



## Synthesis of Biginelli adducts using a Preyssler heteropolyacid in silica matrix from biomass building block

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### ABSTRACT

An efficient, suitable and high yielding method has been developed employing the use of the renewable platform molecule furfural for the synthesis of Biginelli derivatives via a three-component domino reaction through a combination of aldehydes (furfural),  $\beta$ -ketoesters, and urea or thiourea using Preyssler heteropolyacid  $H_{14}NaP_5W_{29}MoO_{110}$  encapsulated in a silica framework as the catalyst. The reaction was carried out under solvent-free conditions, affording very good yields using thermal and microwave heating. Atom economy, an environmentally benign procedure, reuse of catalysts, and short reaction time are some of the important features of this protocol. The Preyssler catalyst embedded in the silica matrix is insoluble in polar and apolar media, which allows easy removal of the reaction products without affecting its catalytic activity.

### 1. Introduction

The Biginelli reaction is a three-component reaction to obtain dihydropyrimidinones (DHPMs) (Bose et al., 2005a, 2005b). This method is an example of a multicomponent reaction (MCR). These reactions are convergent, three or more starting compounds are combined to yield a single product, and basically all or most of the atoms are included in the product structure. Environmentally, the MCRs are effective by themselves, since they offer significant advantages in comparison to the linear synthesis that generally involves more than one step and successive purification processes. Among the virtues of the MCR are speeds, atom economy (close to 100%) (Nair, 2005), a single-step procedure and the consequent decrease in the purification steps. On the other hand, the solvent-free reactions ensure a simpler process free of hazardous solvent waste and low toxicity levels from VOC (Lubineau and Augé, 1999; Gawande et al., 2014).

The reaction involved a  $\beta$ -ketoester, an arylaldehyde and a urea or thiourea derivative (Vdovina et al., 2008). The process was originally catalyzed by mineral acids (Biginelli, 1891), using protic solvents such as ethanol, methanol (Lin et al., 2000) and water (Bose et al., 2005a,

2005b), and aprotic solvents such as tetrahydrofuran (Ranu et al., 2000), dioxane (Quan et al., 2009) or acetonitrile (Fazaeli et al., 2006); an acetic acid medium was needed in some cases (Jauk et al., 2000). Various building blocks were used in the reaction, including different types of esters and 3-oxoalkanoic thioesters, such as chloro- and fluoroacetates, benzoyl acetic esters and tertiary acetamides, mono-substituted alkyl ureas, protected thioureas and guanidines (Nair, 2005; Kappe et al., 2004). In the case of aldehydes, the reaction works with aromatic substituted aldehydes with electron-withdrawing or electron-donating groups (Nadaraj et al., 2013). Aliphatic aldehydes react with difficulty (Yu et al., 2007), while heterocyclic aldehydes derived from furan, thiophene and pyridine afford DHPMs with acceptable yields (Nair, 2005).

Due to the increasing demand for bio-renewable resources as an alternative feedstock for the production of bulk chemicals, furfural and 5-hydroxymethylfurfural (HMF) have gained considerable attention. For example, HMF acts as a bridging molecule linking biomass to fields and chemicals and is also useful for dimethylfuran and other important compounds (Zeitsch, 2001). However, there are few reports on the use of these compounds as building blocks in organic synthesis of low

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environmental impact (Hoydonckx et al., 2012). Furfural is universally obtained from biomass (Rosatella et al., 2011), a standard way to take advantage of and give added value to agricultural and forest residues. The process is simple; pentosans are obtained from these residues. By acid hydrolysis and the cyclodehydration of the formed monosaccharides aldehyde is obtained. A wide variety of compounds of industrial interest can be obtained from furfural, such as furfuryl alcohol and its tetrahydro derivative, furfurylamine, furoic acid and furanacrylic acid, furan and tetrahydrofuran (Subbiah et al., 2013). It can also be used as a starting material for the synthesis of DHPMs (Joseph et al., 2006). These compounds have a pyrimidine core, an important pharmacophore in medicinal chemistry. The 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines (3,4-dihydropyrimidine-2 (1H) -thiones) are attractive compounds since they have a wide range of biological activities as antibacterial, anti-inflammatory, antiviral agents and as modulators of calcium channels (Qu et al., 2013).

