Catalytic Performance of Heteropoly Acids on Different Supports in the Synthesis of Dihydropyrimidones

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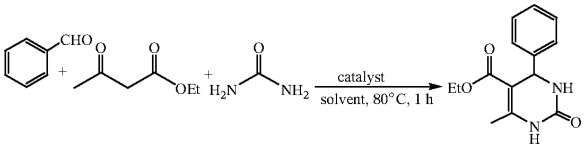
Keggin heteropoly acids supported on solids with different nature were used in the Biginelli reaction in order to obtain dihydropyrimidones. The results show that the activity of the catalysts is dependent on the supports used to obtain the catalysts. This method consistently has the advantages of excellent yield, mild reaction conditions, ease of workup, survival of different functional groups, and short reaction times.

Key words: Supported Heteropoly Acid, Dihydropyrimidone, Biginelli Reaction, Heterogeneous Catalyst, Urea, Thiourea

Introduction

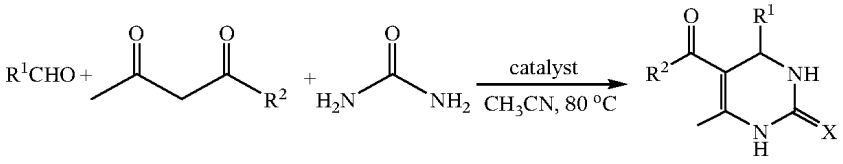
3,4-Dihydropyrimidin-2(*1H*)-ones (DHPMs) have recently emerged as important target molecules duo to their therapeutic and pharmacological properties [1], such as antiviral [2], antimitotic [3], anticarcinogenic [4], antihypertensive activity [5 – 6], and noteworthy, as calcium channel modulators [7]. Moreover, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources and exhibit interesting biological properties [8]. The Biginelli reaction is the most straightforward and simple protocol for the synthesis of DHPMs, and involves a one-pot, but low-yield (25 – 60 %) condensation of β-dicarbonyl compounds with aldehydes and urea in the presence of a strong acid [9]. Subsequent multistep syntheses [10, 11] have afforded somewhat higher yields but do not have the simplicity of the original one-pot Biginelli protocol. Recently, several improved procedures have been reported [12 – 16] using Lewis acids as well as protic acids as promoters. However, in spite of their potential utility, many of these methods involve expensive reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, and incompatibility with other functional groups. In a previous study [17], it was shown that heteropoly acids (HPAs) are good catalysts for organic synthesis. Among many other solid acid

Table 1. Effect of different catalysts under different reaction conditions.



Entry	Catalyst	Solvent	Yield (%)[a]
1	–	CH_3CN	0[b]
2	KSF (0.3 g mL^{-1})	CH_3CN	40
3	Carbon active (0.3 g mL^{-1})	CH_3CN	23
4	K10 (0.3 g mL^{-1})	CH_3CN	41
5	40 % PW/K10 (0.15 g mL^{-1})	CH_3CN	51
6	40 % PMo/K10 (0.15 g mL^{-1})	CH_3CN	47
7	40 % SiW/K10 (0.15 g mL^{-1})	CH_3CN	50
8	40 % PW/KSF (0.15 g mL^{-1})	CH_3CN	66
9	40 % PMo/KSF (0.15 g mL^{-1})	CH_3CN	54
10	40 % SiW/KSF (0.15 g mL^{-1})	CH_3CN	61
11	60 % PW/KSF (0.15 g mL^{-1})	CH_3CN	68
12	20 % PW/KSF (0.15 g mL^{-1})	CH_3CN	55
13	40 % PW/KSF (0.3 g mL^{-1})	CH_3CN	93
14	40 % PW/KSF (0.6 g mL^{-1})	CH_3CN	95
15	40 % PW/KSF (0.3 g mL^{-1})	C_2H_5OH	40
16	40 % PW/KSF (0.3 g mL^{-1})	$C_6H_5CH_3$	55
17	40 % PW/KSF (0.3 g mL^{-1})	$CHCl_3$	50
18	40 % PW/C (0.07 g mL^{-1})	CH_3CN	67[c]
19	40 % PW/C (0.15 g mL^{-1})	CH_3CN	95[c]
20	40 % PW/C (0.3 g mL^{-1})	CH_3CN	98[c]
21	40 % PW/KSF (0.3 g mL^{-1})	CH_3CN	61[d]

[a] Isolated yield; [b] after 10 h; [c] after 20 min; [d] reaction performed at r. t.



