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GREEN AND EFFICIENT SYNTHESIS OF DIHYDROPYRIMIDINONE ANALOGUES *VIA* HPA-CLAY CATALYZED BIGINELLI REACTION

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Abstract. This study introduces an environmentally sustainable approach for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), *via* the Biginelli reaction. A heterogeneous catalyst, Heteropolyacid-Clay (HPA-Clay), is developed by immobilizing $H_5PV_2W_{10}O_{40}$ on Montmorillonite KSF clay. The catalyst exhibits enhanced stability and catalytic efficiency, confirmed through X-ray powder diffraction and scanning electron microscopy. Utilizing a one-pot multi-component strategy under solvent-free conditions, various aldehydes, urea or thiourea, and ethylacetoacetate generate DHPMs with excellent yields and reduced reaction times. Catalysed by 2 mol% HPA-Clay, the process aligns with green chemistry principles, emphasizing cost-efficiency, environmental sustainability, and recyclability. The catalyst demonstrates consistent activity over multiple cycles, highlighting its potential for advancing Biginelli reactions.

Keywords: multicomponent reaction, heteropolyacid, greenchemistry approach, recyclable catalyst.

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Introduction

In the realm of synthetic chemistry, continuous efforts are directed towards streamlining and optimizing molecular synthesis processes [1]. Multicomponent reactions (MCRs) have emerged as invaluable tools in this pursuit, offering a means to efficiently amalgamate multiple molecular components into a singular product [2]. Particularly noteworthy are MCRs that facilitate the formation of carbon-carbon bonds and nitrogen-containing functionalities, as they enable combinatorial synthesis without necessitating intermediate compound isolation [3]. Multicomponent reactions occupy a pivotal position within the domains of organic and medicinal chemistry [4,5]. Their significance lies in their ability to harmonize with eco-conscious principles, curtailing the intricacy of synthetic sequences, minimizing energy consumption, and mitigating waste production [6]. Of paramount importance in drug discovery are nitrogen-containing heterocycles due to their indispensable roles within medicinal chemistry. The imperative for novel synthetic pathways to access fused heterocyclic structures is underscored by their versatile utility in diverse therapeutic applications [7]. Pyrimidine derivatives, especially Biginelli compounds (dihydropyrimidin-2(1*H*)-ones), are of particular interest because these compounds exhibit various biological activities [8], which include antibacterial [9] antifungal [10] anticancer [11], anti-inflammatory, anthelmintic [12], antihypertensive [13] anti-HIV [14], and anti-malarial properties [15] *etc*. Therefore, the synthesis of various 3,4-dihydropyrimidin-2(1*H*)-ones is of paramount importance, and the Biginelli reaction offers a straightforward route to access these dihydropyrimidones. Significant endeavours have been undertaken to enhance yields and fine-tune reaction parameters, driven by the significance of the resultant products. Many researchers are working to prepare their libraries by implementing various modifications using various synthetic techniques to speed up the reaction time and boost yield while utilizing

a variety of different catalysts. Some of the catalysts that have been recently reported include $Cu(OTf)_2$/MW [16], ammonium metavanadate (NH_4VO_3) [17], cerium(IV) ammonium nitrate [18], $Sm(ClO_4)_3$ [19], $La(OTf)_3$ [20], triethylammonium hydrogen sulphate [21], $BiCl_3$ [22] and $Mn(OAc)_3 \cdot 2H_2O$ [23], HCl/EtOH [24], $Yb(PFO)_3$ [25], acidic ionic liquids [26] and other catalysts.

