Silica polymer nanocomposites functionalized with polyphosphoric acid; a mild catalyst for efficient one-pot synthesis of dihydropyrimidinones under environmentally benign conditions

Divya Sachdev^{1,*}

^{1*}National Institute of Food Technology Entrepeneurship and Management-Kundli

Email: Dr Divya Sachdev- divya19sachdev@gmail.com

Department of Agriculture and Environment Sciences

National Institute of Food Technology Entrepeneurship and Management

Kundli --Sonepat, Haryana

* Corresponding author

Abstract

An efficient, mild catalyst was employed for the synthesis of dihydropyrimidinones (DHPMs) via condensation of aldehyde, ethylacetoacetate and urea/ thiourea in the presence of silica polymer nanocomposite functionalized with polyphosphoric acid (PPA). The present methodology offers an advantage of being mild and highly selective wherein a three component reaction proceeds proficiently because of the synergistic role of the hydrophobic polymer and the acidic sites functionalized on silica, which allows easy removal of water molecule formed during the reaction.

¹ ACCEPTED MANUSCRIPT

Keywords

Mesoporous silica, polyphosphoric acid, polymerization, wet-impregnation method,

heterogeneous catalyst, dihydropyrimidinones.

² ACCEPTED MANUSCRIPT

Introduction

Discovery of Ordered mesoporous silica materials (OMS) have gained remarkable attention because of their numerous interesting properties such as large surface area ^{[1-3],} uniform and controllable pore size and flexibility of incorporating the active functional sites. Functionalization of these materials by different organic-inorganic groups can be attained easily and is advantageous for various applications such as ion-exchange, catalysis, adsorption, chemical-optical sensors and drug delivery^[4]. Majorly grafting and co-condensation are the two indispensable routes for surface functionalization of OMS; however there is an alternate route wherein a polymeric layer can be introduced before tethering an active moiety on the silica ^[5]. Although various researchers have tried to incorporate the polymer directly on the silica surface however in most of the cases, the structural order either collapsed completely or became nonporous ^[6]. Therefore wet impregnation method was devised for better dispersal of the active groups. This penetrating network of polymer introduces the degree of hydrophobiocity/ hydrophilicity while improving the strength and flexibility of the material which may tune the material into a highly efficient catalyst^[7].

In recent years, heterogeneous catalysts have been introduced to address the sustainability issues and have emerged as an alternative approach in limiting the homogeneous acid catalysts which are often highly toxic, environmentally hazardous^[8], corrosive and produce lot of wastes. Although, recent trends of organic transformations shows an extensive use of strong acidic sites^[9-11] however in the present state of art it would be desirable and significant to perform the same organic transformations with a mild catalyst and decrease the nontoxic effects of the

³ ACCEPTED MANUSCRIPT

catalyst ^[12-13]. Therefore the current methodology deals with the development of mild and efficient catalyst which can be employed under sustainable and eco-friendly conditions for the synthesis of DHPMs.

Various biologically active compounds especially DHPMs compounds act as a precursor for antibacterial, antitumor, anticancer, anti-inflammatory drugs. So far several catalyst such as ionic liquid^[14-15], NiO₂^[16], supported iron^[17], zeolites ^[18] silica-PPA^[19], ZnO nanoparticles^[20] and various bronsted and lewis acid like dry acetic acid, boric acid ^[21]and alcoholic HCl ^[22] have been employed for carrying out biginelli reaction. However many of these methods are associated with side products resulting in difficult product isolation or needs highly acidic environment. Therefore there is a need of developing a mild catalyst which is highly selective and have no deteriorating effects on the environment, and in this context for the first time we report the use of polyphosphoric acid (PPA) impregnated over hydrophobic polymeric layer (SBA/PS/PPA) for the synthesis of DHPMs.

