The Eurasia Proceedings of Science, Technology,
Engineering & Mathematics (EPSTEM)
ISSN: 2602-3199

The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 2022

Volume 20, Pages 77-83

ICBAST 2022: International Conference on Basic Sciences and Technology

Study of Copper Based Heteropolysalts as Catalysts in the Efficiency of Synthesis of 5-Ethoxycarbonyl-4-Phenyl-6-Methyl-3,4-Dihydropyridin-2(1H)-One

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Abstract: The efficiency of various heteropoly compounds as well-known solid acids is investigated for the three-component condensation reaction of an aldehyde, b-ketoester and urea to afford the dihydropyrimidinones (DHPM). Compared to the classical Biginelli reaction conditions, this new method consistently has the advantage of excellent yields and short reaction time. The objective of this study is the use of Keggin heteropolyacid (HPAs) noted $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$ and $(NH_4)_{3-2x}Cu_xPMo_{12}O_{40}$ in Biginelli cyclocondensation reaction using: benzaldehyde, acetoacetate and urea with ratio (2:2:3) [3]. After synthesis, the prepared catalysts were characterized by: BET surface area, X- ray diffraction, Infra-red spectroscopy and DHPM by FT-IR, ^1H and ^{13}C NMR. The reaction results show that $H_3PMo_{12}O_{40}$ is the best catalyst in our reaction conditions with an excellent yield around 94% which can be explained by significantly higher Brønsted acidity compared to that of traditional mineral catalysts. In the other hand, other excellent yields have been obtained in the presence of $Cu_{0.25}H_{2,50}PMo_{12}O_{40}$ and $(NH_4)_{3,00}Cu_{0,00}PMo_{12}O_{40}$ 89% and 59% respectively. Please use 14-point bold for your article title, with an initial capital letter for any proper nouns.

Keywords: Heteropolysalts, Copper, Catalysis, Biginelli reaction, Green chemistry.

Introduction

Green chemistry expresses a large area of research developing from scientific discoveries about pollution awareness. It uses a set of principles that reduces or eliminates using or generating of hazardous substances (Anastas,2001). Multicomponent reaction (MCR) is a process in which three or more accessible components are combined together in one-pot to produce a final product which shows the features of all the input reactants and therefore, offers the greatest possibilities for molecular diversity in one step with minimum synthetic time and effort (Domling & Ugi,2000; Ugi,2001). Among MCR process, Biginelli reaction is one of the most studied one. It is a one-pot cyclocondensation of an aldehyde, β-ketoester and urea to obtain dihydropyrimidinone heterocyclic systems (Biginelli, 1893).

Previous reported protocols normally required prolonged reaction times and high temperature with moderate yields such as H_2SO_4 (Folkers et al.,1933), $BF_3Et_2O/CuCl$ (Hu et al.,1998), $InCl_3$ (Ranu et al.,2000), $BiCl_3$

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(Ramalinga et al.,2000), TMSCl (Zhu et al.,2005), $LiClO_4$ (Yadav et al.,2001), InBr3 (Fu et al.,2002), phenylpyruvic (Abelman et al.,2003), TMSI (Sabitha et al.,2003), HCl (Lu et al.,2000) and $Cu(NH_2SO_3)_2$ (Liu & Wang, 2009). Therefore, there has been considerable interest to explore mild, rapid, and higher yielding protocol. Many improved protocols have been designed and developed for the synthesis of this kind of entities (Lakshi et al., 2015). On the other hand, the use of catalysis is one of the pillar of Green chemistry (Anastas et al.,2001) that affects energy use and reaction time, increases yield, reduces use of solvents, and lower production of by-products and waste (Scott &Hutchison,2000; Sheldon, 2002).

Thus, heteropolyacids are known as a good catalyst in synthesis of heterocycles. Indeed, heteropolyacids are known to be very acidic and so to display interesting properties in acid catalysis (Kozhenikov, 1998; Mizuno & Misono, 1998). Their significantly higher Brønsted acidity, compared with the acidity of traditional mineral acid catalysts, is of great importance for catalysis (Okuhara et al.,1996, Bonardet et al.,1996). They are characterized by the presence of the Keggin anion of composition MX12O40z- where M is often phosphorous or silicon and X is generally molybdenum or tungsten (Keggin,1993,1994). The acid sites in HPA are more uniform and easier to control than those in other solid acid catalysts.

In the present work we describe successful application, solid catalysis $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$ and $(NH_4)_{3-2x}Cu_xPMo_{12}O_{40}$ as an alternative environmentally benign, recyclable and efficient catalyst for Biginelli reaction under solvent free conditions (Figure 1).

