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Phytic acid: a biogenic organocatalyst for one-pot Biginelli reactions to 3,4-dihydropyrimidin-2(1H)-ones/thiones

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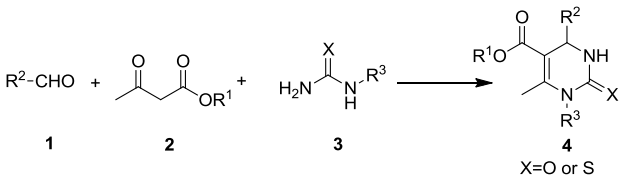
Natural organocatalyst phytic acid catalyzed one-pot Biginelli reactions by coupling of β-ketoesters, aldehydes, and (thio)ureas to afford 3,4-dihydropyrimidin-2(1H)-ones/thiones. This phytic acid catalysis featured with good to excellent isolated yields, solvent-free conditions, simple workup, environmental friendliness, and short reaction time

Introduction

Multicomponent reactions (MCRs) [1] are versatile and efficient in preparing complex biologically active compounds [2] from readily accessible starting materials. The Biginelli reaction, [3] one of the most useful MCRs, was allowed to access to 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (DHPMs) **4** by cyclocondensation of aldehydes **1**, β-ketoester **2**, and (thio)urea **3** in one-pot (Scheme 1). Interest in Biginelli reactions stemed from the step economy of the synthesis, the diversity of the products, and the broad spectrum of the pharmacological activities of DHPMs (Figure 1). For example, Monastrol is able to cross cell membrane as a potent anticancer drug; [4] adducts SQ 32926 and SWO2 can act as antihypertensive agents. [5] In addition, several alkaloids isolated from marine sources containing dihydropyrimidine core exhibited promising biological properties. [6]



Scheme 1 The Biginelli reactions

Based on the original HCl ethanol solution protocol, [3a] many kinds of Lewis acids [7] and several kinds of basic catalysts [8] had been described. In the view points of green chemistry, [9] however, some drawbacks existed in these methods, for instance, volatile organic solvents, heavy metals, unusual chemicals, and harsh or sensitive reaction conditions were employed. Consequently, measures were made to address these issues, for example, by using readily separable and recyclable catalysts such as polyvinylsulfonic acid, [10] hydrotalcite [11] and solid acids, [12] in developing alternative reaction conditions in ionic liquids, [13] by microwave or ultrasonic assistances, [14] and in eutectic mixtures [15] .

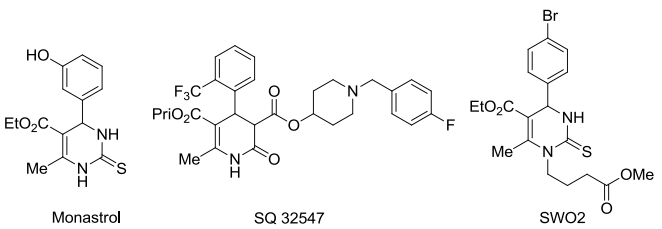


Figure.1 Pharmacologically active DHPMs

New vitality is infused into the classical Biginelli reactions as demonstrated by the application of natural sourced catalysts vitamin B1, [16] tartaric acid, citric acid, [17] bovine serum albumin, [18] and even baker's yeast. [19] Weak carboxylic acids, [20] and moderate phosphoric acid [21] as mild Brønsted acidic organocatalysts [22] attracted our attention. We envisioned a plant origin ubiquitous phosphoric acid – phytic acid (PhyA), will be useful as potential catalyst in organic transformations.

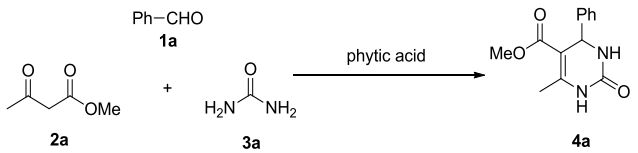
PhyA (myo-inositol hexaphosphate) (Figure 2) is a major form of phosphorus reservoir in plants. [23] It is widely used as chelating agents, food additives, and antioxidants. [24] To the best of our knowledge, no report on PhyA in catalysis was appeared. We probed PhyA as organocatalyst in Biginelli reactions in expectation of the advantages in: (1) naturally abundance, (2)

eco-friendliness, and (3) air, water, and substrate tolerance. Here we reported the the first application of PhyA as a catalyst examplified by Biginelli condensations to 3,4-dihydropyrimidin-2(1H)-ones/thiones in one-pot under solvent-free conditions.