Despite their potential benefits, these chemical processes are challenged by the use of costly or hazardous reagents and are burdened by unfavourable reaction conditions. These conditions encompass the requisition of potent acids, protracted reaction durations, elevated temperatures, stoichiometric catalyst quantities, ecological ramifications, intricate work-up procedures, exacting reaction prerequisites, and a constrained economic feasibility culminating in paltry yields. Consequently, the quest for a novel and efficacious catalyst, one capable of engendering 3,4-dihydropyrimidin-2(1*H*)-ones under conditions that are neutral, reasonable, and pragmatic, while concurrently exhibiting elevated catalytic prowess, abbreviated reaction intervals, recyclability, and straightforward work-up methodologies, assumes paramount significance in surmounting these impediments. Remarkably, heteropolyacids (HPAs) have emerged as catalysts with the potential to facilitate the Biginelli reaction, offering a source for the synthesis of numerous novel compounds. This class of catalysts finds widespread application in the production of high-quality organic compounds, pharmaceuticals, cosmetics, and agrochemicals, owing to their catalytic efficiency and versatility. HPAs have been effectively utilized in various organic transformations, including the synthesis of acylals, tetrahydropyranilation of phenols, thioacetalization, and transacetalization reactions, as they exhibit higher reactivity compared to traditional inorganic and organic acids in solution. Furthermore, they serve as industrial catalysts for numerous liquid-phase processes, encompassing esterification, alkylation, and alcohol dehydration [27,28]. Heteropolyacids (HPAs) are heterogenized by immobilizing them on solid supports to enhance stability, facilitate catalyst recovery, and tailor their catalytic properties. This approach promotes recyclability, minimizes waste, and improves reactivity, aligning with green chemistry principles.

Continuing the exploration of the Biginelli reaction [29] and supported heteropolyacids [30], the authors have developed a precisely formulated HPA-Clay composite as a heterogeneous catalyst. This catalyst assumes a crucial role in enabling a one-pot multicomponent synthesis approach, facilitating the generation of a diverse range of novel dihydropyrimidinone (DHPM) derivatives. The employed methodology is distinguished by its simplicity and is marked by high effectiveness, cost-efficiency, environmental sustainability, and recyclability, in perfect alignment with the principles of green chemistry. The groundbreaking aspect of this research lies in the utilization of the HPA-Clay catalyst as a reusable heterogeneous catalytic system. This represents a significant advancement in the domain of Biginelli reactions, holding substantial promise for further progress in this field. The study showcases a pioneering approach to complex chemical syntheses, emphasizing sustainability and suggesting potential avenues for further developments.

Experimental

Generalities

Chemicals used for this HPA are: Na_2HPO_4, V_2O_5, Na_2CO_3, $Na_2WO_4 \cdot 2H_2O$, 50% sulphuric acid and diethyl ether. All reagents for chemical synthesis were obtained from Sigma Aldrich. All the chemical reactions were monitored by TLC on 0.25 mm silica gel 60 F254 plates (E. Merck) using 2% ceric ammonium sulphate solution for detection of the spots.

^1H and *^{13}C NMR spectra* (with chemical shifts expressed in δ and coupling constants in Hertz) were recorded on Bruker DPX 200, 400 and DPX 500 instruments using $CDCl_3$ or CD_3OD as the solvents with TMS as internal standard. *High resolution mass spectra* (HRMS) were recorded on Agilent Technologies 6540 instrument. *IR spectra* recorded on an FT-IR Bruker (270-30) spectrophotometer (supplementary data).

The crystallinity of the sample (HCNC) was studied by recording X-ray powder diffraction patterns on a Rigaku Miniflex diffractometer, using Ni-filtered CuKα (0.15418 nm) radiation source.

The BET surface area of the catalyst was determined using the instrument SMART SORB 92/93 under liquid Nitrogen.

Scanning electron microscopy (SEM) of the catalyst was carried out using a JEOL JEM-100CXII electron microscope with an ASID accelerating voltage of 40 kV.

Microwave irradiation of the reaction mixture for comparison was done by using a conventional kitchen microwave oven Electrolux EM30EC90SS.

An ultrasonic bath (Soner 206H, Rocker Scientific Co., Ltd) with an operating frequency of 53 kHz and ultrasonic power of 180W was utilized for comparing the methods of preparation Biginelli reactions.

Preparation of $H_5PV_2W_{10}O_{40}\cdot 10H_2O$ (HPA)

Disodium hydrogen phosphate (Na_2HPO_4, 1.775 g, 25 mmol) was dissolved in 50 mL of water and mixed with vanadium pentoxide (V_2O_5, 6.1 g, 100 mmol) dissolved in 20 mL of 1M Na_2CO_3 and the solution so formed was boiled for 30 min (green colour) and then cooled to room temperature. To this solution, sodium tungstate dihydrate ($Na_2WO_4\cdot 2H_2O$, 41.25 g, 250 mmol) dissolved in 20 mL of water (black colour) was added. This solution was kept at 90°C for 30 min (bluish green colour), cooled and to it was added 50% sulphuric acid (50 mL) drop wise, a wine-red solution (pH= 2) was obtained. Extraction of the solution with diethyl ether (100 mL) afforded the orange-red $H_5PV_2W_{10}O_{40}\cdot 10H_2O$ product.