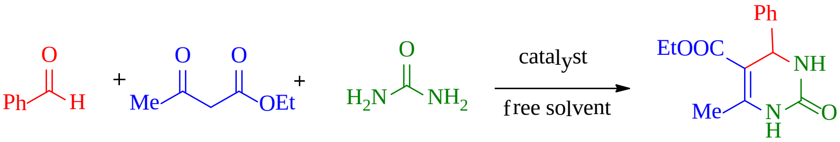

Figure 1.Biginelli reaction under solvent free conditions

Method

Catalysts preparation

$H_{3-2x}Cu_xPMo_{12}O_{40}$ and $(NH_4)_{3-2x}Cu_xPMo_{12}O_{40}$ was synthesized by a cation exchange according to the literrature (Mazari et al.,2013).

Catalysts Characterization

Catalysts morphology was studied by scanning (SEM) using Philips XL30 ESEM and CM10 microscopes. Thermal analysis (TG) were carried out using a Perkin Elmer Stimiltanous Thermal analyzer STA 6000.
Powder XRD patterns of the catalysts were recorded on a SIEMENS D5000 powder diffractometer using Cu-Kα radiation. Crystalline phases were identified through Highscore plus software database.

Catalytic Test

Catalytic activity of $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$ and $(NH_4)_{3-2x}Cu_xPMo_{12}O_{40}$were examined in the Biginelli reaction under mild and solvent free conditions. In a 25 mL single-neck round bottom flask, a mixture of benzaldehyde (1) (2mmol), ethyl acetoacetate (2) (2mmol), urea (3) (3mmol) and 0.2 g of catalyst was kept under regular stirring at 100°C for 1hour (Figure 1). Completion of the reaction was monitored by Thin Layer Chromatography (TLC). Reaction product was washed with boiled ethanol then filtered to remove the catalyst. DHPM product was purified and recrystallized in hot ethanol, then placed in ice bath to afford pure product.

Identification of DHPM is obtained via its melting temperature, Infrared spectroscopic analysis (IR) and 1H and 13C Nuclear Magnetic Resonance (NMR). IR spectra were recorded on Fourrier Transform Spectrometer Shimadzu FTIR-type 8400 and the NMR ones on a Bruker FT-NMR AVIIIHD500. Chemical shifts were expressed in parts per million (ppm) relative to TMS (δ = 0 ppm) and coupling constant J in Hertz (Hz). NMR multiplicities are reported using the following abbreviations: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Results and Discussion

Catalyst Characterizations

IR spectra (Figure 2) of $H_{3-2x}Cu_xPMo_{12}$ salts have the characteristic vibration bands of the Keggin anion in the 1100-300 cm-1 spectral range (Keggin,1993), corresponding to nas(P–Oa), nas(Mo=Od), nas(Mo–Ob–Mo) and nas(Mo–Oc–Mo) located at 1060-1064, 960-965; 866-880 cm^{-1}, respectively. In addition, another vibration band associated to ammonium ions was observed around 1500 cm^{-1}.

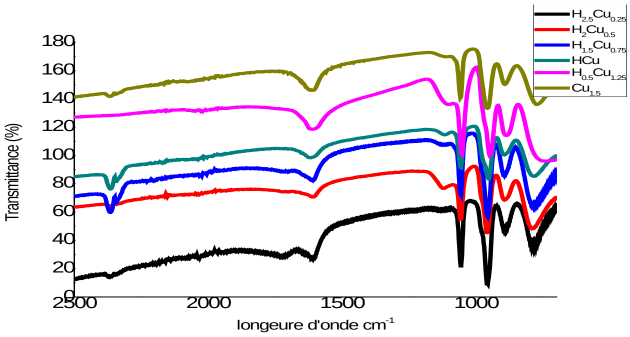

Figure 2. IR spectra of $H_{3-2x}Cu_xPMo_{12}O_{40}$

The X-ray diffractograms of Cu_xPMo_{12} are similar to that of the parent acid $H_3PMo_{12}O_{40}$ (Figure 2),that crystallized in the triclinic system. These results agree with those of IR spectroscopy showing that the ions occupy the counter-ion position in the polyoxometallate.

