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Polyphosphoric acid catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones by grinding under solvent-free conditions

Ying Zhao*, Yongguang Zhao, Jianping Zhang, Hongmei Liu & Liman Liang

College of Chemistry Engineering, Hebei Normal University of Science and Technology, Qinhuangdao 066004, Hebei Province, P. R. China

E-mail: zhaoyingsjz@163.com

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3,4-Dihydropyrimidin-2-(1*H*)-ones have been obtained, in high yield, by grinding ternary mixture of different substituted aromatic aldehydes, ethyl acetoacetate and urea, in the presence of polyphosphoric acid, under solventless conditions. The facile reaction condition, simple isolation and purification procedures of this method make it a good option for the synthesis of dihydropyrimidinones.

Keywords: 3,4-Dihydropyrimidin-2(1*H*)-ones, polyphosphoric acid, synthesis, solvent-free, grinding method

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) and their derivatives exhibit a wide range of therapeutical and pharmacological properties, such as calcium channel blockers, anti-hypertensive agents, anti-tumor, anti-bacterial, α-1a-antagonists and anti-inflammatory behaviors[1,2]. Many improved procedures for the preparation of DHPMs have been reported[3-10]. However, encouraged by the surge of catalytic processes and driven by economic factors, we focused our attention on the development of other alternative inexpensive reagents, low energy consumption, simple processing process and high yields. Grinding method for solid phase organic reaction is one of the important means. Compared with the traditional method, the reaction system of microenvironment is different from that in solution. Local high concentration can increase the reaction speed and improve the yield[11].

We report herein an efficient one-pot synthesis of these products from aryl aldehydes, under solventless conditions with grinding method at RT, using catalyst PPA (**Scheme I**).

Results and Discussion

3,4-Dihydro-2-pyridones were synthesized under solventless conditions from appropriate aryl aldehyde, ethylacetoacetate (methylacetoacetate) and urea in the presence of the catalyst PPA by grinding at RT. All the products were confirmed by melting points and spectral data. The results are summarized in **Table I**.

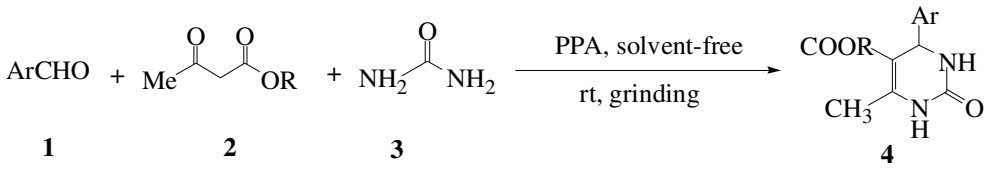
As summarized in **Table I**, aromatic aldehydes with either electron-donating or electron-withdrawing groups, ethyl acetoacetate or methyl acetoacetate and urea in the presence of PPA were reacted at room temperature by dringing, resulting in corresponding 3,4-dihydropyrimidin-2(1*H*)-ones in good to excellent yields.

A variety of reaction conditions were tested with benzaldehyde using PPA as catalyst. Firstly, it was found that different moles ratio of substrates have some effect on the reaction system. When the molore ratio of aldehyde, β-ketoester and urea is 1:1:1.5, the yield of corresponding DHPM is highest. Secondly, the influence of the amount of the catalyst on the reaction yield was studied. It was found that the presence of 0.1 mmol of PPA as a reaction mediator per mmol of reactions provided higher yields, higher amount of PPA did not improved the result to a great extent. The best results were achieved by carrying out the reaction under the optimized conditions: 1:1:1.5 ratios of aldehyde 1, β-ketoester 2, and urea 3 in a one-pot condensation employing refluxing ethanol as solvent in the presence of 0.1 equiv. PPA.

Experimental Section

All liquid reagents were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were measured on Bruker Avance 400 (400 MHz) spectrometer using TMS as internal standard and DMSO as solvent.

Procedure for the synthesis of 3,4-dihydro-pyrimidin-2(1*H*)-ones. A mixture of the aromatic aldehyde 1 (2 mmol), β-ketoesters and 2 (2 mmol) and urea 3 (3 mmol) and PPA (10 mol%) were grinded for 25-30 min at RT. The reaction procedure was monitored by TLC until the aldehyde disappeared. After that, DMF was added to dissolve the reaction mixture. Ice was then added to the filterate to obtain precipitation, which was then washed with cold water (2×5 mL) and 40% EtOH



