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Decatungstodivanadogermanic heteropoly acid ($H_6GeW_{10}V_2O_{40}.22H_2O$): A green and reusable heterogeneous catalyst for the synthesis of Biginelli-type 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones

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ABSTRACT

Decatungstodivanadogermanic acid ($H_6GeW_{10}V_2O_{40}.22H_2O$) was used as a green heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from one-pot three-component cyclocondensation reaction of a β-ketoester, an aldehyde and urea/thiourea under solvent-free conditions is reported. This method provides an efficient and much improved modification of the original Biginelli reaction reported in 1893, in terms of high yields, and short reaction times. It has the ability to allow a wide variety of substitutions in all three components.

***Keywords**: Biginelli reaction, Heteropolyacid, Decatungstodivanadogermanic acid, 3,4-dihydropyrimidin-2-(1H)-ones/thiones, Heterogeneous catalysis.*

1. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogs (DHMPs) have been reported to possess diverse pharmacological activities such as antiviral, antibacterial, antitumor, anti-inflammatory and antihypertensive activity as well as efficacy as calcium channel blockers and α-antagonists [1-4]. Some marine alkaloids (recently isolated) have been attributed to the presence of a dihyhropyrimidinone moiety which exhibit interesting biological activities [5]. In addition, the 2-oxodihydropyrimidine-5-carboxylate core unit is found in nature and in potent HIVgp-120-CD4 inhibitors [6-8]. Thus, the synthesis of dihydropyrimidinones is an ongoing active program in recent years.

In the literature, there are many reported methods for the preparation of dihydropyrimidinones employing different catalysts such as BF_3 [9], heteropoly acids [10-13], solid acids [14], Lewis acids $LiClO_4$ [15], and metal hydrogen sulphates [16]. However, many of these methods have drawbacks such as low yields of the products, long reaction times, high temperature, harsh reaction conditions, difficulties in workup, the use of stoichiometric amounts of catalysts, and the use of metal halides as catalysts. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst in terms of operational simplicity, reusability, economic viability, and greater selectivity. The possibility of performing multi-component reactions under solvent-free conditions with solid catalysts can enhance their efficiency from an economic as well as ecological point of view, so solvent free chemical reactions have received much attention.

In recent years, the use of heteropoly acids (HPAs) has recieved more attention [17-19]. HPAs have several advantages as catalysts which make them economically and environmentally feasible; they are stronger acids than homogeneous acid catalysts such as sulfuric acid or ion exchange resins. In addition, the use of HPAs as catalyst is important in the development of clean technologies, for it avoids the drawbacks of environmental pollution and prevents corrosion of the conventional technologies.

Herein, we report the use of Decatungstodivanado-germanic acid ($H_6GeW_{10}V_2O_{40}.22H_2O$) as a reusable and heterogeneous catalyst for the Biginelli reaction

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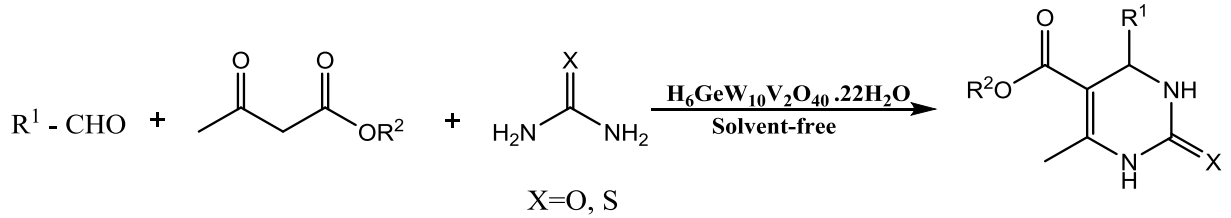


Scheme 1. $H_6GeW_{10}V_2O_{40}.22H_2O$ catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones.

for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones by the reaction of β-ketoester with urea (or thiourea) and various aromatic aldehydes under solvent-free conditions (Scheme 1). To the best of our knowledge, there is no report in the literature on the use of Decatungstodivanadogermanic acid in Biginelli reaction.