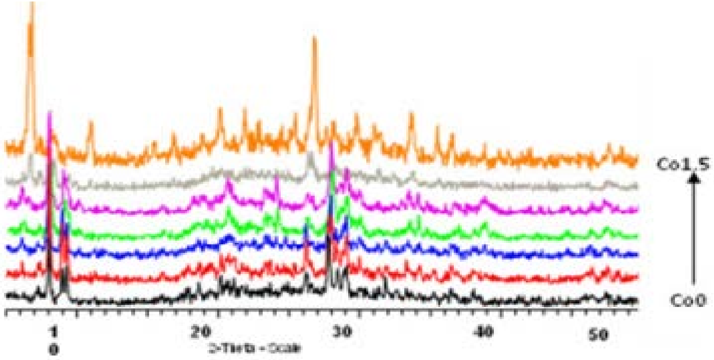

Figure 3. XRD patterns of Co_xPMo_{12} solids

Furthermore, comparison of images from electron microscopy measurement, H_3PMo_{12} and $Cu_{1.5}PMo_{12}$ show different morphologies as a consequence of the substitution of protons by the Cu^{2+} ions (Figure 4).

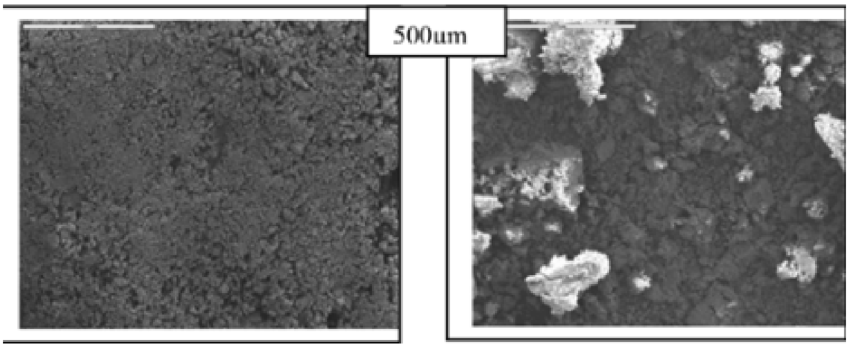

Figure 4. SEM images of H_3PMo_{12} and $Co_{1.5}PMo_{12}$.

Biginelli Reaction

Keggin heteropolyacid (HPAs) noted $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$ and $(NH_4)_{3-2x}Cu_xPMo_{12}O_{40}$ were used as catalysts in Biginelli cyclocondensation reaction using: benzaldehyde, acetoacetate and urea with ratio (2:2:3) (Khiar et al., 2017).

The preliminary catalytic tests performed with $H_3PMo_{12}O_{40}$ (entry 1, table 1) showed that the Biginelli reaction takes place in the homogenous phase and high DHPM yields was obtained. İndeed, the reaction results show that $H_3PMo_{12}O_{40}$ is the best catalyst in our reaction conditions with an excellent yield around 97% which can be explained by significantly higher Brønsted acidity compared to that of traditional mineral catalysts (Sanjeev& Gavisiddapa,2007). In the other hand other excellent yields have been obtained in the presence of $Cu_{0.25}H_{2,50}PMo_{12}O_{40}$ and $(NH_4)_{3,00}Cu_{0,00}PMo_{12}O_{40}$ 89% (entry 2, table 1) and 58% (entry 5, table 2) respectively. However, the high activity obtained with can be explained by the presence of acid protons. İndeed, there was a correlation between the presence of protons and the yield of DHPM.

Table 1. 3,4-Dihydropyrimidin(1H)-one (DHPM) yield via Biginellia reaction in presence of $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$.

Entry	HPA	Yield (%)	T fusion (°C)
1	$H_3PMo_{12}O_{40}$	97.00	204
2	$Cu_{0.25}H_{2,5}PMo_{12}O_{40}$	89.00	202
3	$Cu_{0.5}H_2PMo_{12}O_{40}$	81.04	205
4	$Cu_{0.75}H_{1,5}PMo_{12}O_{40}$	76.1	205
5	$Cu_1HPMo_{12}O_{40}$	68.41	204
6	$Cu_{1.25}H_{0,5}PMo_{12}O_{40}$	60.73	206
7	$Cu_{1.5}PMo_{12}O_{40}$	53.05	203

a. Reaction conditions: Benzaldehyde (2 mmol), ethylacetoacetate (2 mmol) and urea (3 mmol) at 100°C for 1 h under solvent free conditions.

b. Isolated yields after recrystallization.

Table 2. 3,4-Dihydropyrimidin(1H)-one (DHPM) yield via Biginellia reaction in presence of $H_3PMo_{12}O_{40}$ and its ammonium salts $H_{3-2x}Cu_xPMo_{12}O_{40}$.