Preparation of HPA-Clay catalyst

The HPA so formed was dissolved in 150 mL water and added dropwise to 500 mL aqueous suspension of 10 g Montomorillonite KSF. This mixture was stirred for 5 h and the water was evaporated over water bath to get a dry powder, which was kept overnight in hot air oven at 110°C. A portion of this solid was then calcined at 425°C for 3 h to get a heteropoly acid clay nano composite and was named as HCNC. The catalyst was characterized using X-ray powder diffraction (XRD) and scanning electron microscopy.

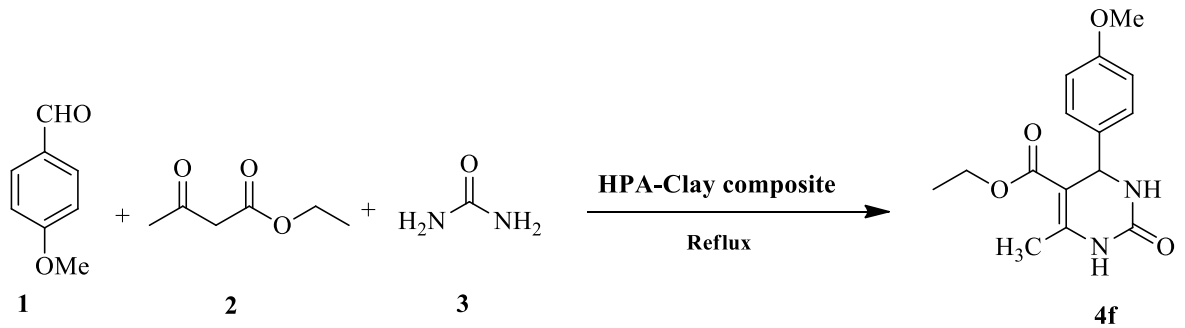
General procedure for the synthesis of DHPM derivatives

In a systematic procedure, a mixture comprising 10 mmol of aldehyde, 15 mmol of 1,3-dicarbonyl compound, 15 mmol of urea or thiourea, and 2 mol% HPA-Clay was subjected to reflux conditions without the use of a solvent, with reaction progress monitored *via* TLC over a 1 h duration. Following the completion of the reaction, the mixture was allowed to cool to room temperature. To this reaction mixture 5 mL of ethanol was added to dissolve the organic constituents and catalyst was removed *via* filtration. Subsequently, the filtrate was dried and introduced into ice-water (30 mL). After undergoing washing and other requisite workup steps, the crude product was dried and dissolved in a small quantity of ethyl acetate to form a saturated solution. To this solution, an excess of hexane was added until precipitation occurred. This turbid solution was left undisturbed until complete settling of the precipitate. The precipitate was then filtered, and if necessary, it was subjected to re-crystallization from ethanol to obtain the pure products. Furthermore, the used solid catalyst was washed with ethanol the dried at 105°C so that it can be reused for a subsequent run of the Biginelli reaction. After partial success of the reaction, search for different conditions to optimize the yield and reaction time was conducted.