2. Experimental

2.1. Materials and Methods

Melting points were measured on an Electro thermal 9100 apparatus and were uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}CNMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d_6. The chemicals used in this work were purchased from Fluka chemical company. Decatungstodivanado-germanic acid ($H_6GeW_{10}V_2O_{40}.22H_2O$) was prepared according to a reported procedure [20].

2.2. Synthesis of Catalyst

0.8 g of GeO_2 was dissolved in a hot solution of 10% NaOH and a solution of 22.8 g of $Na_2WO_4.2H_2O$ in 100 mL of hot water was added to get mixture A. The pH of A was adjusted to 6 with HCl (1:1) and heated for 1h. Then, a solution of 7.5 g of Na_2CO_3 dissolved in 25 mL of hot water was added. The mixture was concentrated to 100 mL by heating. 2.4 g of $NaVO_3.2H_2O$ and 2.5 g of $Na_2WO_4.2H_2O$ were dissolved in 30 mL of hot water, respectively, and the two solutions were mixed to get mixture B. The pH of mixture B was adjusted to 2.5 with H_2SO_4 (1:1). Then, A was added dropwise and the pH was kept 2.5 while dropping. After stirring for 3 h at 60^{o}C, the solution was cooled to room temperature. The cooled solution was extracted with ether in sulfuric acid medium and the extractant was dissolved with a small amount of water. After the ether was evaporated, the remaining mixture was placed in the desiccators until orange crystals were separated out. The final yield was about 70%. Anal. Calcd. for $H_6GeW_{10}V_2O_{40}.22H_2O$: Ge, 2.38; W, 60.18; V, 3.33; H_2O, 12.96. Found: Ge, 2.38; W, 60.06; V, 3.29; H_2O, 12.97% (TG analysis). FT-IR (KBr, cm^{-1}): 3450 υ (O-H); 1620 δ (O-H); 964 υ_{as} (M-O_d); 885 υ_{as} (M-O_b-M); 818 υ_{as} (Ge-O_a); 780 υ_{as} (M-O_c-M); 464 δ (O-Ge-O), (M=W and V; O_a inner oxygen; O_b, corner-shared oxygen; O_c, edge shared oxygen; O_d, terminal oxygen) [20]. UV-Vis spectrum (CH_3CN λ_{max} nm); Od→M, CT); 262 (O_b/c→M, CT).

The number of hydrogen in the HPA and the states of ionization can be determined by potentiometric titration [21]. The potentiometric titration curve (Fig. 1) shows that the six protons of $H_6GeW_{10}V_2O_{40}.22H_2O$ are equivalent and they are ionized in one step.

X-ray powder diffraction is widely used to study the structural features of HPA and can explain their properties [22]. The data of X-ray powder diffraction are listed in Table 1.

The result of X-ray powder diffraction of $H_6GeW_{10}V_2O_{40}.22H_2O$ displays that the diffraction peaks are primarily distributed in four ranges of 2θ which are 7-10^o, 16-22^o, 25-30^o and 33-38^o. The positions and intensities of the main peaks are similar to those expected for the Keggin structure [23]. Combined with IR and UV spectra, certainly $H_6GeW_{10}V_2O_{40}.22H_2O$ possesses Keggin structure.

HPA consists of protons, HPA anions and hydration water. Fig. 2 is the thermogram of $H_6GeW_{10}V_2O_{40}.22H_2O$. The TG curve shows that the total percent of weight loss is 12.96%, which indicates that each HPA molecule has 22 molecules of water and there are three steps of weight loss. The first is the loss of 16 molecules of hydration water, the second is the loss of 6 molecules of protonized water and the third is the loss of 3 molecules of structural water. Thus, the accurate molecular formula of the product is $(H_5O_2)_3H_3GeW_{10}V_2O_{40}.16H_2O$ [24].

