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$H_4SiW_{12}O_{40}\cdot xH_2O$ AS A NEW CATALYST FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE

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Abstract — $H_4SiW_{12}O_{40}\cdot xH_2O$ catalyzed the one-pot three component condensation reactions of aldehydes, 1,3-dicarbonyl compounds and urea in refluxing acetic acid leading to 3,4-dihydropyrimidin-2(1*H*)-one in high yields.

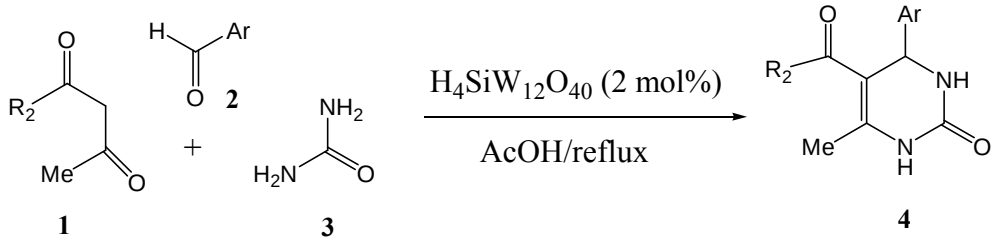
One of the most important objectives now is to adapt classical processes so that pollution effects are kept to a minimum, with both a reduction in energy and consumption of raw materials. In this respect, heterogeneous systems are promising, and a new approach has been undertaken using solid acids chemistry. Solid acids have many advantages such as simplicity in handling, decreased reactor and plant corrosion problems, and more environmentally safe disposal in different chemical processes. Also, wastes and by-products can be minimized or avoided by using solid acids in developing cleaner synthesis routes. On the other hand, any reduction in the amount of liquid acid needed and/or any simplification in handling procedures is required for risk reduction, economic advantage and environment protection,[1] and using an applicable industrial catalyst that is safe and eco-friendly, green and simply recycled in the reaction mixtures has been under attention. In the past two decades, the broad utility of heteropoly acids (**HPAs**) as acid and oxidation catalysts in solution as well as solid state for various industrial processes has been demonstrated for a wide variety of synthetic transformation of organic substrates.[1-3]

Dihydropyrimidinone derivatives (DHPMs) have attached considerable interest in recent years because these types of compounds exhibit attractive pharmacological profiles as calcium channel blockers, antihypertensive agents, α_{1a}-antagonists and neuropeptide Y (NPY) antagonists.[4] In addition, several marine alkaloids containing the dihydropyrimidinone-5-carboxylate motifs also showed interesting biological properties.[5]

Biginelli synthesis involves reaction of ethyl acetoacetate, benzaldehyde and urea in alcohol solution in the presence of a catalytic amount of hydrogen chloride to give 3,4-dihydropyrimidin-2(1*H*)-ones.[6] A major drawback of the classical Biginelli reaction is poor to moderate yields, particularly when substituted aromatic aldehydes were employed. Therefore, several improved procedures for the preparation of Biginelli compounds have been reported during the last two decades.[7,8] Among the improved synthetic methods is to use $BF_3\cdot OEt_2$ as promoter as reported by Hu and Sidler.[9] Later on,

Kappe and co-workers further improved this reaction by employing microwave irradiation in the presence of polyphosphate ether to give higher chemical yields of dihydropyrimidinone products.[10] Recently, the use of lanthanide compounds,[11] Lewis acids,[12-14] silica sulfuric acid,[15] N-bromosuccinimide,[16] alkali hydrogen sulfate,[17,18] $RuCl_3$,[19] 12-molybdatophosphoric acid,[20] $H_3PW_{12}O_{40}$,[21] L-prolin methyl ester hydrochloride,[22] Dowex-50W,[23] $K_5CoW_{12}O_{40}$,[24] and uronium hydrogen sulfates[25] also gave improved yield.

Due to the importance of Biginelli reaction products, the discovery and introduction of better and milder conditions using new catalysts has been under attention. Along this line, using **HPAs**, which are low in toxicity, highly stable towards humidity, recyclable and air stable have found more attention. Among these heteropoly acids, we chose silicotungestic acid which recently was used as a catalyst for the cyclodehydration of 1,4-butandiol to tetrahydrofuran,[26] and large soret effect for silicotungestic acid in a supporting electrode.[27] In this paper, we describe a one-pot method for the Biginelli reaction using silicotungstic acid, $H_4SiW_{12}O_{40}{\cdot}xH_2O$, a recyclable catalyst from the Keggin-type heteroploy acids (Scheme 1).