Results and discussion

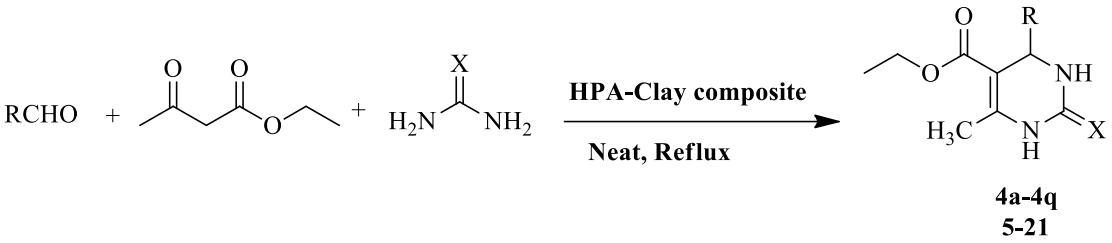
The abovementioned facts served as inspiration for the development of a unique green methodology that involves the synthesis of DHPM analogues *via* the Biginelli reaction. The process uses a multicomponent reaction that is catalysed by a reusable, heterogeneous HPA-Clay catalyst made up of $H_5PV_2W_{10}O_{40}$ supported on Clay. The method uses a three-component, one-pot Biginelli-type reaction to convert various aldehydes, urea, and ethylacetoacetate into the corresponding pyrimidinones while the presence of a catalytic amount of HPA-Clay. The model reaction produced the desired DHPM in a good yield (Scheme1). Reaction presented in Scheme 1 was selected as a model reaction for reaction optimization and catalyst comparison.

The best results were obtained under solvent-free circumstances (neat), utilizing HPA-Clay catalyst equivalent to 2 mol% of HPA, 1.5 equivalents of urea/thiourea, ethyl acetoacetate, and 1 equivalent of aldehyde under reflux conditions for 1 h, giving rise to the required product in good yields *i.e*. 96%. This DHPM was identified by spectral analysis in light of the available literature [16-26,29].



1 **2** **3** **4f**

Scheme 1. The model reaction for the preparation of DHPMs.



Scheme 2. General reaction for the preparation of DHPM analogues.

Table 1

HPA-Clay catalysed synthesis of DHPM in different solvents and under solvent free conditions.

S.No.	*Solvent*	*Time (h)*	*Amount of catalyst (mol %)*	*Yield (%)*	*Temperature (°C)*
1.	1,4-dioxane	6 h	10	65	Reflux
2.	Acetonitrile	5 h	10	77	Reflux
3.	Toluene	7 h	10	71	Reflux
4.	Ethanol	2 h	10	87	Reflux
5.	Solvent free	1 h	10	92	Reflux
6.	Solvent free	1 h	2	96	Reflux
7.	Solvent free	5 minutes	2	70	Microwave at 500°C
8.	Solvent free	30 minutes	2	74	Sonication at 35°C
9.	Ethanol	18 h	2	40	RT (25)
10.	Solvent free	14 h	2	52	RT

para-methoxy benzaldehyde:urea:ethylacetoacetate in the ratio of 1:1.5:1.5.

Encouraged by the initial success in the formation of the compound **4f**, a thorough optimization study was carried out with the aim of reducing the reaction time and space, improving the yields, minimizing the temperature range, and exploring study towards the use of solvents and catalysts for better yields because of the biological and synthetic importance of the DHPMs as described earlier. The use of solvent free conditions had profound effect in terms of time saving as the reaction was complete in 1 h and the yields were excellent (Table 1).

The reaction was also tuned in terms of the amount of catalyst (HPA-Clay) and the optimum amount of the catalyst that produced the best yields in the shortest amount of time was 2 mol%. Additionally, the reaction was observed in a microwave under various temperature conditions, and sonication techniques were also tested. Compound **4f** was produced in a low yield by a microwave-assisted reaction with HPA-Clay as the catalyst. Under ultrasonication at 35°C with a 30 min reaction time were poor. In order to facilitate stirring, the reaction was also carried out at room temperature; however, this prolonged the reaction's completion time and resulted in rather low yields. From the above results, it may be concluded that the temperature affects not only the yield of the products but also the reaction time.

Table 2

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

Compound	*R*	*X*	*Yield (%)*
4a	C_6H_5	O	97
4b	C_6H_5	S	95
4c	4-(Cl)–C_6H_4	O	93
4d	2-(Cl)–C_6H_4	O	89
4e	4-(Br)–C_6H_4	O	93
4f	4-(MeO)–C_6H_4	O	96
4g	2,3-$(OMe)_2$-C_6H_3	O	94
4h	2,4-$(OMe)_2$-C_6H_3	O	95
4i	3,4,5-$(OMe)_3$-C_6H_2	O	97
4j	4-(NO_2)-C_6H_4	O	79
4k	4-(F)-C_6H_4	O	83
4l	2-(Br)-5-(OMe)-C_6H_3	O	87
4m	Piperanal	O	94
4n	2-(NO_2)-C_6H_4	O	81
4o	4-(OH)-C_6H_4	O	78
4p	3-(OH)-4-(OMe)- C_6H_3	O	93
4q	5-(Br)-2-(OMe)-C_6H_3	O	94