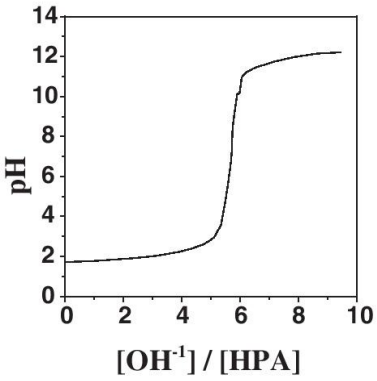


Fig. 1. Potentiometric titration curve of $H_6GeW_{10}V_2O_{40}.22H_2O$.

Table 1. Data of X-ray powder diffraction of $H_6GeW_{10}V_2O_{40}.22H_2O$.

2θ / ^{o}	9.27	10.34	16.76	18.75	19.10	20.76	25.52
d / nm	0.954	0.855	0.529	0.473	0.465	0.428	0.349
I	95.8	100.0	14.6	25.0	47.9	41.7	45.8
2θ / ^{o}	27.09	28.00	29.57	34.70	35.40	36.72	37.79
d / nm	0.329	0.319	0.302	0.529	0.254	0.245	0.238
I	70.8	60.4	27.1	33.3	22.9	35.4	27.1

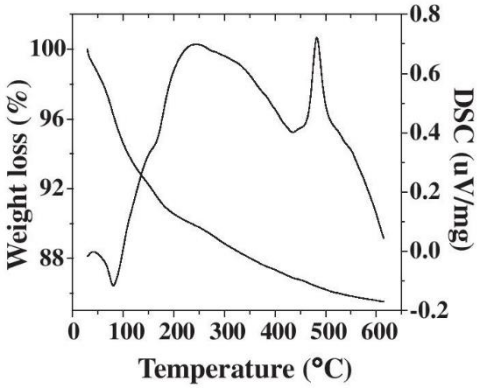


Fig. 2. Thermogram of $H_6GeW_{10}V_2O_{40}.22H_2O$.

In general, we took the temperature of the exothermic peak of DTA curves as the sign of their thermostability [25]. In the DTA curve, there was an exothermic peak at 481.6^{o}C.

2.3. General procedure for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones catalyzed by $H_6GeW_{10}V_2O_{40}.22H_2O$:

A solution of aldehyde (10 mmol), β-ketoester (15 mmol) and urea or thiourea (15 mmol) in solvent-free condition was treated with Decatungstodivanado-germanic acid (3 mol%). The mixture was stirred at 80^{o}C temperature and the progress of the reaction was monitored by TLC. Upon the completion of the reaction, the mixture was cooled to room temperature, ethyl acetate (2×10 mL) was added, and the catalyst was filtered. The solution poured into ice-water (30 mL). The resulting solid product was then removed by filtration and recrystallized from absolute ethanol to give pure product.

Selected Spectroscopic data

5–(Ethoxycarbonyl)–6–methyl–4–phenyl–3,4–dihydro-pyrimidin–2(1H)–one: Mp 205-207 ^{o}C; ^{1}HNMR (DMSO-d_6) δ: 1.09 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 7.1 Hz, OCH_2), 5.05 (d, 1H, *J* = 2.15 -CH), 7.28 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.11, 17.94, 54.91, 60.05, 100.95, 112.85, 113.05, 125.15, 125.81, 129.05, 131.20, 150.16, 155.47, 163.81; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1722, 1638; ESI-MS 261 (M+H); $C_{14}H_{16}N_2O_3$ (260.29); Calcd. C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found. C, 64.63; H, 6.18; N, 10.73; O, 18.47.