A number of synthetic procedures for preparing 3,4-dihydropyrimidin-2-(1H)-ones and thiones (Kadre et al., 2012) involve catalysis by protic acids such as concentrated  $H_2SO_4$  (Bussolari et al., 2000) and HCl (Atwal et al., 1987), and a variety of Lewis acids such as  $InBr_3$  (Fu et al., 2002),  $Yb(OTf)_3$  (Ma et al., 2000),  $Cu(OTf)_3$  (Paraskar et al., 2003),  $ZrCl_4$  (Reddy et al., 2002),  $Mn(OAc)_3$  (Ananda Kumar et al., 2001), ceric ammonium nitrate (CAN) (Yadav et al., 2001) and some ionic liquids (Heidarizadeh et al., 2013). Chemically, the heteropolyacids are remarkable molecular clusters for their structural diversity, their acidic strength and electronic properties. These compounds are complex protonic acids that incorporate polyoxometallic anions (heteropolyanions) with metal-oxygen octahedrons as basic structural units. The  $[NaP_5W_{30}O_{110}]^{14-}$  (sodium 30-tungsto pentaphosphate (V)), known as Preyssler anion, is a large structure that encrypts a  $Na^+$  cation monohydrate in its central cavity. The cavity is formed by five  $PW_6O_{22}$  units derived from the Keggin anion ( $[PW_{12}O_{40}]^{3-}$ ) that have been modified by the elimination of two sets of three  $WO_6$  octahedra from the shared corners. In the solid state, the anion behaves like a pure Bronsted acid, being a stronger acid than conventional solid acids such as  $SiO_2-Al_2O_3$  and the HX and HY zeolites (Bamoharram et al., 2006). The inclusion of a heteropolyacid in the structure of  $SiO_2$  modulates its acidity and makes it more selective (Sathicq et al., 2014).

In this work we report a simple, convenient, efficient, and suitable process for the preparation of Biginelli adduct from a biomass building block. The reactions were performed under solvent-free condition using furfural derivatives, ethyl or methyl acetoacetate and urea or thiourea using Preyssler heteropolyacids encapsulated in silica frameworks (PCSiO<sub>2</sub>) as a solid catalyst. The present methodology has been carried out using conventional heating or microwave irradiation.

## 2. Experimental

### 2.1. General procedure for synthesis of Preyssler acid, $H_{14}[NaP_5W_{29}MoO_{110}]$ , (PA)

Potassium salt of Preyssler anion was prepared by dissolving 23.0 g of  $Na_2WO_4 \cdot 2H_2O$  (0.13 mol) and 2.0 g of  $Na_2MoO_4 \cdot 2H_2O$  (0.01 mol) in 20 mL of hot distilled water with constant agitation; the solution was kept under reflux. Then 27 mL of  $H_3PO_4$ , 85% (0.02 mol) was added by dripping; the resulting solution was kept at reflux for 24 h. Afterwards, 1 mL of concentrated nitric acid was added to the mixture, followed by 10 g of KCl (0.13 mol) with constant stirring. The suspension obtained was centrifuged for 15 min, and the solid was dissolved in 50 mL of hot distilled water and kept cooling (4 °C approx.) overnight. The precipitate obtained ( $K_{14}[NaP_5W_{29}MoO_{110}]$ ) was filtered and dried under vacuum at room temperature. The Preyssler acid was obtained from the potassium salt; a 10% solution of the salt was eluted through a bed of previously activated Dowex® 50WX8 hydrogen form. The exchanged solution was then dried by forced evaporation under an air column (Jeannin et al., 2007; Bamoharram et al., 2006).

### 2.2. Inclusion of Preyssler acid in silica matrix, $H_{14}NaP_5W_{29}MoO_{110}@SiO_2$ (PASI)

The catalyst was synthesized by the sol-gel technique following methodologies already reported by our laboratory (Sathicq et al., 2014).

