. Upon the completion of the reaction, the solvent was evaporated under reduced pressure. After complete removal of solvent, water (25 ml) was added to obtained residue. Subsequently aqueous phase was extracted with dichloromethane (30 ml). Then organic phase was dried over Na_2SO_4 filtered off and the filtrate was removed under reduced pressure After evaporation of solvent the title compound was obtained with 81% yield; melting point: 124 -125°C. Lit.124-128 °C [32] (Fig. 2).

Synthesis of thioethers (5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole)

A solution of 5-methoxy-2-[(4-nitro-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole (3 g, 8.7 mmol) in methanol (15ml), was prepared. Then potassium carbonate (4.14 g, 0.03 mol), 30% sodium methoxide solution (9.9 ml, 0.06 mol) and anhydrous magnesium chloride (0.6 g, 6.3 mmol) were added. The resulting solution was refluxed for 2 hours (the progress of the reaction was monitored by TLC). Upon the completion of the reaction, the solution was cooled to ambient temperature. The mixture was filtered off. The filtrate was extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$. The solution was filtered and filtrate was evaporated to dryness under educed pressure to give the title compound in 75% yield; melting point 121°C. Lit. 119-120° C [32,33].

Synthesis of Omeprazole ((RS)-6-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl)-1H-benzo[d]imidazole): A Typical Procedure

To the stirred solution of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methylthio]-1*H*-benzimidazole (0.1 g, 32.9 mol) in methanol (3 ml), heteropoly acid $H_3PW_{12}O_{40}$ (0.015 g) was added. The mixture was stirred for 30 min at 20-25 °C. To this mixture 34% hydrogen peroxide (0.08 ml, 1.16 mmol) was then added drop wise over a period of 1 h and then kept at 20-25°C, for another 60 min. Then sodium bicarbonate (0.006 g, 0.071 mmol) and another 0.08 g of hydrogen peroxide 34% was added drop wise over a period of 60 min at 20-25°C, and the mixture was stirred for further 60 min. After completion of reaction (monitored by TLC) water (1 ml) and the 25 % (w/w) solution of sodium thiosulfate were added and this mixture stirred for another 60 min. After stirring at 10 °C for 2 hours, the solid was filtered under suction to yield the product (6-methoxy-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1*H*-benzimidazole) (0.104g, 99%).

For further purification, omeprazole was added to a solution of sodium hydroxide in DM water and methanol at 20-25°C. After the addition of activated carbon, the reaction was stirred for 1 h at 20-25°C. Then,

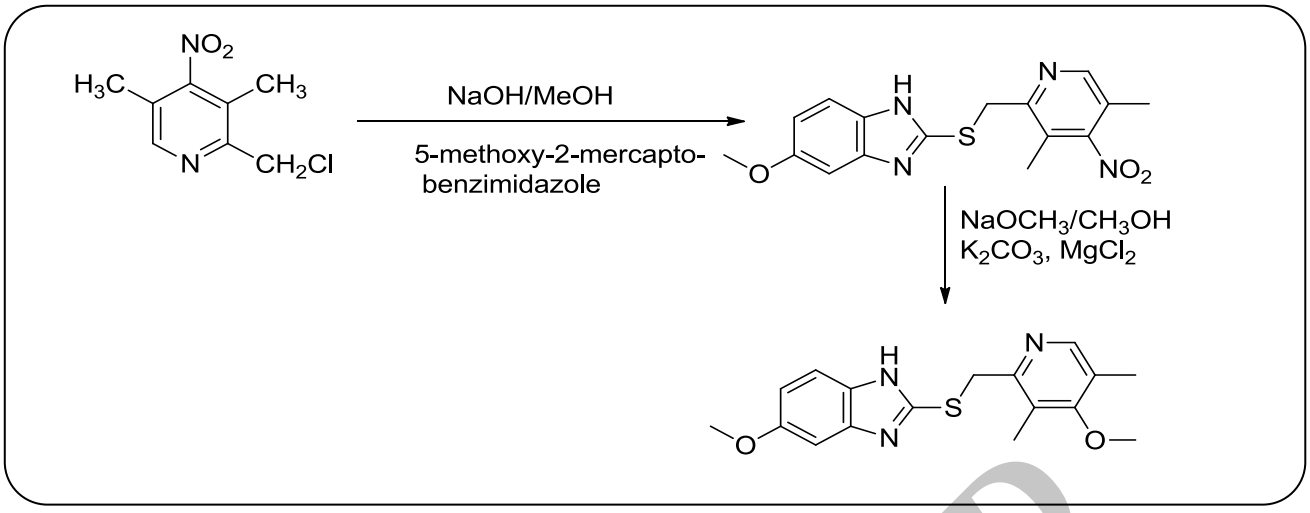


Fig. 2: Synthesis of thioether.