Results and discussion

We initially explored the catalytic effect of PhyA under classical conditions on Biginelli reaction with benzaldehyde, urea, and acetoacetate as substrates to produce DHPM **4a**. Encouraged by the primary result (entry 1, Table 1), solvents and solvent-free reactions were tested. Entries 1 to 4 showed ethanol was an appropriate solvent, which performed better than toluene, dichloromethane, and tap water. Since aldehyde and urea are required in the first step to produce intermediate **5** (Scheme 2), [25c] extremities of non-polar toluene or polar water did not favor interactions between the two. Solvent-free procedure resulted very good yield (entry 5). The loading of the catalyst (entries 5 to 9) was optimal at 10 mol%, increasing PhyA to 15 % and 30 % did not improve yields, and 5 % catalyst received moderate one at the designated reaction time (entry 6).

Table 1: Reaction of benzaldehyde, methyl acetoacetate, and urea under catalysis of phytic acid [a]

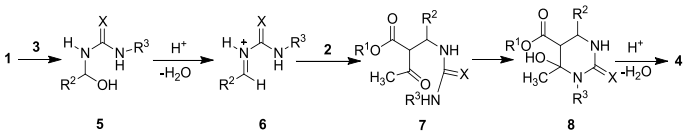


Entry	Solvent	Time (h)	Catalyst loading (mol %)	Yield (%)
1	EtOH [b]	3.5	10	61
2	Toluene [c]	3	10	46
3	CH_2Cl_2 [d]	4.5	10	54
4	H_2O [e]	2	10	40
5	none [f]	1/3	10	81
6	none [f]	1/3	5	51
7	none [f]	1/3	15	82
8	none [f]	1/3	20	80
9	none [f]	1/3	30	79

[a] All the yields are isolated yield, and the molar ratio of benzaldehyde, methyl acetoacetate, and urea is 1:1.2:1.5.
[b] Reaction at 78 ℃. [c] Reaction at 110 ℃. [d] Reaction at 60 ℃. [e] Reaction at 100 ℃. [f] Reaction at 100 ℃.

Next we expanded scopes of the substrates by using methyl/ethyl acetoacetate, a series of substituted benazaldehydes and butylaldehyde, urea/thoiurea, and methyl(thio)urea in combinations under solvent-free condition (Table 2). Condensations of aldehydes, acetoacetates, and ureas produced the corresponding DHPMs (**4a** to **4v**) by good to excellent yields, but aliphatic aldehyde were moderate (**4h** and **4p**). The yields were also good when methylurea was used instead of urea (**4q** to **4u**). Thioureas, as expected, gave similar yields as compared with their counterpart ureas (**4v** to **4d'**). Substitutions on the benzene ring of aromatic aldehydes **1** showed regular influence on the condensations (Table 2). Aromatic aldehydes with electron-donating groups afforded higher yields (e.g. **4b** and **4c**) than those with electron-withdrawing groups (e.g. **4e** and **4m**). Chlorine as activating group by electron-donating conjugative effect resulted yields around 80% (e.g. **4d**, **4r**, and **4y**).

In order to test the limit and expand the scope of phytic acid catalysis in Biginelli-type reactions, we used 1,3-diketones in place of β-ketoesters. As expected, the yields were good to excellent (Table 3) within short time.



Scheme 2 The iminium mechanism of Biginelli reactions

The mechanism of Biginelli reactions was investigated in the last eight decades. [25] Three hypotheses including (1) iminium mechanism, [25c] (2) Knovenagel mechanism, [25b] and (3) enamine mechanism [25d] were widely accepted in Brønsted acid catalysis. The iminium mechanism has been demonstrated to be kinetically and thermodynamically favorable by ESI(+)-MS(/MS) characterization and DTF calculations. [25d]

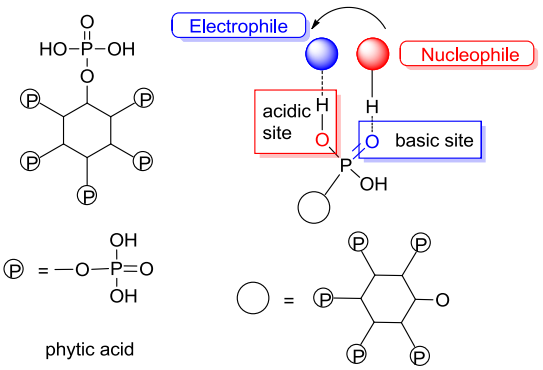


Figure.2 The structure of phytic acid and the Brønsted acidic /Lewis basic pair within one phosphate group

