

SALICYLIC ACID AS A BIO-BASED, NATURAL AND VERSATILE CATALYST FOR GREEN, SOLVENT-FREE AND ONE-POT BIGINELLI SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2-(1H)-ONE/THIONE DERIVATIVES

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Abstract. A green synthetic route for eco-safe and solvent-free preparation of biologically active 3,4-dihydropyrimidin-2-(1H)-ones/thiones derivatives via one-pot, three-component Biginelli condensation reaction of β -keto esters (methyl or ethyl acetoacetate), aromatic aldehyde (benzaldehyde derivatives) and urea or thiourea have been developed using a salicylic acid as a bio-based, natural and versatile catalyst. The notable advantages of this green approach are use of the bio-based, natural, easy-to-handle and readily green catalyst, easy work-up process, absence of hazardous organic solvents, solvent-free conditions with high to excellent yields and short reaction times and one-pot reactions. The products have been characterized by melting points and ¹H NMR spectroscopy.

Keywords: salicylic acid, bio-based and natural catalyst, 3,4-dihydropyrimidin-2-(1H)-ones/thiones derivatives, Biginelli condensation reaction, solvent-free conditions.

1. Introduction

Salicylic acid (SA) is a phenolic phytohormone which is found in plants (White willow (*Salix alba*)). This natural source of salicylic acid (Fig. 1) plays role in plant growth and development, photosynthesis, transpiration, ion uptake and transport [1]. SA also induces specific changes in leaf anatomy and chloroplast structure. SA is involved in endogenous signaling, mediating in plant defense against pathogens [2]. It plays a role in the resistance to pathogens by inducing the production of pathogenesis-related proteins [3]. It is involved in the systemic acquired resistance (SAR) in which a pathogenic

attack on one part of the plant induces resistance in other parts [4].

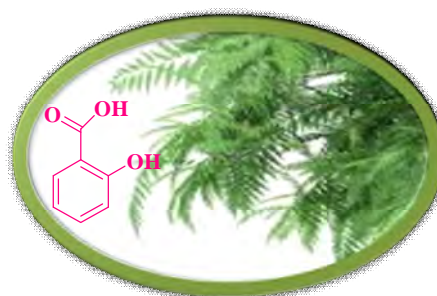


Fig. 1. Structure of salicylic acid

Synthesis of heterocyclic compounds has attracted great interests due to their wide applicability in life and nature. The compounds with pyrimidinone ring systems have been known to exhibit a wide range of pharmacological and biological properties. For example these heterocyclic compounds have been used as calcium channel blockers, α -1a-antagonists [5], mitotic kinesin Eg5 inhibition [6], anti cancer (Mal3-101) [7], anti HIV agent [8], antibacterial and antifungal [9], antiviral [10], antioxidative [11]. The representatives such as batzelladines, ptilomycalines and crambescidines exhibit many biological activities such as anticancer, antifungal, anti HIV, *etc.* [12]. In recent decades, a number of methodologies for preparing these compounds have been reported that is including various catalysts [13-23], some of the limitations of these methodologies are low yields, toxic organic solvents and catalyst, harsh reaction conditions and expensive materials. In recent years, the design and development of bioactive heterocyclic compounds synthesis performed through multi-component reactions (MCRs) [24-28], involving three or more reactants in one-pot, have attracted considerable interest since such processes have improved atom economy, efficiency and convergence. Among various

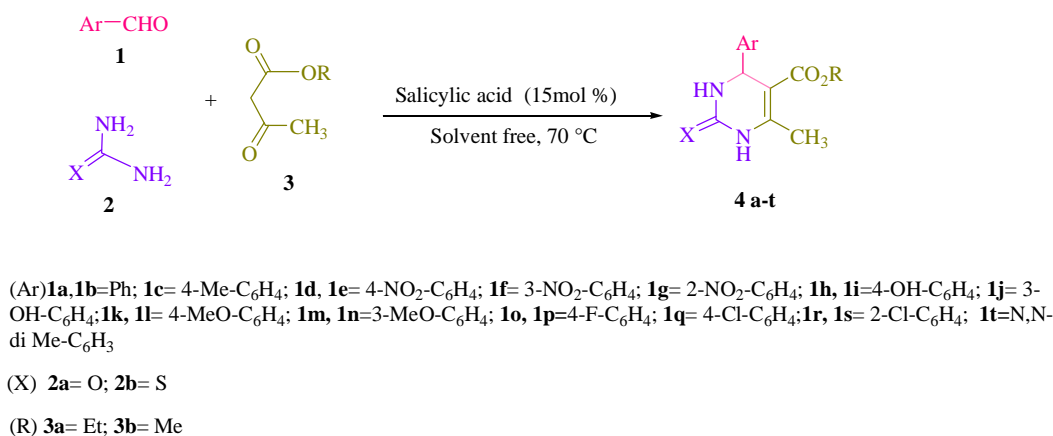
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factors, solvents and catalysts play important roles in green chemistry. Due to, in recent years, one of the important challenges of chemistry researchers is to use green and environmental friendly catalyst that leads to synthesis of target compounds in the absence of hazardous organic solvents. That is why multicomponent domino reactions (MCRs) by using a green catalyst for the synthesis of fine chemicals have attracted our considerable interests.