5–(Ethoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one: Mp 212-213^{o}C; ^{1}HNMR (DMSO-d_6) δ: 1.11 (t, 3H, *J* = 7.04 Hz, OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.03 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.78 (d, 1H, *J* = 2.28, -CH), 7.51 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 8.16 (d, 2H, *J* = 9.16, Ar-H), 9.05 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.22, 18.71, 55.81, 60.15, 101.60, 118.15, 130.37, 138.34, 152.26, 153.41, 159.15, 165.85; IR (ν_{max}.; KBr, cm^{-1}): 3235, 1740, 1631; ESI-MS 306 (M+H); $C_{14}H_{15}N_3O_5$; (305.29); Calcd. C, 55.08; H, 4.95; N, 13.76; O, 26.20. Found. C, 55.10; H, 4.93; N, 13.79; O, 26.16.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one: Mp 202-203^{o}C; ^{1}HNMR (DMSO-d_6) δ: 1.15 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.33 (s, 3H, CH_3), 3.78 (s, 3H, -OCH_3), 4.06 (q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.34 (d, 1H, *J* = 2.28 -CH), 6.82 (d, 2H, *J* = 8.60, Ar-H), 7.22 (d, 2H, *J* = 8.60, Ar-H), 7.76 (s, 1H, NH), 9.26 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ:14.32, 18.80, 55.23, 55.40, 60.17, 101.68, 114.06, 127.97, 136.22, 146.16, 153.59, 159.30, 165.87; IR (ν_{max}.; KBr, cm^{-1}): 3232, 1720, 1638; ESI-MS 291 (M+H); $C_{15}H_{18}N_2O_4$ (290.31); Cacld. C, 62.06; H, 6.25; N, 9.65; O, 22.04. Found. C, 62.08; H, 6.22; N, 9.69; O, 22.02.

5–(Ethoxycarbonyl)–4–(4-chlorophenyl)–6–methyl–3,4– dihydropyrimidin–2(1H)–one: Mp 214-215^{o}C; ^{1}HNMR (DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.14 Hz, OCH_2CH_3), 2.30 (s, 3H, CH_3), 3.91 (q, 2H, *J* = 7.16 Hz, OCH_2CH_3), 5.70 (d, 1H, *J* = 2.28, -CH), 7.21 (d, 2H, *J* = 9.18, Ar-H), 7.69 (s, 1H, NH), 7.94 (d, 2H, *J* = 9.18, Ar-H), 9.16 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.18, 18.62, 55.72, 60.21, 101.55, 118.17, 130.32, 142.29, 152.31, 153.39, 159.17, 165.83; IR (ν_{max}.; KBr, cm^{-1}): 3225, 1720, 1615; ESI-MS 295 (M+H); $C_{14}H_{15}ClN_2O_3$; Calcd. C, 57.05; H, 5.13; Cl, 12.03; N, 9.50; O, 16.29. Found. C, 57.08; H, 5.10; Cl, 12.06; N, 9.47; O, 16.31.

5–(Ethoxycarbonyl)–4–(4-dimethylamino-phenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one: Mp 254–256^{o}C; ^{1}HNMR (DMSO-d_6) δ: 0.99 (t, 3H, *J* = 7.12 Hz, OCH_2CH_3), 2.11 (s, 3H, CH_3), 2.84 (s, 6H, $N(CH_3)_2$), 4.09(q, 2H, *J* = 7.12 Hz, OCH_2CH_3), 5.05 (d, 1H, *J* = 2.21, -CH), 6.42 (d, 2H, *J* = 8.55, Ar-H), 7.12 (d, 2H, *J* = 8.56, Ar-H), 7.15 (s, 1H, NH), 9.05 (s,

1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.28, 18.78, 44.47, 55.23, 60.15, 101.60, 112.05, 125.65, 134.25, 141.16, 153.46, 159.02, 165.24; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 304 (M+H); $C_{16}H_{21}N_3O_3$; (303.36); Calcd. C, 63.35; H, 6.98; N, 13.85; O, 15.82. Found. C, 63.38; H, 6.93; N, 13.87; O, 15.79.

5–(Ethoxycarbonyl)–6–methyl-4-styryl–3,4–dihydropyrimidin–2(1H)–one: Mp231-233^{o}C; ^{1}HNMR (DMSO-d_6) δ: 1.20 (t, 3H, *J* = 7.0 Hz, OCH_2CH_3), 2.21 (s, 3H, CH_3), 4.09 (q, 2H, *J* = 7.05 Hz, OCH_2CH_3), 4.74 (d, 1H, *J* = 4.80, -CH), 6.20 (dd, *J* = 15.8, 6.0 Hz, 1H, CH=C–H), 6.37 (d, *J* = 15.9 Hz, 1H, H–C=CH) 7.21-7.46 (m, 5H, Ar-H), 7.53 (s, 1H, NH), 9.14 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.21, 17.31, 51.84, 59.45, 98.54, 127.34, 128.54, 129.54, 130.59, 131.24, 135.24, 145.34, 153.62, 165.23; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1704, 1652; ESI-MS 287 (M+H); $C_{16}H_{18}N_2O_3$; (286.33); Calcd. C, 67.12; H, 6.34; N, 9.78; O, 16.76. Found. C, 67.15; H, 6.32; N, 9.81; O, 16.73.