To emphasize the merits of the present study, a comparative analysis was conducted on the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**). Various catalysts, including montmorillonite KSF, sulphuric acid, zeolite, silica-sulphuric acid, BF_3-OEt_2/CuCl, $H_3PMo_{12}O_{40}$, and HPA-Clay, were employed under solvent free conditions and at reflux temperature, with a specific focus on reaction times (Table 3).

Table 3

Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro pyrimidin-2(1*H*)-one (4a) using different catalysts.

Entry	*Catalyst*	*Time (h)*	*Yield (%)*
1.	Montmorilonite KSF	48	82
2.	Sulphuric acid	18	71
3.	Zeolite	12	80
4.	Silica sulphur acid	16	91
5.	$BF_3{\cdot}OEt_2$/CuCl	18	71
6.	$H_3PMo_{12}O_{40}$	5	80
7.	HPA-Clay	1	96

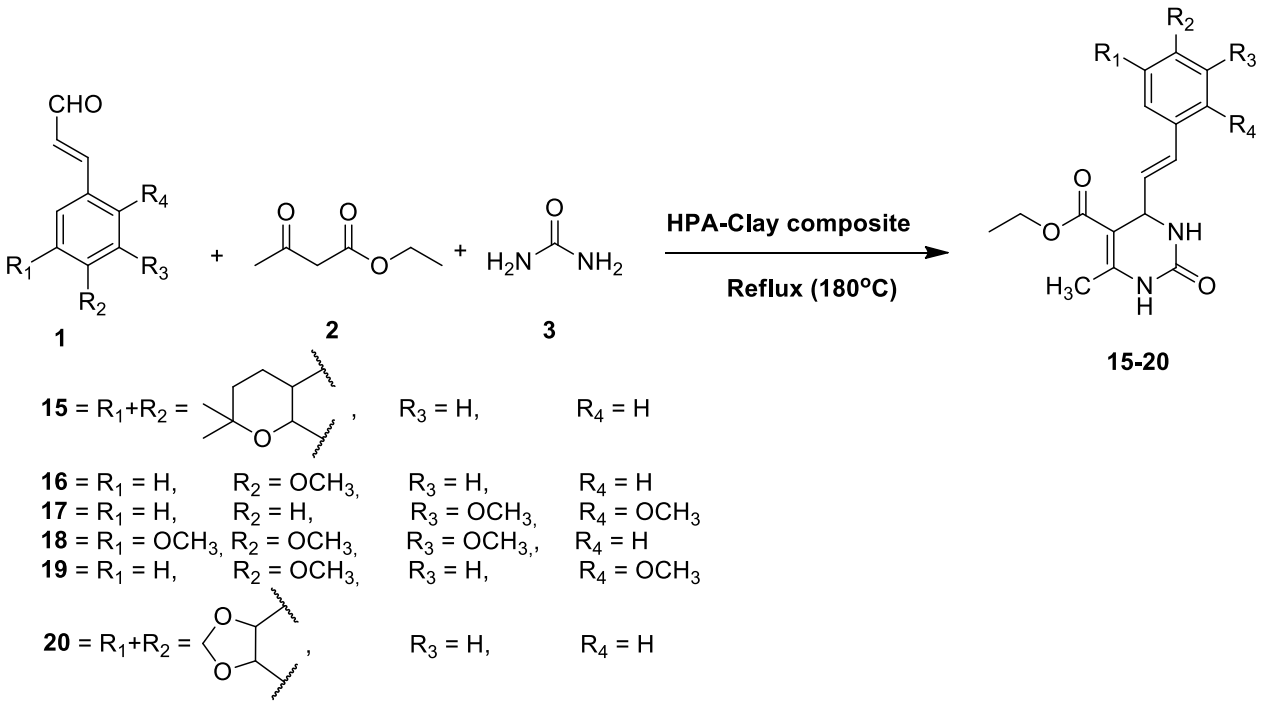
The synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (**4a**) showed different outcomes when compared to the catalytic activity of various catalysts against HPA-Clay. While reactions using these catalysts demanded longer reaction times, montmorilonite KSF stood out with a higher yield (82%) compared to others. However, it's noteworthy that the HPA-Clay catalyst yielded the highest product yield (96%) in the shortest reaction time (1 h). Moreover, the HPA-Clay catalyst demonstrated reusability for up to six cycles without significantly compromising overall reaction yields.