Entry	R^1	R^2	X	Time (min)/yield (%)[a] PW/C[b]	PW/KSF[c]	M. p. (°C) found	reported	
1	C_6H_5	OEt	O	20/95	60/93	201 – 202	202 – 204	[23]
2	3-$NO_2C_6H_4$	OEt	O	80/95	60/95	228 – 230	229 – 231	[23]
3	4-$NO_2C_6H_4$	OEt	O	65/85	60/90	208 – 209	207 – 209	[23]
4	4-$CH_3OC_6H_4$	OEt	O	80/95	60/90	201 – 203	202 – 204	[23]
5	2-ClC_6H_4	OEt	O	90/95	70/70	220 – 222	222 – 224	[23]
6	4-ClC_6H_4	OEt	O	90/90	75/70	212 – 213	212 – 214	[23]
7	4-$CH_3C_6H_4$	OEt	O	60/95	55/95	211 – 212	215 – 216	[23]
8	2-HOC_6H_4	OEt	O	70/50	60/80	202 – 203	201 – 203	[24]
9	3-HOC_6H_4	OEt	O	100/70	60/90	166 – 168	164 – 166	[14]
10	4-$N(Me)_2$-C_6H_4	OEt	O	70/95	60/87	258 – 259	256 – 258	[24]
11	*n*-C_3H_7	OEt	O	90/95	75/65	155 – 156	152 – 154	[24]
12		OEt	O	70/85	60/95	207 – 208	209 – 211	[23]
13		OEt	O	70/90	60/85	213 – 215	215 – 217	[23]
14		OEt	O	90/80	70/70	246 – 248	247 – 248	[26]
15	C_6H_5	OMe	O	50/90	60/85	208 – 209	206 – 208	[23]
16	4-ClC_6H_4	OMe	O	60/93	80/70	205 – 207	204 – 207	[12]
17	4-$CH_3OC_6H_4$	OMe	O	55/95	60/87	192 – 193	190 – 192	[23]
18	4-$NO_2C_6H_4$	OMe	O	60/85	60/87	206 – 209	214 – 215	[23]
19	4-$CH_3C_6H_4$	OMe	O	45/92	60/85	203 – 205	204 – 206	[23]
20	4-$N(Me)_2$-C_6H_4	OMe	O	70/82	70/85	238 – 239	[d]	
21	C_6H_5	Me	O	80/90	70/85	235 – 236	233 – 236	[27]
22	4-$CH_3OC_6H_4$	Me	O	80/95	60/80	169 – 170	166 – 168	[14]
23	4-$NO_2C_6H_4$	Me	O	120/85	60/82	231 (dec.)	230 (dec.)	[23]
24	C_6H_5	OEt	S	60/90	55/95	207 – 209	208 – 210	[23]
25	4-$CH_3OC_6H_4$	OEt	S	60/70	50/95	150 – 152	150 – 152	[23]
26	3-HOC_6H_4	OEt	S	45/90	55/90	185 – 186	184 – 186	[28]
27	4-ClC_6H_4	OEt	S	60/91	60/70	191 – 193	192 – 194	[23]
28	4-$NO_2C_6H_4$	OEt	S	45/85	60/95	110 – 111	109 – 111	[23]
29	4-$CH_3C_6H_4$	OEt	S	65/95	50/95	193 – 195	192 – 194	[23]
30		OEt	S	50/85	55/95	216 – 218	215 – 216	[23]

Table 2. Supported $H_3PW_{12}O_{40}$ catalyzed synthesis of dihydropyrimidin-2(1*H*)-ones and thiones (DHPMs).

[a] Isolated yield; products were characterized by comparison of their spectroscopic data with those reported in the literature; [b] PW/C: 0.15 g mL^{-1}; [c] PW/KSF: 0.3 g mL^{-1}; [d] spectroscopic data reported in the Experimental Section.

systems, HPAs having Keggin-anion structures have received the most attention due to their simple preparation and strong acidity [18, 19]. Especially dodecatungstophosphoric acid (PW) is the most extensively studied [20, 21], since it possesses super acidity [22]. However, some of the major problems associated with HPAs in the bulk form are their low efficiency due to low surface area, rapid deactivation, and relatively poor stability. Attempts to improve the efficiency and stability of HPAs have been made by using various supports. In this context, we had brought out the efficacies of carbon, K 10, and KSF montmorillonite as suitable supports for HPAs in a one-pot synthesis of DHPMs.