### 2.3. General procedure for dihydropyrimidinone synthesis

#### 2.3.1. A method

A mixture of ethyl acetoacetate (130 mg, 1 mmol), furfural (96 mg, 1 mmol), urea (90 mg, 1.2 mmol) and PASi (100 mg, 0.2% mmol active phase) was heated with constant stirring at 80 °C for 4 h (verified by TLC). After cooling, the reaction mixture was dissolved in acetone (3 × 5 mL) and the catalyst was removed by centrifugation. The acetone was removed by evaporation and the crude product was dissolved in the indicated solvent for crystallization of the compound. All dihydropyrimidinones obtained were filtered and dried under vacuum.

#### 2.3.2. B method

A mixture of methyl acetoacetate (116 mg, 1 mmol), 2-furaldehyde (96 mg, 1 mmol), urea (60 mg, 1 mmol), and PASi (100 mg, 1% mmol) was strongly mixed, and the mixture was heated on MW at 120 °C for 15 min (to completion of the reaction, TLC). The same method as that of the purification of the compounds in the A method was used for the crude mixture.

## 3. Results and discussion

In this work we report a solvent-free system to obtain different DHPMs from substituted furfurals in the presence of PASi. The catalyst is easy to make, cheap, easy to recover and reusable.

### 3.1. Effect of solvents and catalyst

When the test reaction (furfural, methyl acetoacetate and urea) was carried out without catalyst (Table 1, entry 1), the product of interest was not detected, but the prolonged heating of the mixture darkened the crude, which is related to the decomposition of furfural and reactions involving atmospheric oxygen (Zeitsch et al., 2001). As another preliminary test, the test reaction was carried out using the active phase (PA) as catalyst (Table 1, entry 0), which produced secondary reactions and a low yield of DHPMs (< 20%). The inclusion of solvents such as ethanol or 2-methyltetrahydrofuran (2-MeTHF) had the same effect (Table 1, entries 4–9). However, the use of the support ( $SiO_2$ ) yielded 40% of the compound but up to six hours of reaction were needed (Table 1, entry 3). When the catalyst PASi was included in the reaction, the reaction was selectively directed towards the formation of DHPMs but the effect of the solvents was the same (Table 1, entries 2, 5, 8).

In previous work of our group (Sathicq et al., 2014), it was demonstrated that the catalyst with the active phase included in the silica framework is more selective than the Preyssler acid (both catalysts are insoluble in the reaction media and acetone, ensuring that there is no leaching into the media or in the separation process). The effect of the variation in the acid strength of the catalyst on the reaction is clear, the potentiometric titration with *n*-butylamine shows that the acid strength of PA is higher ( $E_i = 796$  mV) than that of PASi (100 mg, 0.2% mmol active phase,  $E_i = 309$  mV).

### 3.2. Effect of temperature and reaction times

The test reaction was optimized using PASi as a catalyst. First, the effect of temperature (Table 2) on the process was studied using 100 mg of catalyst, testing five temperatures (40, 60, 80, 100 and 120 °C) for 4 h; the increase in temperature produces an increase in the yields of the isolated DHPMs. However, at higher temperatures (100 and 120 °C)

**Table 1**  
Effect of solvents and catalyst on the yield of Biginelli reactions.<sup>a</sup>

Entry	Catalyst	Solvent	t (h) <sup>b</sup>	Yield (%)
0	PA	free	10	<20 <sup>c</sup>
1	----	free	10	0
2	PASi	free	4	82
3	Support	free	8	50
4	----	2-MeTHF	10	0
5	PASi	2-MeTHF	10	10
6	Support	2-MeTHF	10	30
7	----	Ethanol	10	0
8	PASi	Ethanol	10	0
9	Support	Ethanol	10	0

<sup>a</sup> Reagents and conditions: Furfural (1.0 mmol); methylacetoacetate (1.0 mmol); urea (1.2 mmol); catalyst, 100 mg (PA:  $H_{14}NaP_3W_{29}MoO_{110}$ ; PASi:  $H_{14}NaP_3W_{29}MoO_{110}(15\%)@SiO_2$ ; Support:  $SiO_2$ ); <sup>b</sup> Monitored by TLC (Ethyl acetate: petroleum ether); <sup>c</sup> for 4 hours of reaction.

