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# One-Pot Synthesis of Dihydropyrimidinones by Dodecylphosphonic Acid as Solid Bronsted Acid Catalyst under Solvent-Free Conditions *via* Biginelli Condensation

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Dodecylphosphonic acid is a solid Bronsted acid that catalyzes efficiently the preparation of dihydropyrimidinones by Biginelli condensation under solvent-free conditions. This protocol offers several advantages including high yields, short reaction times, easy work-up, and use of cheap, relatively moderate acidic and safe catalyst.

**Keywords:** Dihydropyrimidinone, Dodecylphosphonic acid, Solvent-free, Biginelli condensation

## INTRODUCTION

Dihydropyrimidinones are attractive organic compounds which show important biological activities such as antiviral, antitumor, antibacterial and anti-inflammatory actions [1-3]. The more convenient procedure for the preparation of dihydropyrimidinones first reported by P. Biginelli in 1893, consists of the one-pot condensation of β-dicarbonyl compounds with aldehydes and urea or thiourea under strongly acidic conditions [4]. One major disadvantage of this method is the low yields especially in the case of aliphatic and some substituted aromatic aldehydes. To circumvent this problem, a variety of new catalysts has been introduced in the literature. In recent years, many protocols involving the use of Lewis and Bronsted acids such as graphite supported lanthanum chloride, [5] alumina supported $MoO_3$ [6], antimony(III) chloride [7], copper(II) tetrafluoroborate [8], bismuth nitrate [9], iron(III) trifluoroacetate and trifluoromethanesulfonate [10], yttrium(III) nitrate hexahydrate [11], $TaBr_5$ [12], TCCA [13], PSSA [14], chloroacetic acid [15], *p*-TsOH [16], HCl [17], acetic acid [18], silica sulfuric acid [19], concentrated $H_2SO_4$ [20], $H_3BO_3$ [21], $HBF_4$ [22], chiral phosphoric acid [23], $H_3PW_{12}O_{40}$ [24], $H_3PMo_{12}O_{40}$ [25], and $Al_2O_3/MeSO_3H$ [26] are reported.

However, some of these catalyzed conditions have certain drawbacks; for example, long reaction times, use of organic solvents and heavy metal salts, harsh reaction conditions such as need of strong acids, anhydrous conditions, requiring inert atmosphere, use of equivalent amounts of introduced reagent, use of microwave irradiation and high temperatures. Finally, in Bronsted acid conditions, acid sensitive aldehydes reacted to low yields. Therefore, in spite of a large number of methods reported for this transformation, there is still need to develop a more efficient, simple, milder protocol using conservational catalyst. In continuation of our studies on catalytic activity of dodecylphosphonic acid (DPA) [27], we report here the application of this solid Bronsted acid for the preparation of dihydropyrimidinones through Biginelli reaction under mild conditions.

## EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance DPX-250 ($^1$H NMR 250 MHz and $^{13}$C NMR 63 MHz). IR spectra were

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obtained using a Shimadzu FT-IR 8300 spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instruments at 70 or 20 eV. Melting points were determined in open capillary tubes in a Büchi-545 circulating oil melting point apparatus. Materials were purchased from Fluka, Aldrich and Merck Chemical Companies.

### General Procedure for the Biginelli Reaction

Dodecylphosphonic acid (10 mol%) was added to a mixture of aldehyde (1 mmol), β-dicarbonyl compound (1 mmol) and urea or thiourea (1.5 mmol). The neat reaction mixture was heated with stirring for appropriate time at 70 ºC. The resulting powder was dissolved in hot ethanol. Then, the solution was poured onto crushed ice. The separated solid was filtered and recrystallized from hot ethanol to afford pure product.

### Typical Spectral Data

**Ethyl 6-methyl-2-oxo-4-(pyridin-3-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, Entry 9).** Brick red solid, m.p.: 205-207 °C. IR (KBr): 3348, 3112, 2977, 1693, 1643 $cm^{-1}$. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 1.05 (m, 3H, $C\underline{H}_3CH_2$-), 2.24 (s, 3H, $CH_3$), 3.92 (m, 2H, $CH_3C\underline{H}_2$-), 5.16 (s, 1H, CH-), 7.35 (m, 1H, arom.), 7.60 (m, 1H, arom.), 7.78 (s, 1H, NH), 8.42 (2H, arom.), 9.28 (s, 1H, NH). $^{13}C$ NMR (63 MHz, DMSO-$d_6$): δ = 13.95, 17.72, 52.06, 59.25, 98.28, 123.73, 133.88, 140.03, 147.81, 148.49, 149.05, 151.80, 165.01. EIMS: *m/z* (%): 261 ($M^+$, 8.4), 232 (45.4), 183 (100.0), 155 (61.8), 137 (54.6), 110 (19.3), 83 (39.5), 57 (84.9). Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.74; H, 5.74; N, 16.08%. Found: C, 59.45; H, 5.80; N, 15.87%.