Experimental

Synthesis of SBA-15

All the chemicals were procured from Sigma-Aldrich and used without further purification. The synthesis of SBA-15 is carried out using Pluronic (P123) (EO20PO70EO20,MW = 5800, Aldrich) as the surfactant and tetra ethoxy ortho-silicate (TEOS) as a silica source, respectively. In a typical synthesis batch with TEOS, 3 g of P123 was dissolved in 100 g of distilled water and 5.9 g of conc. HCl (35%). After stirring for 1 h, 7.3 g of TEOS was added at 35°C while maintaining the molar ratio of P123: H₂O: HCl: TEOS ratio as 1: 5562.9: 86.29: 42.51 and

⁴ ACCEPTED MANUSCRIPT

continued stirring for 24 $h^{[23]}$. Subsequently the mixture was heated for 24 h at 100°C under static conditions in a closed polypropylene bottle. The solid product obtained after the hydrothermal treatment was filtered and dried at 80°C. The template was removed by calcinations at 550°C for 6 h.

Synthesis of PPA functionalized silica polymer nanocomposite (SBA/PS/PPA)

The synthesis methodology of polymer supported silica (SBA/PS) involves the incorporation of vinyl monomers (chlorostyrene and divinyl benzene), cross linkers and radical initiators into the SBA-15 mesopore walls via the wet-impregnation method ^[7,23-24] and equilibrated under reduced pressure to achieve a uniform distribution. The monomers adsorbed on the mesopore walls were subsequently polymerised with temperature programmed heating. Typically, for 30 wt% polymer loading of polymer on SBA-15, 0.114 g of chlorostyrene (80 mol%), 0.0358 g divinylbenzene (20 mol%), 0.0065 g of AIBN, a,a9-azoisobutyronitrile (3% relative to the total vinyl group) were dissolved into 2 ml of solvent (dichloromethane). The resulting mixture is impregnated uniformly into the SBA-15 framework. After impregnating the solution, the sample was heated to 40°C to remove the dichlorobenzene and subjected to freeze--vacuum--thaw to remove the residual solvent and air. The sample was sealed in a pyrex tube and subjected to controlled temperature programming for polymerization. The temperature scheme follows 45°C for 24 h, 60°C for 4 h, 100°C, 120°C and 150°C for 1 h [23-24]. Finally the polymer was washed with ethanol to remove excess of monomers. Samples with 10, 20 and 30 wt% polymer loading were also synthesized under similar conditions and named as SBA/PS. The role of polymer is to make the surface more hydrophobic. Different amounts (5, 10, 20, 30 wt%) of PPA were incorporated

⁵ ACCEPTED MANUSCRIPT

on SBA/PS using ethanol as a solvent. Typically for 20wt% incorporation of PPA, 600mg of PPA was dissolved in 1g of SBA/PS using 5 ml of ethanol. After the impregnation, the solution was kept for 2h at reflux temperature. The resulting mixture was cooled, filtered and washed with excess solvent to remove the residual PPA and dried at 80°C for 12h. Finally the samples were named as SBA/aPS/xPPA, where a and x represents the wt% of polymer and PPA incorporated respectively. Similarly PPA of (5, 10. 20, 30 wt%,) was impregnated over SBA-15 without surface modification and named as SBA/xPPA (imp) where "imp" stands for impregnation^[24].

Synthesis of DHPMs

A mixture of ethyl acetoacetate (1 mmol), aryl aldehyde (1 mmol), urea or thiourea (1.5 mmol), and catalyst in solvent ethanol (15 mL) were heated under reflux for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered under hot condition. The product was extracted from the unreacted reactants by washing with hexane. Finally the product was separated and the yield was calculated. The products formed were confirmed by authentic samples prepared according to the reported methods.

Characterization details

PXRD pattern was recorded on Hecus X-Ray Systems S3 Model using Cu K α radiation (k = 1.5404 A). Nitrogen adsorption--desorption isotherms were measured by using Quantachrome NOVA series. Prior to the measurements, the materials were outgassed at 80°C under vacuum for 12 h. The specific surface area was calculated by the BET method and the pore size

