

SHORT COMMUNICATION

Solvent-free synthesis of 6-unsubstituted dihydropyrimidinones using 2-pyrrolidonium bisulphate as efficient catalyst

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A one-pot three-component Biginelli-like reaction of enaminones, aldehydes with urea/thiourea in the presence of 2-pyrrolidonium bisulphate as an acidic ionic liquid catalyst for the preparation of 6-unsubstituted dihydropyrimidinones is described. The excellent yield, short reaction time, simple procedure and avoidance of the use of organic solvents are some advantages of this method. © 2016 Institute of Chemistry, Slovak Academy of Sciences

Keywords: 6-unsubstituted dihydropyrimidinone, 2-pyrrolidonium bisulphate, enaminone, aldehyde, urea/thiourea

Dihydropyrimidinones (DHPMs) have a wide spectrum of bio-therapeutic activities (Rovnyak et al., 1995; Nagarathnam et al., 1999), exhibiting antiviral (Patil et al., 1995), antibacterial (Kappe, 1993) and antihypertensive (Atwal et al., 1991) properties. The first synthesis of functionalised 3,4dihydropyrimidinones by treating aromatic aldehydes and β -keto esters with urea was reported by Biginelli in 1893 (Dallinger & Kappe, 2005). Recently, the Biginelli-like reaction has been employed to synthesise DHPM using active methylene building blocks including ketone (Safari & Gandomi-Ravandi, 2014), alkyl acetoacetate (Kappe, 2000), acetoxy acetaldehyde (Kolosov & Orlov, 2005), aldehyde (Bailey et al., 2007) and enaminone (Wan & Pan, 2009) in the place of β -ketoester.

Although these methods significantly extended the Biginelli reaction, they suffered from limitations such as low yield, long reaction time, high temperature, use of organic solvent and they require stoichiometric quantities of catalyst. In addition, a few systematic methods have been established to synthesise DHPMs using enaminones (Wan & Pan, 2009; Darwish et al., 2010; Al-Mousawi et al., 2010; Wan et al., 2011; Hassaneen & Abdelhamid, 2013). This could be an effective extension of the Biginelli-like reaction, affording synthesis of a large number of multifunctionalised pyrimidinones.

On the other hand, ionic liquids have gained attention in electrochemistry (Hagiwara & Ito, 2000), the synthesis of nano-structured materials (Antonietti et al., 2014), reaction media and catalysis (Gordon, 2001; Roy et al., 2011). Acidic ionic liquids as "green" media are regarded as promising catalysts replacing cation-exchange resins or solid acids in organic reactions (Tao et al., 2011). Pyrrolidonium acidic ionic liquids have been synthesised in simple procedures and showed excellent conversion and selectivity in different reactions such as the esterification of acetic acid and butanol, synthesis of benzoxanthene derivatives and the preparation of azides and 3,4-dihydropyrimidine-2-(1H)-ones (Huang et al., 2008; Hajipour et al., 2009; Shaterian et al., 2011; Shaterian & Aghakhanizadeh, 2013).

In the present study, an efficient Biginelli-like reaction for preparing 6-unsubstituted dihydropyrimidinones via the condensation of aldehydes, enaminones and urea or thiourea in the presence of

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$$\begin{array}{c} O \\ R^{1} \overset{O}{\overset{}}_{H} + R^{2} \overset{O}{\overset{}}_{I} + H_{2}N \overset{X}{\overset{}}_{NH_{2}} \overset{Solvent free}{\overset{}}_{HSO_{4}} O \\ 0 \overset{\bigoplus}{\overset{}}_{H} HSO_{4} \overset{O}{\overset{}}_{HSO_{4}} \overset{R^{1}}{\overset{}}_{H} X \\ H \\ \end{array}$$

Fig. 1. Synthesis of 6-unsubstituted DHPMs under solvent-free conditions.