**Table 2**  
Effect of temperature and reaction times on product yields (%).<sup>a</sup>

Entry	Temperature (°C)	Time (h)	Yield (%)
1	40	4	-
2	60	4	25
3	80	4	82
4	100	4	32
5	120	4	<5
6	80	0.5	45
7	80	2	77
8	80	6	80

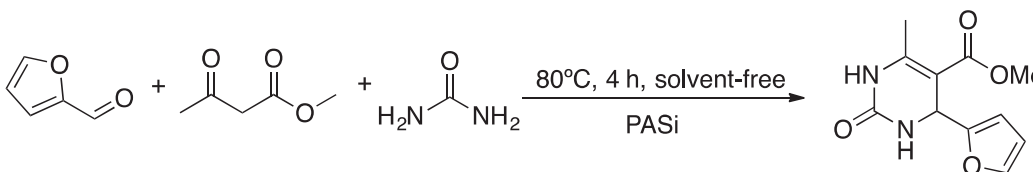
<sup>a</sup> Reagents and conditions: Furfural (1.0 mmol); methylacetoacetate (1.0 mmol); urea (1.2 mmol); 100 mg PASi.

**Table 3**  
Effect of molar ratio of reactants on product yields (%).

Entry	F/A/U (mmol)	Yield (%)
1	1:1:1	70
2	1:1:1.1	75
3	1:1:1.2	83
4	1:1:1.3	82
5	1:1:1.5	78

<sup>a</sup> Reagents and conditions: Furfural (1.0 mmol); methylacetoacetate (1.0 mmol); urea (1.2 mmol); catalyst, 100 mg PASi.

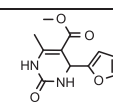
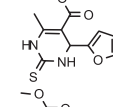
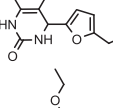
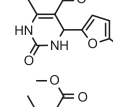
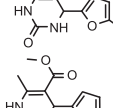
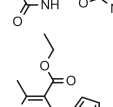
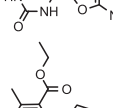
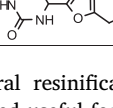
**Table 4**  
Effect of catalyst amount on product yields (%).



Entry	Catalyst amount (%)	Yield (%)
1	5	52
2	15	53
3	30	82
4	60	81

<sup>a</sup>Reagents and conditions: Furfural (1.0 mmol); methylacetoacetate (1.0 mmol); urea (1.2 mmol)

**Table 5**  
Synthesis of dihydropyrimidinones (thiones) from biomass derived from furfural; comparison of yields and green metrics (Atom economy (AE); Process mass intensity (PMI); Turn over frequency (TOF); [Supplementary material](#) indicates how each parameter was calculated) for the A method (T) and B method (MW).

Entry	Compound	AE%	Yield %		PMI		TOF	
			A	B	A	B	A	B
1		87	82	50	2.011	3.344	0.465	4.322
2		88	85	57	1.885	2.867	0.533	5.503
3		88	93	60	1.828	2.657	0.562	6.384
4		88	50	43	3.143	3.676	0.329	4.391
5		87	85	45	1.900	3.548	0.508	4.500
6		89	95	65	1.741	2.399	0.632	6.991
7		89	90	68	1.809	2.275	0.627	7.513
8		89	85	45	1.921	3.439	0.595	5.015

secondary reactions such as furfural resinification predominate, so these temperatures are not considered useful for the reaction.

In the case of the reaction time, the yields show that under the same conditions, the yields of DHPMs increase when the reaction is extended up to 4 h, after which it remains constant (Table 2 entries 3 and 8).

### 3.3. Effect of molar ratio

Moreover, the mechanism of the Biginelli reaction has been extensively studied, particularly the reaction between benzaldehyde, ethylacetoacetate and urea, and it has been established that the

determining step for the process is the condensation reaction between benzaldehyde and urea to produce N-(1-hydroxybenzyl)-ureas that end up cyclizing to form the DHPMs (Kappe, 1997). Assuming that the behavior of the reaction using furfural is similar, it is necessary to examine which the optimum ratio of urea and the other reactants is to obtain the maximum yield (Table 3).