⁶ ACCEPTED MANUSCRIPT

distribution was calculated from the desorption isotherms by the Barrett--Joyner--Halenda (BJH) method. Solid state NMR ³¹P of samples was recorded on AV500S - 500 MHz High Resolution Multinuclear FT-NMR Spectrometer at 121.4 MHz with a 5mm CP/MAS probe and magic spinning frequency of 5 KHz and adenosine triphosphate was chosen as a standard. The IR spectra of samples (as KBr pellets) were recorded using a Schimadzu FTIR spectrophotometer in the range of 400--4000 cm⁻¹. The number of acidic sites on the catalyst surface was determined by titration method. Microstructural characterization was conducted using Tecnai G² F30 S-Twin (FEI; Super Twin lens with Cs = 1.2 mm) instrument operated at an accelerating voltage at 300 kV, having a point resolution of 0.2nm and lattice resolution of 0.14nm. Program Digital Micrograph (Gatan) was used for image processing. Scanning Electron Microscopy was used to confirm the structural morphology of PPA functionalized silica polymer nanocomposites, Energy Dispersive X-ray Analysis (EDX, Oxford INCA250 energy, UK) was also performed. The TEM samples were prepared by drying a droplet of PPA functionalized silica polymer nanocomposites on a carbon grid. EDX was also performed.

Results and Discussion

Characterization of PPA functionalized silica polymer nanocomposites (SBA/PS/PPA)

Powder X-ray diffraction pattern (PXRD) of SBA/PS/PPA samples (Figure.1) at low angles is similar to SBA-15 materials. The diffraction peaks at (100), (110), and (200) planes can be indexed to reflections comprising of two dimensional hexagonal p6mm symmetry indicating that the materials possess ordered mesoporous structure. However an increase in intensity of the SBA/PS/PPA compared to SBA-15 indicates a uniform coating of the polymer on the mesopore

⁷ ACCEPTED MANUSCRIPT

wall ^[7,25-26]. Solid State NMR, P³¹of SBA/PS/PPA (Figure.2) exhibits different peaks centered at -0.3 and -10.85 ppm indicating the distinct nature of phosphorus incorporated inside the silica framework. The peak in the spectra clearly indicates the presence of PPA over the polymeric surface^[27].

N₂ adsorption-desorption isotherms were measured at -196°C using a Quantachrome AS-1MP volumetric adsorption analyzer showed a type IV adsorption isotherm (Figure 3) indicating the mesoporous nature of the samples according to the IUPAC classification. A sharp capillary condensation step at relatively high pressure with an H1 hysteresis loop indicates the presence of large mesopores with narrow pore size distributions^[25,28]. The surface area, pore volume and pore diameter decreased with the incorporation of polymer and PPA too, indicating that the PPA has been incorporated inside the SBA framework. All the structural parameters are included in Table 1.

FT-IR spectrum of the SBA/PS/PPA samples (Figure.4) showed the vibrational frequencies similar to PPA, clearly demonstrating the uniform nature of PPA that sustained on the polymeric surface of SBA-15 mesopores. Moreover the acidity of SBA/PS/PPA was determined by titration method, wherein the number of acidic sites for SBA/PS/PPA (30%), SBA/PS/PPA (20%) and SBA/PS/PPA(10%) was found to be 38.5mmol/g,27.36 mmol/g and 13.51 mmol/g respectively. SEM images along with EDX (Figure.5) indicate uniform morphology of silica polymer nanocomposites functionalized with polyphosphoric acid. HR-TEM images of SEM/PS/PPA along with EDX (Figure.6) indicate the presence of the polymer coating and PPA incorporation

⁸ ACCEPTED MANUSCRIPT

on the mesoporous material. The detailed characterization of SBA/PS/PPA has also been mentioned in our recent publication ^[4,24-25].

Catalytic Studies

Synthesis of DHPMs were optimized on their respective model reactions (Scheme1,where R = H).Various parameters were studied to obtain the suitable conditions for the synthesis of DHPMs compounds[29]. Varied conditions were optimized for the synthesis of different compounds formed via Biginelli reaction.

A comparative study of the catalyst (Table 2) was done wherein careful analysis of the results indicates that the polymer coating has a profound role in the activity and selectivity of the product DHPMs. The catalytic activity was measured in respect to the variations in polymer and PPA content. Although there was no pronounced difference in the catalytic behavior with increase in the polymer content in SBA/PS/PPA but maximum yield was achieved with 30 wt% polymer indicating that the polymer creates the hydrophobic surface which ultimately enhances the diffusion of the products and leads to higher conversion. Varied amount of PPA from (10 to 30 wt %) impregnated over SBA/PS(30)/PPA gave 92% conversion with 98% selectivity of the product DHPMs^[23]. However only 74% conversion with 92% selectivity of DHPMs over SBA/PPA alone was obtained, this may be due to higher surface area and better dispersion of acidic active sites on SBA/PS/PPA than SBA/PPA. It is important to mention here that only 54% conversion and 70% selectivity was obtained on homogeneous PPA, indicating the need of heterogenization of PPA. The best catalyst SBA/PS/PPA (30) was selected for further studies.