**Ethyl 6-methyl-2-oxo-4-phenethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, Entry 10).** White solid, m.p.: 149-152 °C. IR (KBr): 3247, 3116, 2931, 1705, 1651 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 1.21 (m, 3H, $C\underline{H}_3CH_2$-), 1.87 (m, 2H, $PhCH_2C\underline{H}_2$-), 2.28 (s, 3H, $CH_3$), 2.69 (m, 2H, $PhC\underline{H}_2CH_2$-), 4.12 (m, 2H, $CH_3C\underline{H}_2$-), 4.33 (m, 1H, CH-), 5.83 (s, 1H, NH), 7.03-7.30 (m, 5H, arom.), 7.94 (s, 1H, NH). $^{13}C$ NMR (63 MHz, $CDCl_3$): δ = 14.29, 18.59, 30.68, 36.89, 38.14, 51.095, 59.93, 101.38, 125.99, 128.05, 128.29, 128.46, 141.00, 146.97, 154.25, 165.69. EIMS: *m/z* (%): 288 ($M^+$, 0.2), 243 (2.7), 200 (0.4), 183 (100.0), 155 (34.8), 137 (26.8), 91 (20.1). Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72%. Found: C, 67.00; H, 6.85; N, 9.62%.

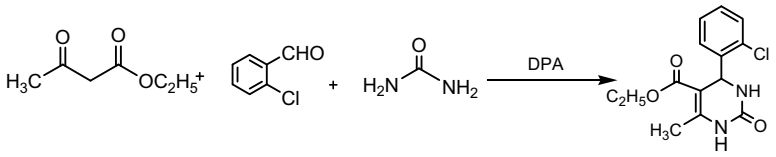
**Ethyl 6-methyl-4-(naphthalen-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, Entry 14).** Pale-yellow solid, m.p.: 173-177 °C. IR (KBr): 3224, 3101, 2939, 1705, 1651 $cm^{-1}$. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 1.08 (m, 3H, $C\underline{H}_3CH_2$-), 2.28 (s, 3H, $CH_3$), 3.83 (m, 2H, $CH_3C\underline{H}_2$-), 5.33 (s, 1H, CH-), 7.42-7.48 (m, 3H, arom.), 7.58 (s, 1H, NH), 7.85-7.98 (m, 4H, arom.), 9.25 (s, 1H, NH). $^{13}C$ NMR (63 MHz, DMSO-$d_6$): δ = 13.89, 17.81, 54.27, 59.13, 98.98, 124.52, 124.84, 125.56, 125.82, 126.20, 127.40, 127.76, 128.26, 132.27, 132.62, 143.20, 148.50, 152.02, 165.29. EIMS: *m/z* (%): 311 (19.5, M+1), 310 ($M^+$, 39.1), 309 (42.2), 280 (50.0), 264 (20.5), 237 (49.1), 183 (100.0), 155 (40.6), 127 (33.2), 110 (17.8), 67 (12.4).

**5-Benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2 (1H)-one (Table 2, Entry 16).** Yellow solid, m.p.: 173-178 °C. IR (KBr): 3406, 3220, 3105, 2912, 1681, 1654, 1620 $cm^{-1}$. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 2.47 (s, 3H, $CH_3$), 5.07 (s, 1H, CH-), 7.17-7.77 (m, 10H, arom.), 8.09 (s, 1H, NH), 9.15 (s, 1H, NH).$^{13}C$ NMR (63 MHz, DMSO-$d_6$): δ = 18.40, 55.15, 109.40, 126.08, 127.11, 128.40, 128.50, 128.66, 131.38, 140.96, 144.19, 145.29, 152.15, 194.26. EIMS: *m/z* (%): 292 ($M^+$, 0.1), 215 (73.7), 187 (51.5), 105 (66.2), 77 (100.0). Anal. Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%. Found: C, 73.78; H, 5.44; N, 9.32%.

**4-Phenyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (Table 2, Entry 17).** Pale-brown solid, m.p.: 226-228. IR (KBr): 3421, 2920, 1651, 1620 $cm^{-1}$. $^1H$ NMR (250 MHz, DMSO-$d_6$): δ = 1.89 (m. 2H, $-CH_2C\underline{H}_2CH_2$-), 2.27 (m, 2H, $-COC\underline{H}_2$-), 2.57 (m, 2H, -C=C-$C\underline{H}_2$-), 4.59 (s, 1H, CH-), 7.04-7.47 (m, 5H, arom.), 8.11 (s, 1H, NH), 9.46 (s, 1H, NH). $^{13}C$ NMR (63 MHz, DMSO-$d_6$): δ = 19.80, 26.38, 30.78, 36.33, 115.47, 126.06, 127.90, 128.32, 144.49, 164.78, 193.17. EIMS: *m/z* (%): 242 ($M^+$, 2.9), 216 (21.1), 91 (16.3), 71 (25.8), 55 (100.0). Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.42; H, 5.83; N, 11.56%. Found: C, 69.70; H, 6.12; N, 11.65%.