### 3.4. Effect of catalyst amount

The mechanism for the formation of the C-N bond between the aldehyde and urea is characteristic of an acid catalysis using a Bronsted-

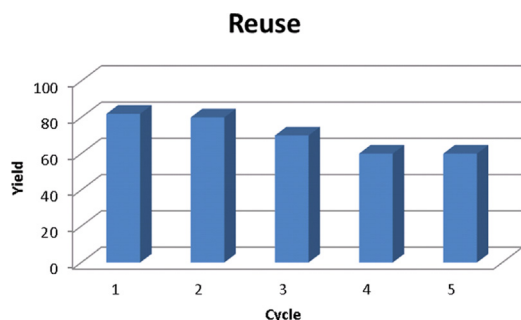


Fig. 1. Catalyst reuse. Product yields (%) (Reaction conditions: Furfural (1 mmol); methylacetoacetate (1 mmol); urea (1.2 mmol); catalyst, 100 mg. solvent-free; temperature, 80 °C; time, 4 h; stirring).

type acid (Nasr-Esfahani et al., 2014), which are expected with the use of PASi. The furfural is sensitive to acid media because the secondary reactions such as resinification and autocondensation occur in certain acid concentrations (Zeitsch et al., 2001). The process was carried out with increasing amounts of catalyst calculated as active phase (5%, 15%, 30% and 60%). At the optimum time of reaction, both 30% and 60% produce yields without significant differences (Table 4).

### 3.5. Effect of A and B methods in the synthesis of dihydropyrimidinones (thiones)

For comparative purposes, the same experiments were carried out using activation by MW (Table 5). In this case, we tested different temperatures and reaction times, finding that the best conditions were 120 °C and 15 min of reaction time.

Based on the obtained results, the reaction was extrapolated to a series of different furfural derivatives with several substituents, obtaining good and excellent results (Table 5). The yields of the MW process were smaller; it should be noted that the conversion times were also shorter. Both results are consistent with the one reported for some DHPMs (Yadav et al., 2001), the difference observed in the turnover frequency (TOF) between both methods indicates that the MW process is more active. However, the PMI measurement showed that the MW activated reaction was less efficient than the one in which conventional heating was used, based on reactant consumption.

Likewise, urea was replaced with thiourea, showing that the method is also valid with acceptable yields. The reuse of the catalyst in the synthesis of furfural, methylacetoacetate and urea derivatives allowed determining that it can be reused up to five times with yields of 82%, 80%, 70% in the first three cycles and a decrease to 60% in the last two uses (Fig. 1). The loss of catalyst activity can be related to the rupture of the structure of the heteropolyacid due to the heating as well as to the coordination of organic species on its surface, a hypothesis that is under study. The identity of all the compounds was confirmed by various spectroscopic techniques (Supporting information).

### 3.6. Catalyst reuse

Stability tests of the catalyst were carried out running five consecutive experiments under the same reaction conditions (Fig. 1). When the reaction finished, the catalyst was separated from the crude mixture by centrifugation, washed with ethyl.

## 4. Conclusion

In summary, we have reported results about the application of biomass-derived HMF in the multicomponent Biginelli reaction. The solvent-free reaction conditions were simple, economical, lower catalyst loading, and higher yield and improved catalyst recyclability. The Biginelli adducts, were obtained from the formation one new C-C bonds

and two C-N bonds in a one-pot stepwise transformation. The present catalytic strategy shows the benefits of Preyssler acid ( $H_{14}NaP_5MoW_{29}O_{110}$ ) as Bronsted acid catalyst in the Biginelli multicomponent reaction. However, it is clear that the acid strength of the active phase is very high for the reaction to proceed with the bulk catalyst. Nevertheless, the inclusion of the catalyst in the silica framework makes it suitable for the reaction, easy to recover and active for reuse. It is shown that in this case the reaction is more favored by conventional heating than by activation by microwaves.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.scp.2018.09.002.

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