⁹ ACCEPTED MANUSCRIPT

The variations in the catalyst weight showed an increasing trend with respect to the catalyst SBA/PS(30)/PPA. The conversion of DHPMs increased linearly with increase in the wt of catalyst (Figure.7) up to 100mg but with further increase in the weight, there was a drop in conversion, indicating that the active centers might have been blocked by the reactants or the product formed inhibits the access of reactants to the catalyst to undergo further reaction.

In order to chose the medium the reaction was performed in various solvents such as ethanol, methanol, acetonitrile, chloroform, dichloromethane, toluene, ethylacetate and the best results were obtained in ethanol solvent with (92%) conversion; 86% yield and 98% selectivity of the dihydropyrimidinone product; this may be due to better stabilization of enol form of ethylacetoacetate ^[30-31] in the presence of polar solvent (scheme 2). Hence ethanol was chosen for further optimization of the synthesis of dihydropyrimidinone.

Furthermore, the higher rate of conversion and selectivity of DHPMs was achieved at 60° C in 6 h (Figure. 8) which remained consistent till 80° C but further increase in temperature led to drop in conversion to ~80%. Moreover with further increase in temperature does not induce changes in the selectivity of DHPMs and a favorable temperature was chosen for the reaction.

A probable mechanism(Scheme2) for the synthesis of DHPMs showed that the reaction progresses in a very smooth manner wherein an intermediate (a, schiff base synthesized from urea and benzaldehyde) could not be detected on a Thin layer chromatography (TLC) which may be due to the unstable nature of aliphatic schiff base (B) formed in step 2. Subsequently the ethanol stabilized enol form of ethylacetoacetate (acting as a nucleophile) reacts with Schiff base (an electrophilic transition state). SBA/PS/PPA plays a vital role in controlling the rate of the

¹⁰ ACCEPTED MANUSCRIPT

reaction by constantly removing the water from the reaction (water repelling property due to hydrophobicity), thereby resulting in an enhanced acidity and regeneration of catalyst during the course of the reaction. In order to see the reusability of the catalysts, the catalyst after the completion of reaction, was filtered thoroughly first with methanol, water and then with acetone^[29].

The catalyst was dried at 120°C and subjected for fresh reaction. Recycling of the catalyst was repeated for 5 cycles without any significant loss in the activity and selectivity indicating the non-leaching behavior of the acidic contents from the catalyst during the course of the reaction^[29]. The optimized conditions were employed for the synthesis of other substituted DHPMs and it was observed that the yield of DHPMs increased in presence of electron donating groups on aldehydes (Table3).

Conclusion

A novel mild acidic functionalized catalytic system SBA/PS/PPA that allowed the precise control of the polymeric moiety along with the successful dispersion of polyphosphoric acid was successfully employed for the synthesis of DHPMs with high yield and selectivity. The plausible mechanism clearly depicts the role of the SBA/PS/PPA catalyst in an increased rate of formation of the product DHPMs. This can be attributed to the combination of hydrophobicity, textural properties and the presence of bronsted acidic sites.

¹¹ ACCEPTED MANUSCRIPT

Acknowledgements

DS thanks Department of Science and Technology for financial support via DST-Fast track project SB/FT/CS-011/2013. I would like to acknowledge the support of Dr Ajit Kumar, Vice Chancellor, NIFTEM. Thanks are due to Delhi University for conducting SEM and adsorption isotherm, IISc-Bangalore for SSNMR, of the samples.

¹² ACCEPTED MANUSCRIPT

References

[1] Feng, X.; Fryxell, G.; Wang, L.-Q.; Kim, A. Y.; Liu, J.; Kemner, K. *Science* **1997**, 276, 923.

[2] Al-Sharab, J. F.; Mikmeková, E.; Das, S.; Goswami, A.; El-Sheikh, S. M.; Ismail,A. A.; Hesari, M.; Maran, F.; Asefa, T. *Microsc. Microanal.* 2014, 20, 1900.