R_2= OEt, Me

Scheme 1

Table 1. $H_4SiW_{12}O_{40}$ Catalyzed Reaction of Aldehydes, Urea and 1,3-Dicarbonyl Compounds

Entry	ArCHO	R_2	Time (h)	Yield (%)[a]	Mp (˚C) Found	Mp (˚C) Reported
4a	C_6H_5CHO	OEt	6	80	203-205	202-204[9]
4b	4-Cl-C_6H_4CHO	OEt	7	90	210-212	213-215[9]
4b	4-Cl-C_6H_4CHO	OEt	22	<10[b]	-	
4c	4-NO_2-C_6H_4CHO	OEt	8	90	209-212	208-211[9]
4d	4-CN-C_6H_4CHO	OEt	8	82	127-129	-
4e	2-Cl-C_6H_4CHO	OEt	7	90	215-217	215-218[10]
4f	3-NO_2-C_6H_4CHO	OEt	7	90	227-229	226-227[10]
4g	4-Me-C_6H_4CHO	OEt	5	91	172-174	172[9]
4h	2-MeO-C_6H_4CHO	OEt	5	90	259-260	259-260[15]
4i	4-MeO-C_6H_4CHO	OEt	4	91	204-206	201-203[9]
4j	Furfural	OEt	4	80	204-205	203-205[12]
4k	2-thiophen-carbaldehyde	OEt	4	83	195-197	-
4l	C_6H_5CHO	Me	6	84	229-231	233-236[8]
4m	4-MeO-C_6H_4CHO	Me	4	85	169-171	170-172[15]
4n	4-NO_2-C_6H_4CHO	Me	8	88	229 (dec)	230(dec)[11]

[a]Isolated yield. [b]The reaction was performed in acetic acid solution and in the absence of $H_4SiW_{12}O_{40}$.

In the present communication, urea, ethyl acetoacetate, and aldehydes were converted to the corresponding pyrimidinones in a three-component one-pot Biginelli-type reaction in the presence of a catalytic amount of $H_4SiW_{12}O_{40}$. The best condition to prepare the dihydropyrimidinones were achieved when 2 mol% of **HPA**, 1.5 equivalent of urea and 1 equivalent of both ethyl acetoacetate and aldehyde were heated under reflux for 4-8 h, affording the desired product in good yields (Table 1). It's well known that Biginelli reaction is an acid promoted reaction, so to validate the effect of catalyst ($H_4SiW_{12}O_{40}$), we accomplished the reaction of 4-chlorobenzaldehyde, ethyl acetoacetate and urea in acetic acid solution and without catalyst. As shown in Table 1, the conversion of this reaction into desired product was less than 10% after 22 h refluxing in AcOH. We found that this method is effective with a variety of substituted aromatic aldehydes independently of the nature of the substituents on the aromatic ring, representing an improvement to the classical Biginelli's methodologies.

In conclusion, we reported here a catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2(1*H*)-ones using $H_4SiW_{12}O_{40}$ as an efficient, recyclable and eco-friendly heterogeneous inorganic catalyst. $H_4SiW_{12}O_{40}$ is non-corrosive and environmentally benign and presents fewer disposal problems.

EXPERIMENTAL

General: Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. IR spectra were run on a Shimadzu Infra Red Spectroscopy IR-435. The ^{1}H NMR was run on Avance Bruker AQS 300 MHz and 400 MHz. With TLC using silica gel SILG/UV 254 plates the progress of reaction was followed. All the products (except **4d** and **4k**) are known compounds and were characterized by IR and ^{1}H NMR spectroscopic data and their mps. compared with reported literature values.

General procedure:

A solution of aldehyde (10 mmol), β-ketoester (10 mmol) and urea (0.9 g, 15 mmol) in acetic acid (5 mL) was treated with $H_4SiW_{12}O_{40}\cdot xH_2O$ (2 mol%, 0.05 g). The reaction mixture was heated at reflux temperature and the progress of the reaction was monitored by TLC using petroleum ether: ethyl acetate as eluent. Upon completion of the reaction pured into ice-water (30 mL). The resulting solid product was then removed by filtration and recrystallized from ethanol to afford the pure product.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4a):[21] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.09 (t, 3H, J= 6.9 Hz), 2.24 (s, 3H), 3.97 (q, 2H, J= 6.8 Hz), 5.13 (s, 1H), 7.15-7.27 (m, 3H), 7.31 (d, 2H, J= 6.0 Hz), 7.74 (s, 1H), 9.20 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4b): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.08 (t, 3H, J= 7.0 Hz), 2.25 (s, 3H), 3.97 (q, 2H, J= 7.0 Hz), 5.14 (d, 1H, J= 2.6 Hz), 7.25 (d, 2H, J= 8.2 Hz), 7.39 (d, 2H, J= 8.2 Hz), 7.78 (s, 1H), 9.26 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c):[18] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.08 (t, 3H, J= 7.2 Hz), 2.27 (s, 3H), 3.98 (q, 2H, J= 7.2 Hz), 5.29 (d, 1H, J= 2.9 Hz), 7.51 (d, 2H, J= 8.5 Hz), 7.78 (s, 1H), 8.19 (d, 2H, J= 8.5 Hz), 9.29 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-cyanophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4d): IR (KBr): 3235, 3110, 2221, 1700, 1635 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.07 (t, 3H, J= 7.1 Hz), 2.25 (s, 3H), 3.97 (q, 2H, J= 7.1 Hz), 5.21 (s, 1H), 7.42 (d, 2H, J= 8.2 Hz), 7.80 (d, 2H, J= 8.2 Hz), 7.88 (s, 1H), 9.33 (s, 1H). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 14.48, 18.29, 54.28, 59.79, 98.69, 110.55, 119.20, 127.81, 133.00, 149.77, 150.47, 152.28, 165.55.