Synthesis of novel 3,4-dihydropyrimidin-2(1H)-one derivatives

Aldehydes of many types, including aromatic and aliphatic aldehydes, were employed to investigate the newly developed Biginelli reaction. Some of these aldehydes were made synthetically, while others were modified from natural sources. In addition to creating a new library of DHPM products (Scheme 3, Table 4) not previously documented in the literature, the use of these aldehydes was intended to broaden the scope of the Biginelli reaction. Elemental analysis and spectroscopic methods have been used to establish the structures of the newly synthesized compounds.

Catalyst characterization

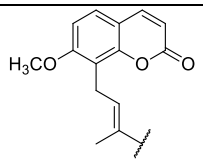
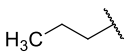
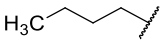
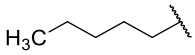
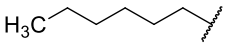
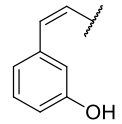
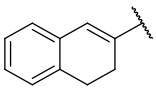
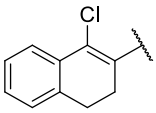
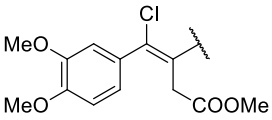
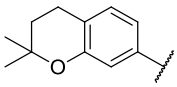
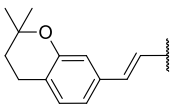
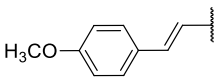
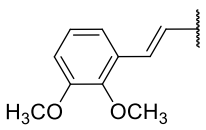
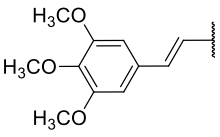
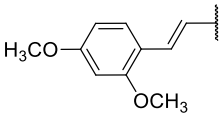
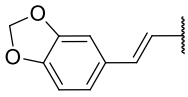
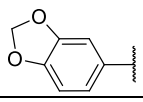
From the XRD prototype, it has been confirmed that the synthesized catalysts are well crystalline in nature (Figure 1). The sample was scanned over the range 2.00-79.99 on 2θ scale with steps 0.011° and step time 13.6 s. The powder XRD patterns of the HCNC were more crystalline and show additional reflections which are characteristics of HPA. This confirmed that HPA is well supported on Montomorillonite KSF and also improves the crystallinity of the supported catalysts. The XRD pattern of the catalyst shows a very low intensity reflection at 2θ= 9.9, which may be due to the residual 2:1 (T-O-T) structure of Montomorillonite KSF. The increase in specific surface area and formation of mesopores results because of delamination during the process of preparation. HPA loading on montomorillonite increases the phase crystallinity, which increases the available active acidic sites for the reactions. It is obvious that the peaks are very sharp which provide evidence that the sample is exceedingly crystalline. The B.E.T. surface area of the catalyst was determined and found to be 80.4762 m²/g.



Scheme 3. General procedure for preparation of novel DHPM analogues.

Table 4

Novel 3,4-dihydropyrimidin-2(1*H*)-ones.

Compound	*R*	*Yield (%)*
5		96
6		93
7		95
8		93
9		89
10		93
11		96
12		94
13		95
14		92
15		92
16		92
17		87
18		89
19		88
20		90
21		93

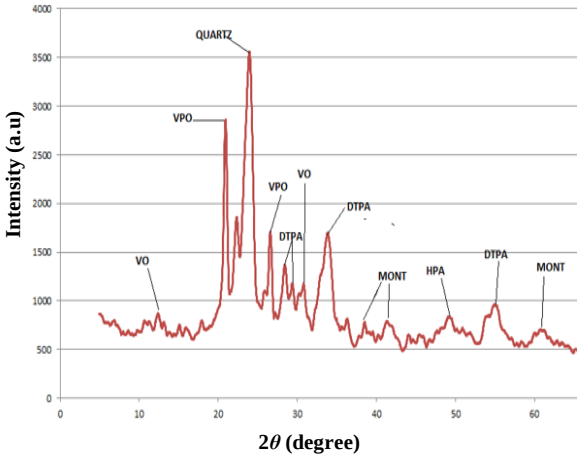


Figure 1. Powder X-ray diffraction for heteropolyacid supported on montomorillonite.