[3] Han, Y.; Zhu, Y.; Zhang, D. Adv. Hierach. Nanostruct. Mat. 2014, 1.

[4] Dubey, A.; Sachdev, D.; Srivasatava, N. M. Advanced Materials Letters 2013, 4,

39.

[5] Wight, A.; Davis, M. Chem. Rev. 2002, 102, 3589.

[6] Clippel, F.; Dusselier, M.; Van de Vyver, S.; Peng, L.; Jacobs, P. A.; Sels, B. F. *Green Chem.* **2013**, *15*, 1398.

[7] Choi, M.; Kleitz, F.; Liu, D.; Lee, H. Y.; Ahn, W.-S.; Ryoo, R. J. Am. Chem. Soc.2005, 127, 1924.

[8] Astruc, D.; Lu, F.; Aranzaes, J. R. Angew. Chem. Int. Ed. 2005, 44, 7852.

[9] Macquarrie, D. J.; Tavener, S. J.; Harmer, M. A. Chem. Commun. 2005, 2363.

[10] Liu, F.; Kong, W.; Wang, L.; Yi, X.; Noshadi, I.; Zheng, A.; Qi, C. *Green Chem.***2015**, *17*, 480.

¹³ ACCEPTED MANUSCRIPT

[11] Hodgson, G. K.; Impellizzeri, S.; Hallett-Tapley, G. L.; Scaiano, J. C. *RSC Adv*.2015, 5, 3728.

[12] Qian, D.; Zhang, J. Beilstein J.Org. Chem. 2011, 7, 808.

[13] Boeck, F.; Blazejak, M.; Anneser, M. R.; Hintermann, L. *Beilstein J.Org.Chem.***2012**, *8*, 1630.

[14] Sharma, N.; Sharma, U. K.; Kumar, R.; Sinha, A. K. *RSC Adv.* **2012**, *2*, 10648.

[15] Ramos, L. M.; Ponce de Leon y Tobio, A. Y.; dos Santos, M. R.; de Oliveira, H.
C.; Gomes, A. F.; Gozzo, F. C.; de Oliveira, A. L.; Neto, B. A. *The J.Org.Chem.* 2012, 77, 10184.

[16] Lal, J.; Sharma, M.; Sahu, P. K.; Agarwal, D. D. *Proc.Nat.Acad.Sci.A-Ph.Sci.***2013**, *83*, 187.

[17] Girija, D.; Naik, H. B.; Kumar, B. V.; Sudhamani, C.; Harish, K. *Arab.J.Chem.*2014.

[18] Moosavifar, M. Comp.R. Chemie. 2012, 15, 444.

[19] Zeinali-Dastmalbaf, M.; Davoodnia, A.; Heravi, M. M.; Tavakoli-Hoseini, N.;Khojastehnezhad, A.; Zamani, H. A. *ChemInform* 2011, 42.

[20] Handore, K. N.; Bhavsar, S. V.; Pande, N.; Chhattise, P. K.; Sharma, S. B.;
Dallavalle, S.; Gaikwad, V.; Mohite, K. C.; Chabukswar, V. V. *Polym-Plast.Tech.Eng.* 2014, *53*, 734.

¹⁴ ACCEPTED MANUSCRIPT

[21] Tu, S.; Fang, F.; Miao, C.; Jiang, H.; Feng, Y.; Shi, D.; Wang, X. *Tetrahedron Lett.* **2003**, *44*, 6153.

[22] Zeinali-Dastmalbaf, M.; Davoodnia, A.; Heravi, M. M.; Tavakoli-Hoseini, N.;Khojastehnezhad, A.; Zamani, H. A. *ChemInform* 2011, 42, no.

[23] Sachdev, D.; Dubey, A. Catal. Lett. 2011, 141, 1548.

[24] Sachdev, D.; Wilson, G. R.; Sharma, A. New J. Chem. 2015.

[25] Sachdev, D.; Dubey, A. Catal. Commun. 2013, 39, 39.

[26] Che, S.; Liu, Z.; Ohsuna, T.; Sakamoto, K.; Terasaki, O.; Tatsumi, T. *Nature***2004**, *429*, 281.

[27] Errede, L.; Newmark, R. A.; Hill, J. R. *Macromol.* **1986**, *19*, 651.