5–(Methoxycarbonyl)–4–(4-methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one: Mp 192-193^{o}C; ^{1}HNMR (DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 3.92 (s, 3H, -$COOCH_3$), 3.75 (s, 3H, -OCH_3), 5.22 (d, 1H, *J* = 2.21 -CH), 6.76 (d, 2H, *J* = 8.58, Ar-H), 7.18 (d, 2H, *J* = 8.58, Ar-H), 7.62 (s, 1H, NH), 9.15 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 18.61, 53.36, 55.05, 55.87, 108.54, 113.21, 128.47, 137.64, 148.54, 154.16, 160.81, 165.94; IR (ν_{max}.; KBr, cm^{-1}): 3242, 1721, 1637; ESI-MS 277 (M+H); $C_{14}H_{16}N_2O_4$; (276.29); Calcd. C, 60.86; H, 5.84; N, 10.14; O, 23.16. Found. C, 60.89; H, 5.81, N, 10.17; O, 23.13.

5–(Methoxycarbonyl)–4–(4-nitrophenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–one: Mp 237-239 ^{o}C; ^{1}HNMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 3.90 (s, 3H, -$COOCH_3$), 5.51 (d, 1H, *J* = 2.15, -CH), 7.42 (d, 2H, *J* = 9.11, Ar-H), 7.44 (s, 1H, NH), 8.05 (d, 2H, *J* = 9.10, Ar-H), 9.05 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 18.64, 52.40, 55.40, 109.60, 113.23, 128.31, 137.20, 149.65, 155.45, 160.36, 166.20; IR (ν_{max}.; KBr, cm^{-1}): 3232, 1724, 1631; ESI-MS 292 (M+H); $C_{13}H_{13}N_3O_5$; (291.26); Calcd. C, 53.61; H, 4.50; N, 14.43; O, 27.47. Found. C, 53.64; H, 4.47, N, 14.46; O, 27.44.

5–(Ethoxycarbonyl)–4–(4–methoxyphenyl)–6–methyl–3,4–dihydropyrimidin–2(1H)–thione (**1j**): Mp 154-156^{o}C; ^{1}HNMR (DMSO-*d6*) δ: 1.17 (t, 3H, *J* = 7.11 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 4.12 (s, 3H, -OCH_3), 4.15 (q, 2H, *J* = 7.10 Hz, OCH_2CH_3), 5.44 (d, 1H, *J* = 2.15 -CH), 7.11 (d, 2H, *J* = 8.15, Ar-H), 7.37 (d, 2H, *J* = 8.11, Ar-H), 7.84 (s, 1H, NH), 9.43 (s, 1H, NH); ^{13}CNMR (DMSO-d_6) δ: 14.32, 18.05, 55.24, 55.49, 60.45, 101.84, 114.32, 127.74, 137.25, 147.15, 159.45, 165.62, 182.48; IR (ν_{max}.; KBr, cm^{-1}): 3240, 1725, 1635, 1574, 1540; ESI-MS 307 (M+H); $C_{15}H_{18}N_2O_3S$; (306.38); Calcd. C, 58.80; H, 5.92; N, 9.14; O, 15.67; S, 10.47. Found. C, 58.84; H, 5.89; N, 9.17; O, 15. 64; S, 10.49.