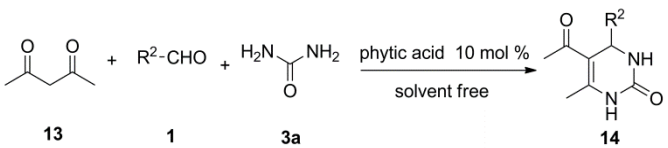
The phosphoric acid catalyst PhyA was able to function as ordinary Brønsted acid to catalyze Biginelli reascions through iminium mechanism [25c] (Scheme 2). Phosphoric acid, however, in a sense, was particular for the structure of phosphoric acid exhibited mild Brønsted acidity in –OH group and typical Brønsted/Lewis basic site in P=O group together (Figure 2). [22] In addition, phosphoric acids acted as bifunctional catalysts *via* both their acidic site –OH and basic P=O moiety had been exploited and substantiated theoretically recently. [22a, 27] The acidic site in –OH and basic site in P=O of phosphate group showed cooperative effect on both nucleopile and electrophile as substrates in one reaction. [22a,27]

Table 2: Phatic acid catalysis in Biginelli reactions to 3,4-dihydropyrimidin-2-(1*H*)-ones [a]

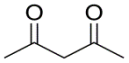
Product	R^1	R^2	R^3	X	Time (h)	Yields (%)	Yields(%) lit [b]	Mp (℃)
4a	Me	-C_6H_5	H	O	0.3	81	--	213.4-215.4
4b	Me	4-(OH)-C_6H_4	H	O	2	86	--	251.0-252.5
4c	Me	4-(OCH_3)-C_6H_4	H	O	4	89	--	199.9-200.3
4d	Me	4-(Cl)-C_6H_4	H	O	4	81	--	209.6-210.0
4e	Me	4-(NO_2)-C_6H_4	H	O	6	66	--	246.1-246.7
4f	Me	3-(Cl)-C_6H_4	H	O	4.5	53	--	249.1-250.7
4g	Me	3-(NO_2)-C_6H_4	H	O	4	68	--	284.6-258.4
4h	Me	n-Bu	H	O	10	57	--	168.1-168.6
4i	Et	-C_6H_5	H	O	3	89	70 [8b], 85 [12b]	209.9-212.0
4j	Et	4-(OH)-C_6H_4	H	O	3	86	55 [8b], 78 [12b]	238.7-239.2
4k	Et	4-(OCH_3)C_6H_4	H	O	3	81	58 [8b], 86 [12b]	207.9-209.0
4l	Et	4-(Cl)-C_6H_4	H	O	3.5	86	85 [12b]	216.7-217.0
4m	Et	4-(NO_2)-C_6H_4	H	O	7	66	91 [12b]	215.5-216.1
4n	Et	3-(Cl)-C_6H_4	H	O	4.5	76	--	199.9-201.0
4o	Et	3-(NO_2)-C_6H_4	H	O	6	64	78 [12b]	233.5-234.1
4p	Et	n-Bu	H	O	11	56	--	175.6-178.2
4q	Me	-C_6H_5	-CH_3	O	0.5	96	--	196.8-197.0
4r	Me	4-(Cl)-C_6H_4	-CH_3	O	2	81	--	142.6-143.4
4s	Me	3-(NO_2)-C_6H_4	-CH_3	O	8	60	--	209.4-209.8
4t	Et	-C_6H_5	-CH_3	O	0.6	94	--	179.8-181.1
4u	Et	4-(OCH_3)-C_6H_4	-CH_3	O	4.5	85	--	139.2-139.7
4v	Me	-C_6H_5	H	S	0.6	85	--	226.4-227.5
4w	Et	-C_6H_5	H	S	0.6	94	50 [8b], 67 [12b]	204.6-207.7
4x	Et	4-(OCH_3)-C_6H_4	H	S	3	80	87 [31]	152.7-154.4
4y	Et	4-(Cl)-C_6H_4	H	S	3	78	89 [31]	192.0-194.0
4z	Me	-C_6H_5	-CH_3	S	3.5	87	--	163.7-164.6
4a'	Me	4-(OCH_3)-C_6H_4	-CH_3	S	3	85	--	157.2-158.2
4b'	Me	3-(Cl)-C_6H_4	-CH_3	S	3	77	--	144.2-151.5
4c'	Et	-C_6H_5	-CH_3	S	1.5	85	--	150.3-151.3
4d'	Et	4-(OCH_3)-C_6H_4	-CH_3	S	2.5	83	--	87.9-90.0

[a] Reaction at 100 °C; all the yields are isolated ones; the molar ratio of β-ketoesters, aldehydes, and (thio)ureas is 1.2:1:1.5, the catalyst loading is 10 mol %.
[b] Some yields of DHPMs under solvent-free condition in some literatures.