As part of our ongoing research program on the development of green methodologies [29, 30] attempts were directed to synthesize one of Biginelli-type reactions [31] and herein, we report a bio-based, natural and highly efficient salicylic acid catalyst for green, eco-safe and simple preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives under thermal and solvent-free conditions with excellent yields and short reaction times (Scheme 1).



Scheme 1. Synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives

2. Experimental

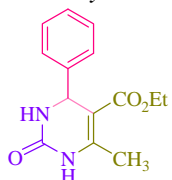
2.1. General

Melting points of all compounds were determined using an Electro thermal 9100 apparatus. ¹H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d₆ as solvents. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

General procedure for preparation of 3, 4-dihydropyrimidin-2-(1H)-ones/thiones derivatives (4a-t)

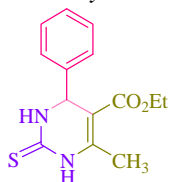
A mixture of aldehyde derivatives (**1**, 1.0 mmol) and urea/thiourea (**2**, 1.5 mmol), ethyl/methyl acetoacetate (**3**, 1.0 mmol) was heated under solvent-free conditions at 343 K for appropriate time in the presence of salicylic acid (15 mol %). After completion of the reaction (by thin layer chromatography TLC) the mixture was cooled to room temperature, cold water was added and the precipitate was separated with filtration followed by recrystallization from ethanol to afford the pure products (**4a-t**). Spectra data of products are represented below:

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (4a)



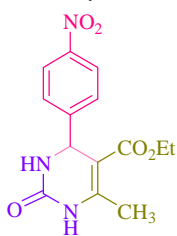
Yield 91 %; mp. 471–473 K; ¹H NMR (400 MHz, DMSO-d₆): 1.10 (3H, t, *J*=7.2 Hz, CH₃CH₂), 2.26 (3H, s, CH₃), 3.99 (2H, q, *J*=7.2 Hz, CH₂O), 5.15 (1H, s, H_{benzylic}), 7.26 (3H, d, *J*= 7.2 Hz, H_{Ar}), 7.33 (2H, t, *J*=7.2 Hz, H_{Ar}), 7.76 and 9.21 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione (4b)



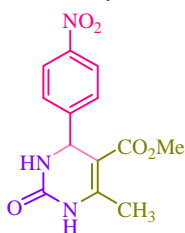
Yield 89 %; mp. 481–483 K; ¹H NMR (400 MHz, DMSO-d₆): 1.11 (3H, t, *J*=7.2 Hz, CH₃CH₂), 2.31 (3H, s, CH₃), 4.02 (2H, q, *J*=7.2 Hz, CH₂O), 5.19 (1H, s, H_{benzylic}), 7.23 (2H, d, *J*=7.2 Hz, H_{Ar}), 7.28 (1H, t, *J*=7.2 Hz, H_{Ar}), 7.36(2H, t, *J*=7.2 Hz, H_{Ar}), 9.68 and 10.36 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4d)



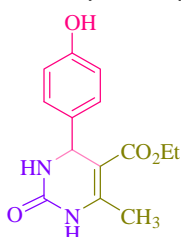
Yield 88 %; mp. 481–483 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 1.10 (3H, t, $J=9.6$ Hz, CH_3CH_2), 2.28(3H, s, CH_3), 3.99 (2H, q, $J=9.2$ Hz, CH_2O), 5.27 (1H, s, $\text{H}_{\text{benzylic}}$), 7.50-7.53 (2H, m, H_{Ar}), 7.23 (2H, d, $J=9.2$ Hz, H_{Ar}), 7.92 and 9.38 (2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4e)