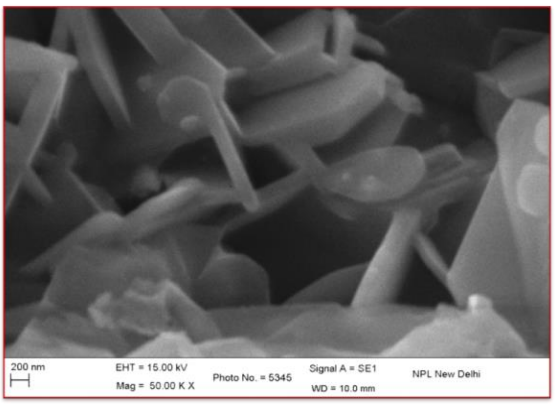


Figure 2. SEM image of heteropolyacids clay nanocomposite.

To study the morphology of the catalyst scanning electron microscopy (SEM) of sample was carried out. The SEM image of the gross morphology of the HPA-Clay is displayed in Figure 2. The SEM image is a confirmation for coarse surface (thus elevated surface area), which is able to absorb substrate and/or reagent to a high extent. It was observed that HPA particles were randomly distributed over the support surface. It should be noted that HPA layer formed in the present work was constituted by several aggregates of HPA particles and not by a continuous film.

Catalyst recyclability

Due to the scarcity of green catalysts, an assessment was done within the domain of green chemistry to investigate the possibility of catalyst recycling. The adoption of easily recoverable and recyclable catalysts is a promising technique that offers a substantial opportunity to develop efficient catalysts for converting diverse aldehydes into pyrimidinones under mild reaction conditions.

The HPA-Clay-Nanocomposite (HCNC) catalyst displayed stability in water after a 4 h immersion, with no activity loss observed.

Furthermore, it demonstrated the ability to be reused several times without significant activity degradation. The recyclability and reusability of the catalyst were demonstrated in six cycles in a model reaction, as shown in Figure 3.

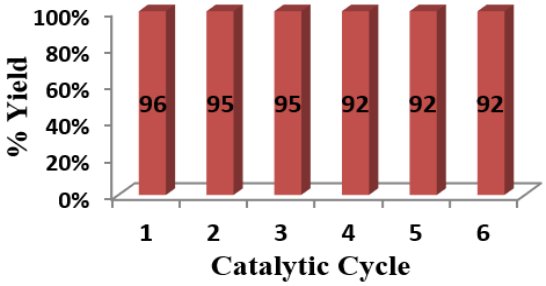


Figure 3. Recyclability of the catalyst.

Conclusion

This study introduces an environmentally friendly methodology utilizing a heteropolyacid-clay (HPA-Clay) catalyst in the Biginelli reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs). Employing a solvent-free, one-pot multicomponent approach, a diverse range of DHPMs is successfully synthesized with notable yields and reduced reaction times. The utilization of 2 mol% HPA-Clay as the catalyst aligns with green chemistry principles, emphasizing economic efficiency, environmental sustainability, and recyclability. The demonstrated potential of the catalyst in advancing Biginelli reactions for drug development is underscored by its consistent activity over multiple cycles. The HPA-Clay composite catalyst represents a significant advancement, offering a reusable heterogeneous catalytic system for one-pot multicomponent synthesis. Recognized for its simplicity, cost-effectiveness, and environmental sustainability, this methodology contributes to ongoing efforts in synthetic chemistry. The catalyst's stability and practical utility are evidenced by its recyclability and reusability for up to six cycles. This approach, aligned with green chemistry principles, addresses challenges inherent in conventional chemical processes, presenting a noteworthy contribution to the field of sustainable synthesis.

Supplementary information

Supplementary data are available free of charge at http://cjm.ichem.md as PDF file.

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