Table 1. Synthesis of 6-unsubstituted DHPMs in the presence of 2-pyrrolidonium bisulphate as $catalyst^a$

	$H \rightarrow O + H_2N +$							
	1	11		111	ľ	∕a–IVr		
Entry	\mathbb{R}^1	\mathbb{R}^2	Х	Product	Time/min	Yield/%	$M.p./^{o}C$	
1	Н	Н	0	IVa	120	92 $(65)^b$	$282 - 284^{b}$	
2	4-Me	Н	Õ	IVb	120	$90 (86)^c$	$231-234^{c}$	
3	4-OMe	Н	0	IVc	150	$87 (85)^c$	$229-231^{c}$	
4	3-OMe	Н	0	IVd	135	88	175 - 177	
5	$4-NO_2$	Н	0	IVe	110	$95 \ (92)^c$	$251 - 253^{c}$	
6	4-CN	Н	Ο	IVf	120	94	264 - 265	
7	4-Cl	Н	0	IVg	120	93	257 - 260	
8	4-Br	Н	0	IVh	120	91	255 - 257	
9	2-I	Н	0	IVi	120	88	202 - 205	
10	$2-Cl, 5-NO_2$	Н	0	IVj	150	92	201 - 202	
11	3-OMe	$4-NO_2$	0	IVk	120	92	238 - 240	
12	4-CN	$4-NO_2$	0	IVl	120	93	166 - 168	
13	Н	Н	\mathbf{S}	IVm	135	$90 \ (95)^c$	$278 - 280^{c}$	
14	4-Me	Н	\mathbf{S}	IVn	150	$89 \ (91)^c$	$279-281^{c}$	
15	$4-NO_2$	Н	\mathbf{S}	IVo	120	$93 \ (93)^c$	$266 - 268^{c}$	
16	4-Cl	Н	\mathbf{S}	IVp	120	$91 \ (95)^c$	$269-271^{c}$	
17	4-Br	Н	\mathbf{S}	IVq	135	$89 \ (89)^c$	$283 - 285^{c}$	
18	$2-Cl, 5-NO_2$	Н	\mathbf{S}	IVr	120	91	235 - 238	

a) Reactions were performed at 80 °C using benzaldehyde (1 mmol), enaminone (1 mmol), urea/thiourea (1.2 mmol) and [Hnhp][HSO₄] (10 mole %) under solvent-free conditions; b) reported by Darwish et al. (2010); c) reported by Wan and Pan (2009).

2-pyrrolidonium bisulphate ([Hnhp][HSO₄]) as an acidic ionic liquid catalyst under solvent-free conditions (Fig. 1) is reported.

Materials were purchased from Merck (Germany) and Aldrich (USA) chemical companies and used without further purification. 2-Pyrrolidonium bisulphate (Shaterian et al., 2011) and enaminones (Sun et al., 2006) were prepared following the reported procedures. The samples were analysed using an FT-IR vector 22 spectrometer (Bruker Vector in KBr matrix (Germany)). NMR spectra were recorded using a Bruker DRX 400 AVANCE instrument (Germany) (400.1 MHz for ¹H, 100.6 MHz for ¹³C) with DMSO as the solvent. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Agilent 5975C (USA) mass spectrometer operating at an ionisation potential of 70 eV.

General procedure for the synthesis of 6-unsubstituted DHPMs: a stirred mixture of aldehyde (1 mmol), enaminone (1 mmol), urea or thiourea (1.2 mmol) and 10 mole % of 2-pyrrolidonium bisulphate (0.0183 g) was allowed to react in an oil bath at 80 °C for the appropriate time (Table 1). The progress of the reaction was monitored by TLC. After the reaction was complete, the mixture was cooled to ambient temperature and water (5 mL) was added. The catalyst was dissolved in water and filtered for separation of the crude product. The residue was washed twice with 5 mL of water. Then the product was purified by recrystallisation in EtOH/H₂O (1 : 1, vol.). All the products were characterised by their spectral data (¹H NMR, ¹³C NMR, IR and MS).

Initially, to optimise the reaction conditions, the



Table 2. Optimisation of type of solvent for synthesis of 5-benzoyl-4-(4-nitro-phenyl)-3,4-dihydro-1H-pyrimidin-2-one^a

a) Reactions were performed using 4- nitrobenzaldehyde (1 mmol), phenyl enaminone (1 mmol), urea (1.2 mmol) and $[\text{Hnhp}][\text{HSO}_4]$ (10 mole %); b) yields refer to isolated products.