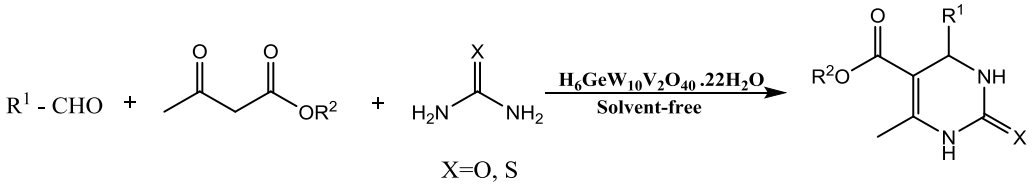
3. Results and Discussion

To study the generality of this process, a variety of substituted aromatics, carrying either electron donating or withdrawing substituents, aliphatic and heterocyclic aldehydes were examined (Table 2). Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aliphatic aldehydes such as propanal and pentanal also reacted well (Table 2, entries 12–14). Such aldehydes normally show extremely poor yields in the Biginelli reaction. It is interesting to note that in the case of the acid-sensitive aldehydes such as furfural and cinnamaldehyde, DHPMs were achieved in excellent yields without the formation of any side products, which are normally observed in the presence of protic acids (Table 2, entries 15–17). Furthermore, the experimental results showed that besides ethylacetoacetate, acetylacetate and methylacetoacetate could also be used, and the corresponding DHPMs were produced in high to excellent yields (Table 2, entries 19–28). Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1*H*)-thiones which are also of much interest with regard to biological activity [22] (Table 2, entries 29-35). Noteworthy is the recently identified lead compound, monastrol (Table 2, entry 31), of a new class of anticancer agents that act as cell division (mitosis) blockers [23]. Thus, variations in all three compounds have been accommodated very comfortably. It is interesting to observe the remarkable stability of a variety of functional groups such as ether, nitro, hydroxyl, halides, heterocyclic moieties and conjugated C=C double bond under the reaction conditions.

This work has also been extended to observe the effect of solvent on the reaction (Table 3, entries 1-6). In this regard, solvent free condition was found to be the best condition when considering the reaction yields and environmental damage (Table 3, entry 3).

In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin -2(1*H*)-one (entry1 in Table 2) in the presence of montmorillonite KSF, sulfuric acid, zeolite, silica sulfuric acid, $BF_3.OEt_2$/CuCl, $H_3PMo_{12}O_{40}$, $H_3PW_{12}O_{40}$ with $H_6GeW_{10}V_2O_{40}.22H_2O$ with respect to the reaction times (Table 4). The yield of product in the presence of $H_6GeW_{10}V_2O_{40}.22H_2O$ is comparable with these catalysts. However, reaction in the presence of these catalysts required longer reaction times than $H_6GeW_{10}V_2O_{40}.22H_2O$.

Table 2. Heteropolyacids catalyzed synthesis of dihydropyrimidin-2-(1*H*)-ones/thiones (DHPs)[a].



X=O, S

Entry	R^1	R^2	X	Yield (%)[b]	Ref [c]
1	C_6H_5	OEt	O	93	[26]
2	3-NO_2-C_6H_4	OEt	O	90	[26]
3	4-NO_2-C_6H_4	OEt	O	91	[26]
4	4-CH_3O-C_6H_4	OEt	O	96	[26]
5	2-Cl-C_6H_4	OEt	O	91	[26]
6	3-Cl-C_6H_4	OEt	O	90	[26]
7	4-Cl-C_6H_4	OEt	O	91	[26]
8	4-CH_3-C_6H_4	OEt	O	95	[26]
9	2-OH-C_6H_4	OEt	O	60	[27]
10	3-OH-C_6H_4	OEt	O	73	[26]
11	4-N(Me_2)-C_6H_4	OEt	O	96	[27]
12	C-C_6H_{11}	OEt	O	68	[15]
13	*n*-C_3H_7	OEt	O	57	[27]
14	*n*-C_5H_{11}	OEt	O	52	[15]
15	Ph-CH=CH	OEt	O	90	[26]
16	C_4H_3O	OEt	O	95	[26]
17	C_4H_3S	OEt	O	93	[26]
18	$C_{10}H_8$	OEt	O	79	[27]
19	C_6H_5	OMe	O	93	[26]
20	3-Cl-C_6H_4	OMe	O	90	[28]
21	4-Cl-C_6H_4	OMe	O	91	[9]
22	4-CH_3O-C_6H_4	OMe	O	97	[26]
23	4-NO_2-C_6H_4	OMe	O	75	[26]
24	4-CH_3-C_6H_4	OMe	O	96	[26]
25	4-N(Me_2)-C_6H_4	OMe	O	88	[29]
26	C_6H_5	Me	O	93	[30]
27	4-CH_3O-C_6H_4	Me	O	91	[30]
28	4-NO_2-C_6H_4	Me	O	72	[30]
29	C_6H_5	OEt	S	94	[26]
30	4-CH_3O-C_6H_4	OEt	S	97	[26]
31	3-OH-C_6H_4	OEt	S	71	[31]
32	4-Cl-C_6H_4	OEt	S	85	[26]
33	4-NO_2-C_6H_4	OEt	S	87	[26]
34	4-CH_3-C_6H_4	OEt	S	96	[26]
35	C_4H_3S	OEt	S	89	[26]