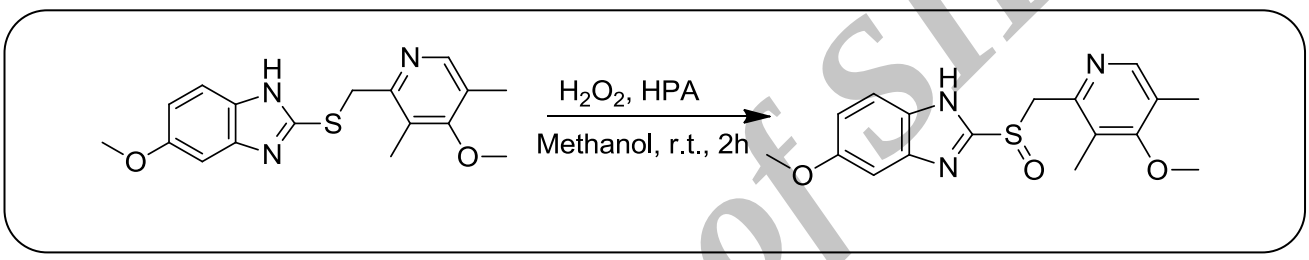


Fig. 3: Synthesis of omeprazole.

the suspension was filtered and the aqueous phase was adjusted to pH 7.5 - 8 with acetic acid 50% and stirred for further 30 min. Filtration under suction yielded the product in 88% yield. To remove all the impurities within pharmacopeia limits, the second purification process was performed by dissolving the obtained product in sodium hydroxide solution and activated carbon. This protocol reduced the yield to 80% (Fig. 3).

The optimized conditions found and secured for the synthesis of omeprazole synthesis was applied to the synthesis of lansoprazole (entry 2), pantoprazole (entry 3) and rabeprazole (entry 4) which are shown in Table 1.

Initially, the reaction of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylthio]-1H-benzimidazole (1 equiv.) in methanol at room temperature in the presence of H_2O_2 and $H_3PW_{12}O_{40}$ was examined. For comparison, three types of heteropolyacids, including Preyssler, $H_{14}[NaP_5W_{30}O_{110}]$, Keggin, $H_3[PW_{12}O_{40}]$ and $H_4[SiW_{12}O_{40}]$, and Wells-Dawson types $H_6[P_2W_{18}O_{62}]$ were tested and the results were shown in Table 2.

Selected Analytical Data

(RS)-6-methoxy -2- ((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1H-benzo[d]imidazole (omeprazole) entry 1.

IR (KBr): 3059, 3005, 2984, 2943, 1402, 1203, 1076, 1016 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ= 2.09 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.77 (dd, 2H, CH_2), 6.90-7.54 (m, 3H, ArH), 8.18 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.39, 13.32, 55.69, 59.80, 60.59, 76.73, 77.16, 77.58, 126.38, 126.92, 148.69, 149.59, 164.31 ppm.R_t: 20.258 min.

(RS)-2-([3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl] methylsulfinyl)-1H-benzo[d]imidazole (lansoprazole) entry 2.

^1H NMR (300 MHz, $CDCl_3$): δ= 2.16 (s, 3H, CH3), 4.90 (m, 2H, CH2), 5.00 (q, 2H, OCH2CF3), 7.05 (d, 2H, ArH), 7.25 (m, 1H, ArH), 7.65 (m, 2H, ArH), 8.25 (d, 1H, ArH).

Table 1: Optimized condition for the synthesis of proton pump inhibitors.