5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4e): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 0.98 (t, 3H, J= 6.9 Hz), 2.29 (s, 3H), 3.88 (q, 2H, J= 6.8 Hz), 5.62 (s, 1H), 7.18-7.34 (m, 3H), 7.40 (d, 1H, J= 7.3 Hz), 7.72 (s, 1H), 9.28 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4f): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.09 (t, 3H, J= 7.0 Hz), 2.26 (s, 3H), 3.99 (q, 2H, J= 7.0 Hz), 5.30 (d, 1H, J= 3.5 Hz), 7.64-7.69 (m, 2H), 7.91 (d, 1H), 8.08 (s, 1H), 8.13 (d, 1H, J= 7.8 Hz), 9.38 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4g): ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.10 (t, 3H, J= 7.0 Hz), 2.25 (s, 3H), 3.97 (q, 2H, J= 7.0 Hz), 5.10 (d, 1H, J= 3.1 Hz), 7.10 (d, 4H, J= 3.2 Hz), 7.69 (s, 1H), 9.16 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(2-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4h): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.02 (t, 3H, J= 7.0 Hz), 2.26 (s, 3H), 3.78 (s, 3H), 3.90 (q, 2H, J= 7.0 Hz), 5.48 (s, 1H), 6.80-7.05 (m, 3H), 7.22 (d, 1H, J= 7.8 Hz), 7.27 (s, 1H), 9.11 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4i):[19] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (t, 3H, J= 7.2 Hz), 2.24(s, 3H), 3.76 (s, 3H), 3.98 (q, 2H, J= 7.2 Hz), 5.10 (d, 1H, J= 3.2 Hz), 6.79 (d, 2H, J= 8.7 Hz), 7.17 (d, 2H, J= 8.7 Hz), 7.25 (s, 1H), 8.94 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(furyl)-3,4-dihydropyrimidin-2(1*H*)-one (4j):[17] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.13 (t, 3H, J= 7.0 Hz), 2.22 (s, 3H), 4.02 (q, 2H, J= 6.9 Hz), 5.20 (d, 1H, J= 2.5 Hz), 6.09 (d, 1H, J= 2.3 Hz), 6.35 (s, 1H), 7.55 (s, 1H), 7.79 (s, 1H), 9.30 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(thionyl)-3,4-dihydropyrimidin-2(1*H*)-one (4k):
IR (KBr): 3228, 3116, 1700, 1640 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.15 (t, 3H, J= 7.0 Hz), 2.21 (s, 3H), 4.05 (q, 2H, J= 7.0 Hz), 5.40 (s, 1H), 6.88-6.93 (m, 2H), 7.34 (d, 1H, J= 4.5 Hz), 7.90 (s, 1H), 9.30 (s, 1H). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 14.59, 18.12, 49.79, 59.84, 100.26, 123.98, 125.09,

127.14, 149.09, 149.20, 152.71, 165.49.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4l): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.10 (s, 3H), 2.28 (s, 3H), 5.25 (s, 1H), 7.17-7.27 (m, 3H), 7.31 (d, 2H, J= 6.5 Hz), 7.83 (s, 1H), 9.19 (s, 1H).

5-Acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4m): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.01 (s, 3H), 2.30 (s, 3H), 3.82 (s, 3H), 5.21 (d, 1H, J= 3.2 Hz), 6.88 (d, 2H, J= 7.5 Hz), 7.04 (d, 2H, J= 7.5 Hz), 7.42 (s, 1H), 9.11 (s, 1H).

5-Acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4n): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.11 (s, 3H), 2.29 (s, 3H), 5.32 (s, 1H), 7.51 (d, 2H, J= 8.2 Hz), 7.79 (s, 1H), 8.20 (d, 2H, J= 8.2 Hz), 9.27 (s, 1H).

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