Results and Discussion

At first the three-component condensation reaction of benzaldehyde, ethyl acetoacetate and urea was performed in the presence of catalytic amounts of supports only (Table 1, entries 2 – 4). Supports show low activity in this reaction. The synthesis could not be achieved in the absence of the catalyst (Table 1, entry 1). To improve the activity of HPAs with increasing the ac-

Table 3. Reusability of catalysts in the reaction of benzaldehyde, ethyl acetoacetate, and urea.

Run	Time (min)/yield (%)	
	40 % PW/C	40 % PW/KSF
1	20/95	60/93
2	20/90	60/88
3	20/86	60/86
4	20/82	60/84

tive site accessibility, three supported HPAs were produced. It was found that the HPAs supported on K 10 showed poor effect to improve the yield of the product (Table 1, entries 5 – 7). When using KSF and carbon as supports, the results seemed to be better. To establish the optimal conditions, a set of experiments varying the weight percent of PW on the solid, the catalyst loading, and the solvent were carried out (Table 1, entries 8 – 20). Usually, tungsten HPAs are preferred over molybdenum ones as acid catalysts because of their stronger acidity and higher thermal stability. Results show that the use of just 0.3 g mL^{-1} of 40 wt.-% PW on KSF is sufficient to promote the reaction. There are no improvements in the reaction yields by increasing the amount of the catalyst from 0.3 to 0.6 g mL^{-1} (Table 1, entry 14). It seems that acetonitrile is a much better solvent than all other solvents tested (Table 1, entries 13, 15 – 17). In the case of carbon-supported PW the best catalyst to prepare the DHPMs was achieved when 0.15 g mL^{-1} of 40 wt.-% PW on C was used (Table 1, entries 18 – 20). When the reaction was performed at r. t., the yield of the product was low (Table 1, entry 21), thus, all further reactions were performed at 80 °C.

Encouraged by these results, several substituted aromatic, aliphatic and heterocyclic aldehydes, different β-dicarbonyl compounds and urea or thiourea were examined under the optimized conditions (Table 2). Compared to the classical Biginelli method [9] an important feature of the present protocol is the ability to tolerate the variation in all the three components. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(*1H*)-thiones (Table 2, entries 24 – 30) which are also of much interest with regard to biological activity [13]. The reaction conditions are mild enough to tolerate sensitive functionalities such as a conjugated C=C bonds and heterocyclic moieties without the formation of any side products, which are normally observed in the presence of protic acids due to their polymerization under acidic conditions. The catalyst can be filtered off after the reaction, and after washing the solid residues with acetone, the remaining material can be reloaded with fresh reagents for further runs. Low loss of activity was observed demonstrating that supported PW can be reused as a catalyst in the Biginelli condensation (Table 3).

Conclusion

In summary, supported HPAs were found to be highly efficient, reusable, inexpensive and ecofriendly solid acid catalysts for the synthesis of dihydropyrimidin-ones or -thiones. High yields of the products, short reaction times, mild reaction conditions and a simple experimental procedure and product isolation make this protocol complementary to the existing methods. An important feature of the present protocol is the ability to tolerate the variation in all the three components, and the absence of side products in any run.

Experimental Section

$H_3PW_{12}O_{40}$, $H_4SiW_{12}O_{40}$, and $H_3PMo_{12}O_{40}$ hydrate from Aldrich and Merck were used. Carbon and KSF montmorillonite clay were obtained from Fluka. All chemical reagents and solvents were analytical grade and were purchased from Fluka. Melting points were determined using a digital Gallenkamp apparatus and are uncorrected. The tungsten content in the catalyst was measured by inductively coupled plasma (ICP atomic emission spectroscopy) with a Spectro Ciros CCd spectrometer. ^{1}H NMR spectra were recorded with a Bruker Avance 200 MHz NMR spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard.