Table 3: Reaction of aldehydes, 1,3-diketone compounds, and urea [a]



13 1 3a 14

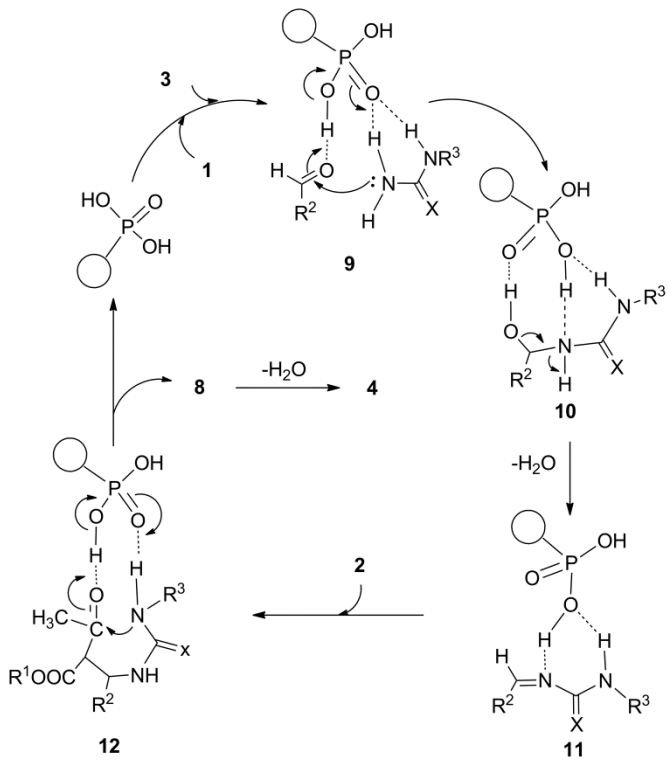
Product	R^2	1,3-diketone	Time (h)	Yield (%)	Mp (℃)
14a	-C_6H_5		2/3	65	242.3-243.0
14b	4-(OH)-C_6H_4		1	89	261.4-261.6

[a] Reaction at 100 ℃; all the yields are isolated ones; the molar ratio of 1,3-diketone, aldehydes, and urea is 1.2:1:1.5.

Phytic acid possessed six phosphate groups. [26] Each phosphate group contained two hydroxyl group and one phosporyl group. According to the bifunctional behavior of phosphoric acids [22, 27] and on the basis of iminium mechanism [25c] in principle, we proposed that phytic acid could catalyze Biginelli reactions through a bifunctional activation mode. The plausible steps were shown in scheme 3. Initially, interactions as in **9** were formed probable through hydrogen bonding (HB) in which the the acidic –OH of PhyA paired with carbonyl of aldehyde **1**, and –NH of urea **3** paired with the basic P=O. [22a, 27] Subsequently, the urea nitrogen attacked carbonyl, and the intermediate of type **10** was formed. [22b, 27] The intermediate state **11** might be formed after releasing one molecule of water from **10**. Then the transition state **12** might be stabilized under the HB of phytic acid. Finally, cyclization to **8** and elimination off another molecule of water yielded the target product **4**.

The existence of hydrogen bonding could be detected by various methods such as IR spectrum, [28] electron spectrum, [29]

and NMR. [30] In order to investigate the proposed mechanism, the NMR studies were carried out. Here, our main aim was to evaluate the possibility of the first step interactions as in **9**. The results of NMR detection were shown in Figure 3 and Figure 4. In the ^{1}H NMR spectrum of the original urea in D_2O, the signal of the protons of urea was at 4.70 ppm. When PhyA was added, the urea protons gave a wider peak and the peak slight shifted toward low field (PhyA/urea = 0.4/1, 4.76 ppm; PhyA/urea = 0.6/1, 4.78 ppm). This phenomenon may indicate the P=O of PhyA affected the protons of –NH–, and the effect might be caused by the hydrogen bonding between PhyA and urea. [30] Next, the effect of PhyA on benzaldehyde was examined. The chemical shift of the proton of –CHO was not very obvious because the solubility of PhyA in $CDCl_3$ was poor. But when the PhyA was added, the width of the proton peak of –CHO was increased, which might be caused by the hydrogen bonding between the –OH of PhyA and the oxgen of –CHO (Figure 4). These phenomenons suggested that the three interactions as in **9** could be formed possibly. Morover, these results may demonstrate the H-bond interactions between the substrates and catalyst in the proposed bifunctional activation mode. On the basis of the bifunctional catalysis behavior of phosphoric acid in activation of carbonyl [27] and the results of NMR investigation, the bifunctional activation mode may be suggested.