- [28] Han, Y.-J.; Kim, J. M.; Stucky, G. D. Chem. Mater. 2000, 12, 2068.
- [29] Naik, M. A.; Sachdev, D.; Dubey, A. Catal. Commun. 2010, 11, 1148.
- [30] Markov, P.; Shishkova, L.; Zdravkova, Z. Tetrahedron Lett. 1972, 13, 4017.
- [31] Powling, J.; Bernstein, H. J. Am. Chem. Soc. 1951, 73, 4353.

¹⁵ ACCEPTED MANUSCRIPT

Table1. Structural Parameters of functionalized mesoporous silica nanocomposites.

Materials	Surface area	Pore Volume	Pore Size
	(m ² /g)	(cm ³ /g)	(nm, #9)
SBA-15	678	1.2	7.4
SBA/PPA(30)	391	0.43	4.7
SBA/PS(30)	312	0.59	4.0
SBA/PS(30)/PPA(30)	221	0.46	3.8
SBA/PS(30)/PPA(10)	114	0.20	2.8

¹⁶ ACCEPTED MANUSCRIPT

Table 2 Effect of varied catalyst on the conversion of DHPMs

Catalyst*	DHPMs		
	Conversion ^a (%)	^b Selectivity(%)	
PPA	54 (48%)	70	
SBA/PPA(30)	74 (70%)	92	
SBA/PPA(20)	70 (67%)	92	
SBA/PPA (10)	66 (65%)	92	
SBA/PS/PPA (30)	92 (86%)	98	
SBA/PS/PPA(20)	82 (77%)	96	
SBA/PS/PPA(10)	76 (70%)	98	

^aethyl acetoacetate -1 mmol, benzaldehyde -1 mmol, urea-1.5 mmol, catalyst-100mg solventethanol Temperature- 60°C. %Conversion as indicated from the authentic samples.* () parenthesis indicates the percentage loading

^bselectivity of the product only () parenthesis in the (%) conversion column indicates (%) isolated yield.

¹⁷ ACCEPTED MANUSCRIPT

Table 3 Effect of substituent on the yield of DHPMs

Substituted	X	^a %yield
aldehydes		
СНО	0	86
CHO	0	92
CHO	0	75
CHO NO ₂	0	65

¹⁸ ACCEPTED MANUSCRIPT

СНООН	S	80
CHO	S	50

^aConditions as indicated in Table 2

¹⁹ ACCEPTED MANUSCRIPT



Fig 1: PXRD pattern of mesoporous silica and functionalized mesoporous silica (a) SBA-15 (b) SBA/PS/PPA

²⁰ ACCEPTED MANUSCRIPT



Fig2: ³¹P spectra of mesoporous silica polymer nanocomposites functionalized with PPA (SBA/PS/PPA).

²¹ ACCEPTED MANUSCRIPT



Fig 3: Nitrogen adsorption-desorption isotherms of SBA/PS and SBA/PS/PPA.

²² ACCEPTED MANUSCRIPT



Fig.4: FT-IR spectra of polyphosphoric acid and functionalized mesoporous silica (a) PPA (b) SBA/PS/PPA.

²³ ACCEPTED MANUSCRIPT



Fig 5 SEM showing uniform morphology of Polyphosphoric acid functionalized silica polymer nanocomposites (SBA/PS/PPA) with EDX

²⁴ ACCEPTED MANUSCRIPT



Polymeric layer

Fig.6 TEM image of polyphosphoric acid functionalized silica polymer nanocomposite (SBA/PS/PPA) with EDX.

²⁵ ACCEPTED MANUSCRIPT



Fig.7 Effect of catalyst weight on the conversion of DHPMs. (Conditions as given in Table 2)

²⁶ ACCEPTED MANUSCRIPT



Fig.8 Effect of [19]reaction temperature on the conversion of DHPMs. (Conditions as given in Table 2)

²⁷ ACCEPTED MANUSCRIPT



Scheme 1. Biginelli Reaction

²⁸ ACCEPTED MANUSCRIPT



Scheme2 Plausible reaction mechanism for the synthesis of DHPMs (Conditions as given in Table 2)

²⁹ ACCEPTED MANUSCRIPT