[a] Reaction conditions: aldehyde (10 mmol), β-ketoester (15 mmol), urea or thiourea (15 mmol), $H_6GeW_{10}V_2O_{40}.22H_2O$ (3 mol%), Solvent-free, reflux at 80°C.
[b] Isolated yields
[c] Products were characterized by comparison of their spectroscopic data with those reported in the literature.

Table 3. Synthesis of DHPs in the presence of $H_6GeW_{10}V_2O_{40}.22H_2O$ (3 mol%) in different solvents[a].

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$H_6GeW_{10}V_2O_{40}.22H_2O$	EtOH	4	73
2	$H_6GeW_{10}V_2O_{40}.22H_2O$	CH_3CN	5	82
3	$H_6GeW_{10}V_2O_{40}.22H_2O$	Solvent free	3	96
4	$H_6GeW_{10}V_2O_{40}.22H_2O$	CH_2Cl_2	7	68
5	$H_6GeW_{10}V_2O_{40}.22H_2O$	$CHCl_3$	10	57
6	$H_6GeW_{10}V_2O_{40}.22H_2O$	THF	10	48

[a] All reactions were carried out at 80°C reflux temperature

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

Entry	Catalyst	Time (h)	Yield (%)	Ref
1	Montmorilonite KSF	48	82	[32]
2	Sulfuric acid	18	71	[33]
3	Zeolite	12	80	[34]
4	Silica sulfuric acid	6	91	[31]
5	$BF_3.OEt_2$/CuCl	18	71	[9]
6	$H_3PMo_{12}O_{40}$	5	80	[35]
7	$H_3PW_{12}O_{40}$/MWI	90 Sec	92	[11]
8	$H_6GeW_{10}V_2O_{40}.22H_2O$	3	93	This work

Table 5. Reusability of the catalyst for the synthesis of 5-ethoxycarbonyl-4-methoxyphenyl-6-methyl-3,4-dihydro pyrimidin-2(1H)-one[a].

Cycle	1st	2nd	3rd	4th
Time (h)	3	3	3	3
Yield (%)[b]	93	89	86	82

[a]Reaction conditions: aldehyde (10 mmol), β-ketoester (15 mmol), urea or thiourea (15 mmol), $H_6GeW_{10}V_2O_{40}.22H_2O$ (3 mol%), Solvent-free, reflux at 80°C.
[b] Isolated yields.

In order to confirm the reusability of $H_6GeW_{10}V_2O_{40}.22H_2O$ catalyst, after the first use in the condensation of arylaldehyde, β-ketoester and urea/thiourea, it was separated from the reaction mixture and washed with ethyl acetate. The recovered catalyst was found to be reusable for four cycles without significant loss in activity (Table 5).

4. Conclusion

In conclusion, we have investigated the application of a V-containing HPA as a green and recyclable heterogeneous catalyst for the condensation of arylaldehyde, β-ketoester and urea/thiourea in solvent free conditions. It is an efficient, mild and green method for the synthesis of DHPs. It is noteworthy that the catalyst can be used for subsequent cycles without appreciable loss of activity. In contrast to many other acids, the storage of this non-hygroscopic and non corrosive solid heteropoly acid does not require special precautions, e.g., it can be stored on a bench top for months without losing its catalytic activity.

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