Scheme 3 A plausible mechanism of Biginelli under phytic acid catalysis in bifunctional activation mode

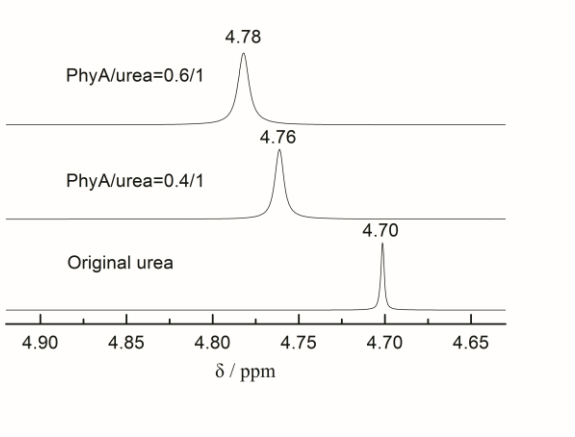


Figure.3 Chemical shifts of urea protons in the ^{1}H NMR spectrum observed by different ratio of urea and PhyA in D_2O

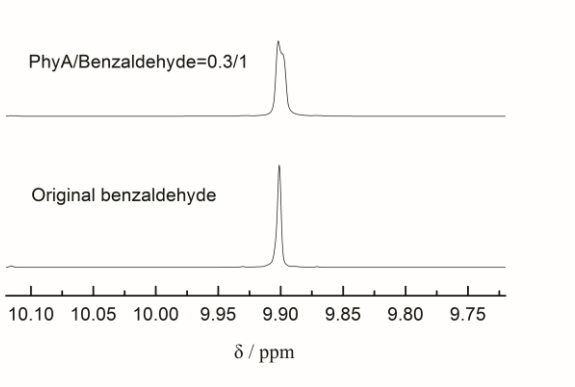


Figure.4 Chemical shifts of the protons of –CHO on benzaldehyde in the ^{1}H NMR spectrum observed by different ratio of benzaldehyde and PhyA in $CDCl_3$

Conclusions

In summary, we demonstrated phytic acid as a natural phosphoric acid in organocatalysis examplified in Biginelli reactions under solvent-free condition. Compared with other catalysts under solvent-free condition, [8b, 12b, 31] the scope of PhyA was wide and yields were similar. A plausible Brønsted acidic bifunctional activation mode by the acidic site (–OH) and basic site (P=O) of phytic acid in the condensations was proposed. Moreover, the preparation featured with good to excellent isolated yields, solvent-free conditions, simple workup, environmental friendliness, and short reaction time.

Experimental

Melting points were determined on a Kofler hot stage. ^{1}H and ^{13}C NMR spectra were recorded in DMSO or $CDCl_3$ solutions. The ^{1}H NMR spetral measurements were performed at 300 MHz and ^{13}C NMR were at 75 MHz.

General procedure for the synthesis of DHPMs

Aldehyde (3 mmol), β-ketoesters or 1,3-diketones compounds (3.6 mmol), ureas or thioureas (4.5 mmol), phytic acid (0.3 mmol, 10 mol %) in solvent-free condition were heated at 100 ℃ under stirring for the time as show in Table 3. After completion of the reaction determined by TLC, the mixture was

cooled to room temperature and ethonal (10 mL) was added (the unreacted substrates and PhyA will dissolve in ethanol and the product will separate crystals out). The resultant solid was separeted from the mixture by filtration and the collected solid was rinsed with ethanol (3 × 10 mL) and water (3 × 10 mL), then dried in vacuum at 40 ℃ to afford the desired product as a crystalline solid.

Notes and references

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†. Electronic Supplementary Information (ESI) available: [Characterization date (^{1}H, ^{13}C) for the 3,4-dihydropyrimidin-2(1*H*)-ones/thiones]. See DOI: 10.1039/b000000x/

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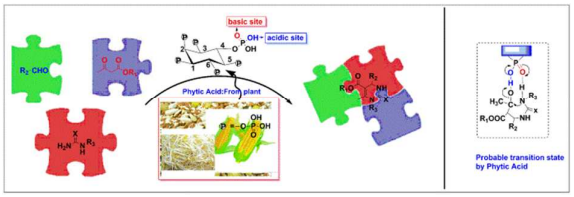

The novelty of the work: PhyA as a biogenic organocatalyst for Biginelli reactions under solvent-free conditions with good yields and by a plausible bifunctional mechanism.