Preparation of the catalyst

The catalysts were prepared using solutions of dodecatungstophosphoric acid (PW), dodecatungstosilicic acid (SiW), or dodecamolybdophosphoric acid (PMo). The solutions were used to impregnate activated carbon, KSF, and K 10 montmorillonite as supports.

For the preparation of HPA/KSF (or HPA/K 10), KSF (or K 10), montmorillonite was dried in an oven at 120 °C for 2 h prior to its use as support. The appropriate amount of HPA (according to the weight percent of HPA relative to the support) was dissolved in 4 mL of dry methanol and added dropwise to 5.0 g of predried KSF (or K 10) with constant stirring to produce the supported catalyst.

For the preparation of PW/C, carbon was first subjected to an acid and base treatment to remove impurities. The catalyst was prepared by the pore filling impregnation technique with PW solutions. After the impregnation, all catalysts were dried at r. t. for 24 h and calcinated at 200 °C for 3 h.

Typical procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and -thiones

A mixture containing an appropriate β-dicarbonyl compound (2 mmol), aldehyde (2 mmol), urea or thiourea (3 mmol) and supported HPA (0.15 and 0.3 g mL^{-1} for PW/C and PW/KSF, respectively) in acetonitrile (5 mL) was stirred rapidly and heated at 80 °C in a preheated oil bath for an appropriate time (Table 2). After completion of the reaction as indicated by TLC, the mixture was filtered to remove the catalyst, and the filtrate was poured into crushed ice. After stirring for several minutes, the solid product was filtered, washed with cold water (2 × 30 mL) and recrystallized from ethyl acetate/*n*-hexane or ethanol (1 : 3) to afford pure products. All products were identified by comparing their spectral and physical data with those of authentic samples [12, 23 – 27].

5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1H)-one (entry 9). M. p. 166 – 168 °C. – ^{1}H NMR (200 MHz): δ = 1.11 (t, J = 6.9 Hz, 3H), 2.24 (s, 3H), 4.01 (q, J = 6.9 Hz, 2H), 5.06 (d, J = 3 Hz, 1H), 6.65 (m, 3H), 7.08 (t, J = 7.8 Hz, 1H), 7.66 (s, 1H), 9.16 (s, 1H), 9.35 (s, 1H).

4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (entry 16). M. p. 205 – 207 °C. – ^{1}H NMR (200 MHz): δ = 2.24 (s, 3H), 3.56 (s, 3H), 5.13 (d, J = 3.3 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.79 (s, 1H), 9.30 (s, 1H).

5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (entry 18). M. p. 206 – 209 °C. – ^{1}H NMR (200 MHz): δ = 2.29 (s, 3H), 3.56 (s, 3H), 5.28 (s, 1H), 7.44 – 8.20 (m, 4H), 7.94 (s, 1H), 9.35 (s, 1H).

4-(4-N,N-Dimethylaminophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (entry 20). M. p. 238 – 239 °C. – ^{1}H NMR (200 MHz): δ = 1.71 (s, 3H), 2.82 (s, 6H), 3.74 (s, 3H), 5.55 (s, 1H), 6.44 – 6.91 (m, 4H), 7.56 (s, 1H), 8.97 (s, 1H).

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2-(1H)-one (entry 22). M. p. 169 – 170 °C. – ^{1}H NMR (200 MHz): δ = 2.10 (s, 3H), 2.30 (s, 3H), 3.74 (s, 3H), 5.25 (d, J = 3 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 9.23 (s, 1H).

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (entry 27). M. p. 191 – 193 °C. – ^{1}H NMR (200 MHz): δ = 1.10 (t, J = 6.6 Hz, 3H), 2.27 (s, 3H), 4.04 (q, J = 6.6 Hz, 3H), 5.18 (s, 1H), 7.22 – 7.47 (m, 4H), 9.70 (s, 1H), 10.39 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-thione (entry 30). M. p. 216 – 218 °C. – ^{1}H NMR (200 MHz): δ = 1.13 (t, J = 6.7 Hz, 3H), 2.29 (s, 3H), 4.08 (q, J = 6.7 Hz, 2H), 5.44 (s, 1H), 6.92 – 6.98 (m, 2H), 7.36 (d, J = 4.1 Hz, 1H), 9.78 (s, 1H), 10.48 (s, 1H).

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