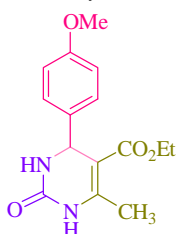
Yield 91 %; mp. 485–487 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 2.28(3H, s, CH_3), 3.55 (3H, s, OCH_3), 5.28 (1H, s, $\text{H}_{\text{benzylic}}$), 7.52 (2H, d, $J=8.4$ Hz, H_{Ar}), 7.22 (2H, d, $J=8.8$ Hz, H_{Ar}), 7.93 and 9.40 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4h)



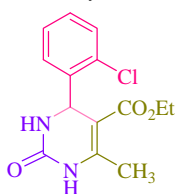
Yield 82 %; mp. 507–509 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 1.11 (3H, t, $J=9.6$ Hz, CH_3CH_2), 2.50 (3H, s, CH_3), 3.98 (2H, q, $J=9.2$ Hz, CH_2O), 5.04 (1H, s, $\text{H}_{\text{benzylic}}$), 6.68-7.04(4H, m, H_{Ar}), 7.64 and 9.13(2H, 2s, 2NH), 9.35 (1H, s, OH).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4k)



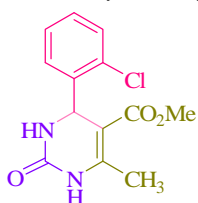
Yield 87 %; mp. 475–477 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 1.11 (3H, t, $J=9.6$ Hz, CH_3CH_2), 2.24(3H, s, CH_3), 3.73 (3H, s, OCH_3), 3.99 (2H, q, $J=9.6$ Hz, CH_2O), 5.09 (1H, s, $\text{H}_{\text{benzylic}}$), 6.89 (2H, d, $J=8.4$ Hz, H_{Ar}), 7.15(2H, d, $J=8.8$ Hz, H_{Ar}), 7.70 and 9.18 (2H, 2s, 2NH).

5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4r)



Yield 84 %; mp. 493–495 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 1.00 (3H, t, $J=9.2$ Hz, CH_3CH_2), 2.31 (3H, s, CH_3), 4.02 (2H, q, $J=9.2$ Hz, CH_2O), 5.63 (1H, s, $\text{H}_{\text{benzylic}}$), 7.25-7.34 (3H, m, H_{Ar}), 7.41 (1H, d, $J=8.8$ Hz, H_{Ar}), 7.73 and 9.29(2H, 2s, 2NH).

5-Methoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4s)



Yield 85 %; mp. 522–524 K; $^1\text{H NMR}$ (400 MHz, DMSO-d_6): 2.31 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.62 (1H, s, $\text{H}_{\text{benzylic}}$), 7.28-7.34 (3H, m, H_{Ar}), 7.42 (1H, d, $J=7.2$ Hz, H_{Ar}), 7.72 and 9.36(2H, 2s, 2NH).

3. Results and Discussion

Due to the reasonable needs of green, versatile and efficient catalyst, we explored salicylic acid as a bio-based and natural catalyst for one-pot and facile synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives by three-component condensation Biginelli reaction of aryl aldehydes (**1**, 1.0 mmol), urea/thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol). In an initial endeavor benzaldehyde (1.0 mmol), urea (1.5 mmol) and ethyl acetoacetate (1.0 mmol) were selected as the model substrates. To obtain the optimized reaction conditions, we changed temperature and the amount of the catalyst. The results are summarized in Table 1. Consequently, at the tested temperatures and different amount of the catalyst, the condensation of endeavor benzaldehyde, urea and ethyl acetoacetate was best catalyzed by 15 mol % salicylic acid as the reaction was completed within high yield (Table 1, entry 4). It is important to note that in the absence of the catalyst no product was observed (Table 1, entry 1). We also investigated different temperatures for the model reaction (Table 1). It was observed that the fast reaction occurred on raising the temperature from room temperature to 353 K and the yield of preferred product increased significantly (Table 1). We were satisfied to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 343 K to afford the desired product (**4a**) in 91 % yields within 10 min (Table 1,

entry 4). Further increase in the temperature did not affect the product yield (Table 1, entry 8). To ascertain the scope of the present reaction, with optimized conditions in hand, three-component reaction of aryl aldehydes (**1**, 1.0 mmol), urea/thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) was examined and these results were summarized in Table 2. We were pleased to find that all substrates were converted to the corresponding products in high to excellent yields (82–95 %).

The proposed mechanistic route of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones synthesis in the presence of salicylic acid is shown in Scheme 2. In this probable mechanism the salicylic acid catalyses Biginelli condensation *via* acylimin intermediate (A). The reaction of aldehydes (1) and urea (2) generates an acylimin intermediate (A), which further reacts with the activated 1,3-dicarbonyl compound (B) producing an open-chain ureide (C) undergoing subsequent cyclization and dehydration to give the major product (4).