## RESULTS AND DISCUSSION

During preliminary studies, the condensation of 2-chlorobenzaldehyde, ethyl acetoacetate, and urea was utilized as the model for finding the optimization conditions (Scheme 1). We can observe that a trace of product (25%) could be

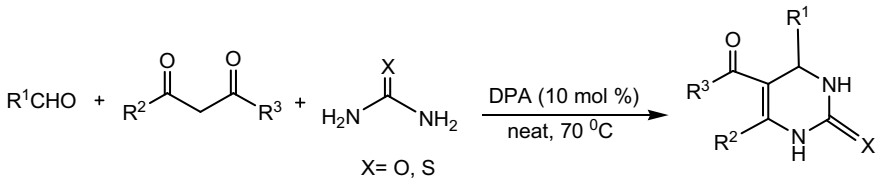



*Scheme 1*

**Table 1.** Optimization of Reaction Conditions in the Presence of DPA

| Entry | Solvent | Catalyst (mol%) | Temperature (ºC) | Time | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Solvent-free | - | 70 | 6 (h) | 25 |
| 2 | Solvent-free | 5 | 70 | 1 (h) | 80 |
| 3 | Solvent-free | 10 | 70 | 38 (min) | 85 |
| 4 | Solvent-free | 20 | 70 | 1 (h) | 85 |
| 5 | Solvent-free | 10 | R.T. | 2 (h) | N.R. |
| 6 | $H_2O$ | 10 | Reflux | 6 (h) | N.R. |
| 7 | $CH_3CN$ | 10 | Reflux | 6 (h) | 25 |
| 8 | Toluene | 10 | Reflux | 3 (h) | 53 |
| 9 | Ethanol | 10 | Reflux | 5 (h) | 40 |
| 10 | $CH_2Cl_2$ | 10 | Reflux | 3 (h) | 20 |

[a]Isolated Yield.




*Scheme 2*

detected when a mixture of aldehyde, 1,3-dicarbonyl compound and urea was heated at 70 ºC for 6 h in the absence of DPA (entry 1, Table 1). Then the reaction was investigated in different conditions. According to the data in Table 1, the best conversion was obtained by carrying out the reaction with 1:1:1.5 mole ratios of aldehyde, ethyl acetoacetate and urea respectively at 70 ºC in solvent-free conditions (entry 3, Table 1).

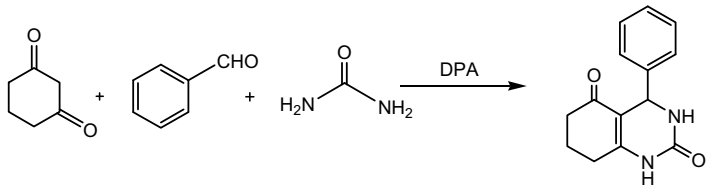
In order to study the generality of the procedure, a series of aromatic aldehydes with the electron-donating and electron-withdrawing substituents were reacted with ethyl acetoacetate and urea under the optimized conditions, according to Scheme 2, to provide the corresponding dihydropyrimidinones in high yields in 4-38 min (entries 1-8 and 13, Table 2). 3-Phenylpropanal, as an aliphatic aldehyde, and 3-phenylpropenal, as a α,β-unsaturated aldehyde, also obtained the desired product in high yields under the same conditions (entries 10 and 11, Table 2). Also heterocyclic aromatic compounds, such as 3-pyridinecarboxaldehyde, 2-thiophene-carboxaldehyde and 2-furancarboxaldehyde produced the corresponding dihydropyrimidinones in 47%, 91% and 96%, respectively when reacted with ethyl acetoacetate in the presence of urea and DPA (entries 9, 12 and 14, Table 2).