Scheme I

Table I — Synthesis of 3,4-dihydropyrimidin-2-ones using PPA as catalyst

Entry	Ar	R	Time (min)	Yield[a] (%)	m.p.(°C)	
					Found	Reported
a	C_6H_5	C_2H_5	25	84	203~204	204~206 (Ref 8)
b	4-$CH_3OC_6H_4$	C_2H_5	25	88	200~202	201~203 (Ref 8)
c	4-HOC_6H_4	C_2H_5	25	93	227~228	227~228 (Ref 10)
d	3,4-(OCH_2O)-C_6H_3	C_2H_5	25	91	185~187	184~186 (Ref 8)
e	3-CH_3O-4-HO-C_6H_3	C_2H_5	25	90	228~230	229~233(Ref 10)
f	2-ClC_6H_4	C_2H_5	30	86	215~216	217~219 (Ref 8)
g	4-ClC_6H_4	C_2H_5	30	85	212~213	212~215 (Ref 8)
h	4-$O_2NC_6H_4$	C_2H_5	30	84	203~205	205~207 (Ref 8)
i	3-$O_2NC_6H_4$	C_2H_5	30	86	224~225	226~228 (Ref 8)
g	C_6H_5	CH_3	25	87	208~219	210~212 (Ref 8)
k	4-$CH_3OC_6H_4$	CH_3	25	89	195~196	195~197 (Ref 8)
l	4-HOC_6H_4	CH_3	25	91	234~236	235~236 (Ref 10)
m	3,4-(OCH_2O)C_6H_3	CH_3	25	90	246~248	245~247 (Ref 8)
n	3-CH_3O-4-HO-C_6H_3	CH_3	25	92	256~257	258~260 (Ref 10)
o	2-ClC_6H_4	CH_3	30	85	225~226	225~227 (Ref 8)
p	4-ClC_6H_4	CH_3	30	91	204~205	205~207 (Ref 8)
q	4-$O_2NC_6H_4$	CH_3	30	89	238~240	239~241 (Ref 8)
r	3-$O_2NC_6H_4$	CH_3	30	85	282~283	280~282 (Ref 8)

[a]Isolated yields

(3×5 mL). After drying and it was purified by recrystallization from the hot ethanol, pure products **4** were obtained. Spectral data of some products are given below:

Compound 4g: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H, NH), 7.85 (s, 1H, NH), 7.21-7.34 (m, 4H, ArH), 5.11 (s, 1H, CH), 3.57 (s, 3H, OCH_3), 2.21 (s, 3H, CH_3); IR (KBr): 3218, 3089, 1701, 1656 cm^{-1}.

Compound 4n: ^{1}H NMR (400 MHz, DMSO-d_6): δ: 9.15 (s, 1H, NH), 7.63 (s, 1H, NH), 6.62~6.81 (m, 3H, ArH), 5.89 (s, 2H, CH_2), 5.07 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); IR (KBr): 3246, 2985, 1705, 1647 cm^{-1}.

Compound 4o: ^{1}H NMR (400 MHz, DMSO-d_6): δ: 9.19 (s, 1H, NH), 7.69 (s, 1H, NH), 6.68~6.86 (m, 3H, ArH), 5.99 (s, 2H, CH_2), 5.07(s, 1H, CH), 3.56 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); IR (KBr): 3234, 2961, 1700, 1648 cm^{-1}.

Compound 4q: ^{1}HNMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1H, NH), 8.20 (d, J = 8.4 Hz, 2H, ArH), 7.93 (s, 1H, NH), 7.50 (d, J = 8.4 Hz, 2H, ArH), 5.28 (s, 1H, CH), 3.53 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3). IR (KBr): 3233, 3113, 1703, 1643 cm^{-1}.

Conclusions

PPA catalyst provides an efficient and much improved modification of Biginelli reaction. The yields of the one-pot Biginelli reatcion increased to 84-93%. This improved modification of Biginelli reaction is a simple, timesaving and high yielding process.

References

1 Rovnyak G C, Kimball S D, Beyer B, Cucinotta G, DiMarco J D, Gougoutas J, Hedberg A, Malley M, McCarthy J P, Zhang R & Moreland S, *J Med Chem*, 38, **1995**, 119.

2 Atwal K S, Rovnyak G C & Kimball S D, *J Med Chem*, 33, **1990**, 2629.

3 Jin T S, Wang H X, Xing C Y, Li X L & Li T S, *Synth Commun*, 34, **2004**, 3009.
4 Lu J, Wang F L, Bai Y J & Li W H, *Chin J Org Chem*, 22, **2002**, 788 (in Chinese).
5 Yadav J S, Reddy B V S, Srinivas R, Venugopal C & Ramalingam T, *Synthesis*, **2001**, 1341.
6 Wang C, Zhang Y Q, Li G S, Li J C & Li X L, *Chin J Org Chem*, 23, **2003**, 1416 (in Chinese).
7 Peng J J & Deng Y Q, *Chin J Org Chem*, 22, **2002**, 71 (in Chinese).
8 Jin T S, Zhao Y, Liu L B & Li T S, *Indian E-Journal of Chemistry*, 2, **2005**, 288.
9 Cepanec I, Mladen L, Filipan L M & Grungold I, *Tetrahedron*, 63, **2007**, 11822.
10 Jin T S, Zhao Y, Liu L B & Li T S, *Chin J Org Chem*, 26, **2006**, 975 (in Chinese).
11 Geng L J, Li J T & Wang S X, *Chin J Org Chem*, 25, **2005**, 608 (in Chinese).