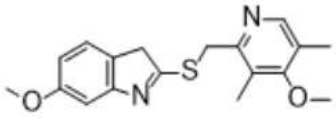
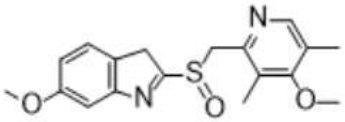
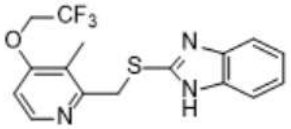
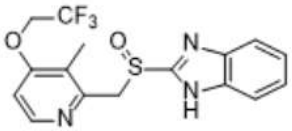
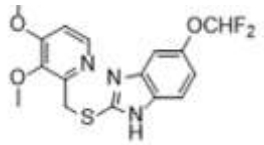
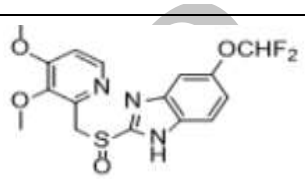
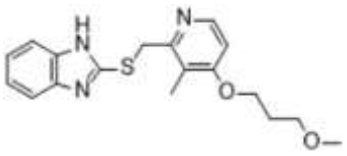
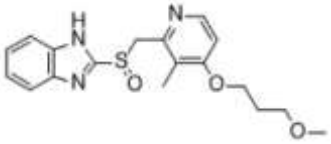
Entry	Sulfides	Reaction Condition	Products	Yields (%)
1		H_2O_2 $H_3PW_{12}O_{40}$ Methanol rt, 2h		80
2		H_2O_2 $H_3PW_{12}O_{40}$ Methanol rt, 2h		64
3		H_2O_2 $H_3PW_{12}O_{40}$ Methanol rt, 2h		30
4		H_2O_2 $H_3PW_{12}O_{40}$ Methanol rt, 2h		45

Table 1: Optimization of the reaction conditions[a].

Entry	HPA	Oxidant	Solvent	Time	Yield[b] %
1	$H_3PW_{12}O_{40}$	H_2O_2	Methanol	2h	80
2	$H_4[SiW_{12}O_{40}]$	H_2O_2	Methanol	5h	15
3	$H_{14}[NaP_5W_{24}Mo_{11}O]$	H_2O_2	Methanol	5h	46
4	$H_6[P_2W_{18}O_{62}]$	H_2O_2	Methanol	5h	10
5	$H_{14}[NaP_5W_{30}O_{110}]$	H_2O_2	Methanol	5h	21
6	$H_3PW_{12}O_{40}$	H_2O_2	Ethanol	5h	60
7	$H_3PW_{12}O_{40}$	H_2O_2	Ethanol/H_2O (1:1)	4h	84
8	$H_3PW_{12}O_{40}$	H_2O_2	Methanol /H_2O (1:1)	5h	81
9	$H_3PW_{12}O_{40}$	H_2O_2	H_2O	4h	73

(RS)-6-(Difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl]-1H-benzo[d]imidazole (pantoprazole) entry 3.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 3.79 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.33 (dd, 2H, CH_2), 6.75 (dd, 1H, ArH), 6.89-7.28 (m, 3H, ArH), 7.47 (d, 1H, ArH), 8.24 (d, 1H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ =165.0, 159.2, 147.8, 146.7, 145.4, 145.1, 120.4, 118.4, 116.3, 111.9, 108.8, 108.3, 61.8, 57.9, 56.8.

(RS)-2- ([4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methylsulfinyl)-1H-benzo[d]imidazole (rabeprazole) entry 4.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.95(m, 2H, CH_2), 2.16 (S, 3H, CH_3), 3.24 (S, 3H, OCH_3), 3.48 (m, 2H, OCH_2), 4.08(t, 2H, OCH_2), 4.41 (d, 1H, CH_2), 4.72 (d, 1H, CH_2), 6.88 (m, 2H, ArH), 6.92 (d, 1H, ArH), 7.45 (m, 2H, ArH), 8.27 (d, 1H, ArH).

RESULTS AND DISCUSSIONS

In continuation of our research interests on the application of heteropolyacids in selective oxidation [34-36], and with the aim of finding a new application of this type of efficient and green catalysts in pharmaceutical industry, after examination of different HPAs, we utilized a thermally and hydrolytically stable $H_3PW_{12}O_{40}$ as a super acid as an example. [37].

Initially, the reaction of 5-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl) methylthio)-1H-benzo[d]imidazole (1 equiv.) in the presence of H_2O_2 and $H_3PW_{12}O_{40}$ was examined in methanol at room temperature which gave the desired product in excellent yield.