Table 3. Effect of [Hnhp][HSO4] catalyst-loading on model
reaction a

Entry	Amount of catalyst/mole $\%$	Time/h	$\mathrm{Yield}/\%^b$
1	-	5	20
2	5	5	60
3	10	2	95
4	20	5	75

a) Reactions were performed using 4-nitrobenzaldehyde (1 mmol), phenyl enaminone (1 mmol), urea (1.2 mmol) and $[\text{Hnhp}][\text{HSO}_4]$ at 80 °C; b) yields refer to isolated recrystallised products.

effects of the catalyst and solvent were investigated using 4-nitrobenzaldehyde, phenyl enaminone and urea as a model (Tables 2 and 3). This reaction was observed to perform well under solvent-free conditions in comparison with commonly used organic solvents such as acetonitrile, ethanol, methanol, water and hexane (Table 2, entries 1–6). To verify the efficiency of the catalyst, the amount of $[Hnhp][HSO_4]$ on the reaction was investigated. At a mild temperature, a low yield of the product was achieved in the absence of [Hnhp][HSO₄]. To evaluate the quantity of catalyst required, 5–20 mole % of $[Hnhp][HSO_4]$ was used and the products were obtained with 60-95 % yields. In addition, decreasing the amount of catalyst from 10 mole % to 5 mole % reduced the yield significantly from 95 % to 60 %. However, increasing the quantity of catalyst from 10 mole % to 20 mole % reduced the yield from 95 % to 75 % (Table 3, entries 1-4). Accordingly, 10 mole % of catalyst was selected as the optimal amount of catalyst for this reaction.

In order to evaluate the general character of this method, different 6-unsubstituted DHPMs were synthesised using a variety of aldehydes and enaminones reacting with urea or thiourea in the presence of $[Hnhp][HSO_4]$ at 80 °C under solvent-free conditions (Table 1).

As indicated in Table 1, aromatic aldehydes with both electron-withdrawing and electron-donating substituents performed well with phenyl enaminone and urea in the presence of 2-pyrrolidonium bisulphate under solvent-free conditions at 80 °C in affording the desired products with excellent yields (Table 1, entries 1– 10). 4-Nitrophenyl enaminone reacted smoothly with various aromatic aldehydes and urea under the same reaction conditions to afford excellent yields of the corresponding DHPMs (Table 1, entries 11–12).

Similarly, a reaction of different aromatic aldehydes with phenyl enaminone and thiourea under the optimal reaction conditions afforded 3,4dihydropyrimidin-2(1H)-thiones with excellent yields (Table 1, entries 13–18). In general, electron-withdrawing groups were observed to accelerate the reaction in comparison with electron-donating groups.

Mechanistically (Maheswara et al., 2008; Darwish et al., 2010), the reaction may proceed via imine formation from aldehyde and urea and the subsequent addition of the enaminone to the imine followed by intramolecular condensation removing dimethylamine to afford 6-unsubstituted DHPM (Fig. 2).

To display the merit of the present procedure for 6unsubstituted DHPM synthesis via the one-pot threecomponent reaction between aldehydes, enaminones and urea, the results obtained with $[\text{Hnhp}][\text{HSO}_4]$ were compared with some of those reported in the literature (Table 4). Although all the methods are effective, the present method affords a comparatively high yield of the product in a short time using only 10 mole % of catalyst.

In summary, a simple, convenient and eco-friendly approach is described for the synthesis of 6-unsubsti-

1128

Entry	Catalyst, amount/mole $\%$	Conditions	$\mathrm{Yield}^b/\%$	Time/h	Reference
1	TMSCl, 150	DMF, 85 °C	89	10	Wan and Pan (2009)
2	AcOH or HCl, few drops	Dioxane, reflux	65	-	Darwish et al. (2010)
3	$[\text{Hnhp}][\text{HSO}_4], 10$	Solvent free, $80^{\rm o}{\rm C}$	92	2	This work

Table 4. Evaluation of present method in comparison with some other reported methods^a

a) Reaction between benzaldehyde, phenyl enaminone and urea; b) yields refer to isolated recrystallised products.



Fig. 2. Plausible mechanism for synthesis of 6-unsubstituted DHPM derivatives.

tuted DHPMs by a one-pot three-component Biginellilike reaction of various aldehydes, enaminones and urea/thiourea in the presence of 2-pyrrolidonium bisulphate as an ionic liquid catalyst. This method affords excellent yields, short reaction time, simple work-up procedure and solvent-free conditions.

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Supplementary data

The supplementary data associated with this article (Solvent-free synthesis of 6-unsubstituted dihydropyrimidinones using 2-pyrrolidonium bisulphate as efficient catalyst) can be found in the online version of this paper (DOI: 10.1515/chempap-2016-0048).

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