Entry	HPA	Yield (%)	T fusion (°C)
1	$(NH_4)_{0.5}Cu_{1.25}PMo_{12}O_{40}$	42.25	206
2	$(NH_4)_1CuPMo_{12}O_{40}$	44.17	204
3	$(NH_4)_{1.5}Cu_{0,75}PMo_{12}O_{40}$	49.94	205
4	$(NH_4)_2Cu_{0,5}PMo_{12}O_{40}$	52.30	204
5	$(NH_4)_{2.5}Cu_{0.25}PMo_{12}O_{40}$	58	203
6	$(NH_4)_3PMo_{12}O_{40}$	59.31	205

The reusability of $Cu_{0.25}H_{2,50}PMo_{12}O_{40}$ was investigated under optimal (and typical) operating conditions (0.2 g catalyst, reaction temperature 100 °C, reaction time 1 h). Used $Cu_{0.25}H_{2.5}PMo_{12}O_{40}$ sample was recovered by filtration, washed with water, dried overnight at 100°C and reused in the next runs without further purification. DHPM yield is given in Figure 4 for each run. After three reaction cycles, DHPM yield decreased with 10% between the first un second run and 48% between the second and the third run in the presence of $Cu_{0.25}H_{2.5}PMo_{12}O_{40}$. This study showed that the $Cu_{0.25}H_{2.5}PMo_{12}O_{40}$ system is active for the Biginelli reaction. However, the high activity obtained with can be explained by the presence of acid protons. İndeed, there was a correlation between the presence of protons and the yield of DHPM.

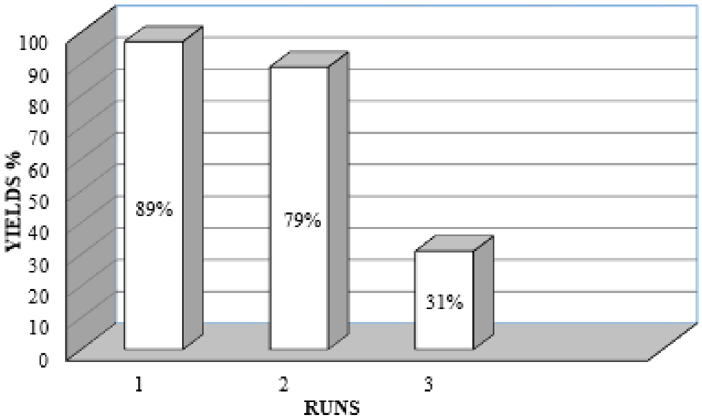

Figure 4. Recyclability of $Cu_{0.25}H_{2.5}PMo_{12}O_{40}$ catalyst for the synthesis of DHPM

Physical data for 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyridin-2(1H)-one (DHPM).

Mp 201– 205°C. IR (KBr): νmax = 3245 cm − 1, 3100 cm − 1, 2960 cm − 1, 1720 cm − 1, 1630 cm − 1, 1540 cm − 1, 1490 cm − 1. 1 H NMR (Figure 5) (500 MHz, DMSO-d6): δ = 9.19 (s, 1H, NH), 7.73 (s, 1H, NH), 7.34 (s, 5H, C6 H5), 5.15 (s, 1H, J = 2.87 Hz, CH), 4.01 (q, J = 6.5 Hz, 2H, OCH2 CH3), 2.51 (s, 3H, CH3), 1.11 (t, J = 6.5 Hz, 3H, OCH2 CH3) ppm. 13C NMR (Figure 6) (125 MHz, DMSO-d6): δ = 165.7 (COOEt), 152.5 (C2), 148.8 (C6), [145.3, 128.8, 127.7, 126.7] C arom, 99.7 (C5), 59.6 (OCH2 CH3), 54.4 (C4), 18.2 (CH3), 14.5 (OCH2 CH3) ppm.

Conclusion

In conclusion, using HPAs in Biginelli process can offer high yields of DHPMs, mild reaction conditions, simple experimental procedure and product isolation and recyclability of materials without considerable loss in its activity. Then, protocol should be complementary to the existing methods. It leads not only to economical automation but also to reduce hazardous pollution to achieve environmentally friendly processes with can enter in the field of green chemistry.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Acknowledgements or Notes

* This article was presented as an oral presentation at the International Conference on Basic Sciences and Technology (www.icbast.net) held in Antalya/Turkey on November 16-19, 2022.

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To cite this article:

Khiar, C., Mazari, T., Roch Marchal, C., & Rabia, C. (2022). Study of copper based heteropolysalts as catalysts in the effiency of synthesis of 5- ethoxycarbonyl-4-phenyl-6-methyl-3,4, -dihydropyridin-2(1H)- one. *The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM), 20,* 77-83.