The reaction of other acyclic 1,3-dicarbonyl compounds

**Table 2.** DPA Catalyzed Synthesis of Dihydropyrimidinones under Solvent-Free Conditions

| Entry | $R^1$ | $R^2$ | $R^3$ | X | Yield (%)[a] | Time (min) | M.p. (°C) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | Reported |
| 1 | $C_6H_5$ | $CH_3$ | $OC_2H_5$ | O | 90 | 30 | 198-200 | 98-200[b] |
| 2 | 4-$ClC_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 85 | 33 | 207-210 | 211-213[b] |
| 3 | 2-$ClC_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 85 | 38 | 214 | 216-218[c] |
| 4 | 4-$NO_2C_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 93 | 4 | 200-203 | 205-207[c] |
| 5 | 3-$NO_2C_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 85 | 20 | 226-227 | 229-230[d] |
| 6 | 4-$(CH_3)_2CHC_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 83 | 22 | 196-197 | 196-197[b] |
| 7 | 4-$CH_3OC_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 92 | 19 | 199-201 | 201-203[e] |
| 8 | 2-$CH_3OC_6H_4$ | $CH_3$ | $OC_2H_5$ | O | 85 | 38 | 260 | 262[f] |
| 9 | 3-Pyridyl | $CH_3$ | $OC_2H_5$ | O | 47 | 27 | 205-207 | - |
| 10 | $PhCH_2CH_2$ | $CH_3$ | $OC_2H_5$ | O | 83 | 32 | 149-152 | - |
| 11 | Ph CH=CH | $CH_3$ | $OC_2H_5$ | O | 76 | 31 | 232 | 232-235[g] |
| 12 | 2-Thienyl | $CH_3$ | $OC_2H_5$ | O | 91 | 10 | 206-208 | 207-208[h] |
| 13 | 2-Furyl | $CH_3$ | $OC_2H_5$ | O | 96 | 20 | 200-201 | 201-203[i] |
| 14 | 2-Naphtyl | $CH_3$ | $OC_2H_5$ | O | 95 | 14 | 173-177 | - |
| 15 | $C_6H_5$ | $CH_3$ | $CH_3$ | O | 85 | 23 | 232 | 233-236[j] |
| 16 | $C_6H_5$ | $CH_3$ | $C_6H_5$ | O | 75 | 24 | 173-178 | - |
| 17 | $C_6H_5$ | -$CH_2CH_2CH_2$- | | O | 55 | 17 | 226-228 | - |
| 18 | $C_6H_5$ | $CH_3$ | $OC_2H_5$ | S | 88 | 28 | 208 | 208-210[k] |
| 19 | 4-$ClC_6H_4$ | $CH_3$ | $OC_2H_5$ | S | 82 | 37 | 178 | 180-182[l] |
| 20 | 4-$CH_3OC_6H_4$ | $CH_3$ | $OC_2H_5$ | S | 90 | 13 | 150 | 150-152[k] |

[a]Isolated Yield. [b]Ref. [15]. [c]Ref. [28]. [d]Ref. [29]. [e]Ref. [18]. [f]Ref. [30]. [g]Ref. [19]. [h]Ref. [31]. [i]Ref. [32]. [j]Ref. [33]. [k]Ref. [5]. [l]Ref. [34].




*Scheme 3*

such as acetylacetone and benzoylacetone was also run with benzaldehyde and urea in the presence of DPA and under solvent free conditions and the corresponding dihydropyrimidinones were obtained in high yields (entries 15 and 16, Table 2). The behaviour of 1,3-cyclohexadione as a cyclic 1,3-dicarbonyl compound, which had not been studied before in Biginelli condensation, was investigated by this protocol and the bicyclic product was prepared in moderate yield (Scheme 3, entry 17, Table 2).

The preparation of 2-thioxo-dihydropyrimidinones was also investigated by the same protocol. Benzaldehyde and its 4-chloro and 4-methoxy derivatives were treated with ethyl acetoacetate and thiourea in the presence of DPA at 70 °C under solvent free conditions and the related Biginelli products

**Table 3.** Comparison the Efficiency of Different Bronsted Acid Catalysts in Synthesis of 5-Ethoxycabonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-one

| Catalyst (10 mol%) | Time (min) | Temperature ($^{o}$C) | Yield (%) |
|---|---|---|---|
| DPA | 30 | 70 | 90 |
| Chloroacetic acid[a] | 180 | 90 | 92 |
| Acetic acid[a] | 180 | 90 | 80 |
| Phosphotungstic acid[a] | 180 | 90 | 87 |
| Phosphommolybdic acid[a] | 180 | 90 | 80 |
| Potassium hydrogen sulfate[a] | 180 | 90 | 78 |
| Trifluroacetic acid[a] | 180 | 90 | 72 |
| Bromoacetic acid[a] | 180 | 90 | 80 |
| Trichloroacetic acid[a] | 180 | 90 | 71 |
| *p*-Toluenesulfonic acid[a] | 180 | 90 | 88 |

[a]Ref. [15]

were obtained in high yields (entries 18-20, Table 2).

The data in Table 3 show that 5-ethoxycabonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-one (entry 1, Table 2) is formed in the presence of DPA in higher yield (except chloroacetic acid), faster and milder conditions than in the presence of other Bronsted acid catalysts.

In conclusion; we have developed an efficient procedure for one-pot synthesis of dihydropyrimidinones and its 2-thioxo counterparts under solvent-free conditions. This protocol offers several advantages including high yields, short reaction times, easy work-up, and use of cheap, relatively moderate acidic and safe catalyst.

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