For comparison, three types of heteropolyacids, including Preyssler, $H_{14}[NaP_5W_{30}O_{110}]$, Keggin, $H_3[PW_{12}O_{40}]$ and $H_4[SiW_{12}O_{40}]$, and Wells-Dawson types $H_6[P_2W_{18}O_{62}]$ were tested under the identical reaction conditions. (Fig. 3, Table 2).

The results in Table 2, indicates that the nature of the catalyst plays an important role on their catalytic activities, since the highest yield of product, achieved when the reaction was conducted in the presence of $H_3[PW_{12}O_{40}]$ as catalyst. Due to the complicated nature of the reaction, obtaining the variety of products, it seemed rather difficult to make an exact assessment of the catalyst role. However, we make some assumptions that are in agreement with the experimental data and described in literature. The results of this study showed that $H_3PW_{12}O_{40}$ is an effective catalyst for this purpose having the highest acidity compared to the other studied catalysts. Many properties of the heteropolyacids in solution depend on the concentration, the pH value of the solution, the reaction temperature, and other factors such as solvent type and catalyst structure. The relative activity of Keggin heteropolyacids primarily depends on their acid strength. Other properties, such as the oxidation potential as well as the thermal and hydrolytic stability are also important. Generally, if the reaction yield is controlled by the catalyst acid strength, $H_3PW_{12}O_{40}$ shows the highest catalytic activity in the Keggin series. In most cases, reactions catalyzed by heteropoly acids may be represented by the conventional mechanisms of Bronsted acid catalysis. Heteropolyacids are capable of protonating the substrate and activating it for subsequent chemical reactions more effectively than usual inorganic acids. It is suggested that, product yield hasbeen affected by acidic properties of the heteropolyacids by the protonation of the substrate followed by the conversion of the ionic intermediate to yield the reaction product. The role of acid in this reaction could be attributed to the polarization of the O-O bond in oxidant to produce the reactive oxygen transfer agent.

Besides, it is interesting to note that $H_3PW_{12}O_{40}$, was more active than that containing silicon $H_4SiW_{12}O_{40}$ within the Keggin primary structure. The acid strength of crystalline HPAs decreases in the series PW > SiW > PMo > SiMo which is identical to that in solutions (Table 2) [38]. Usually, relative catalytic activities of HPAs are consistent with this order both in homogeneous and in heterogeneous systems [39]. With respect to the product yield has been controlled by acidic properties of the heteropoly acids, this result is regular. As shown in Table 2, Dawson structures (entries 2,4) and Preyssler heteropolyacids (entries 3,5) were given less promising results compared to$H_3PW_{12}O_{40}$ (entry 1). These results seemed reasonable according to the higher acidic character of Keggin type heteropolyacids. With increasing in anion charge, the acidic strength will decrease.

Solvent screening to obtain higher yields was conducted in methanol and ethanol with low environmental and health hazards and in their combination with water which are more favorable according to the environmental concerns compared to

the pure alcohols. The results suggested that higher yields were obtained in methanol at room temperature within 2 h while increasing the temperature did not effect on the isolated yield. Heteropolyacids with different structures and compositions will differ in the catalytic activity in water and organic solvents. The activity series may differ in different solvents or for different substrates. The solvent molecules can place these molecular orbitals at the appropriate level. It is suggested that the solvent effects are dominated by the interactions of the polarized polyanions with the solvent, to place the molecular orbitals at the appropriate level and or to lower the activation energy. Apparently, in our reaction, this effect is higher for methanol.

CONCLUSIONS

In conclusion, we reported an efficient method for the synthesis of omeprazole in gram scales using hydrogen peroxide and in the presence of different HPAs at room temperature in last step. Interestingly, no over oxidation product was detected. Among HPAs, used $H_3PW_{12}O_{40}$ gave the best result. We believe this approach, is worthwhile to be conducted at bench scale. The satisfactory and comparable result should actually lead to pilot plant design.

AUTHORS' CONTRIBUTIONS

ME: Collaboration in design and synthesis of target compounds, identifying of the structures of target compound and manuscript preparation. MMH: Collaboration in design and manuscript preparation. MT: Collaboration in design, LF: Collaboration in design, FFB: Synthesis and characterization of catalyst and manuscript preparation. All authors read and approved the final version of this manuscript.

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