Comparison of catalytic ability of some catalysts reported in the literature for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives are shown in Table 3. This study reveals that salicylic acid has shown its extraordinary potential to be an alternative bio-based, green, readily, highly efficient, low-cost and economical catalyst for the Biginelli reaction. In addition, the use of solvent-free conditions with high to excellent yields and short reaction times in the reaction with both urea and thiourea are the notable advantages of this present methodology.

Table 1

Optimization of the reaction condition on the synthesis of **4a**

Entry	Salicylic acid, mol %	Temperature, K	Time, min	Isolated yield, %
1	Catalyst free	343	360	no product
2	5	343	40	39
3	0	343	20	67
4	15	343	10	91
5	15	room temperature	360	no product
6	15	313	35	46
7	15	333	15	73
8	15	353	10	91
9	20	343	10	92

Note: Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and salicylic acid were heated under various temperatures for the appropriate time

Table 2

Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones derivatives

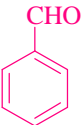
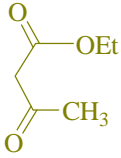
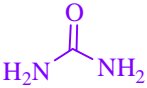
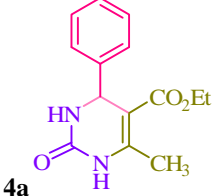
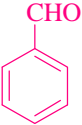
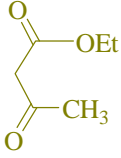
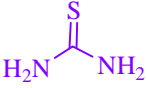
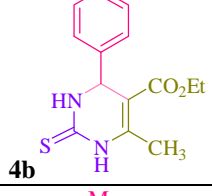
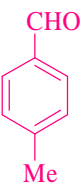
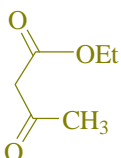
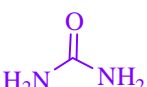
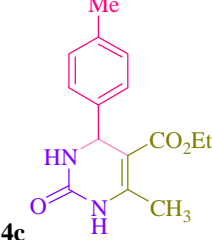
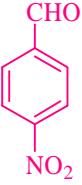
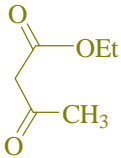
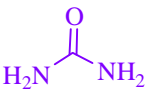
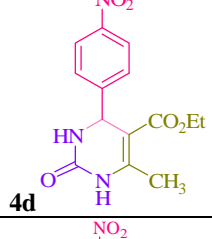
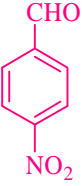
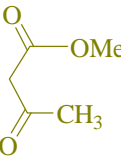
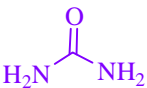
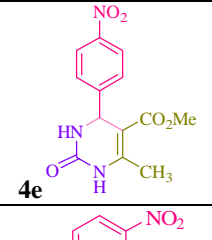
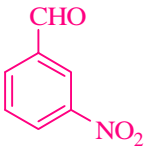
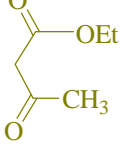
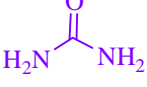
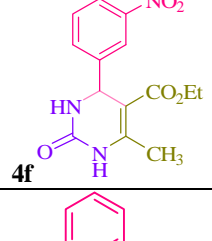
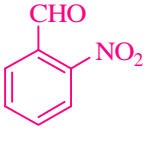
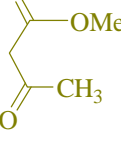
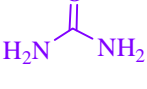
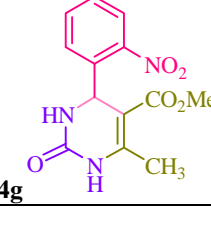
Entry	Substrate	Substrate	Substrate	Product ^a	Time, min	Yield ^b , %	mp, K	Lit. mp, K
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1					10	91	471–473	473–475 [14]
2					10	89	481–483	481–483 [14]
3					10	93	475–477	477–478 [15]
4					15	88	481–483	480–482 [14]
5					10	91	485–487	487–489 [14]
6					15	90	496–498	498–500 [19]
7					10	93	550–552	547–550 [19]

Table 2 (continued)


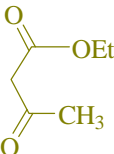
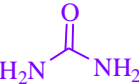
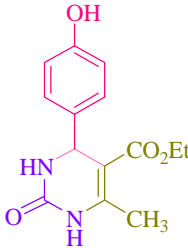
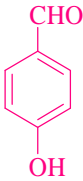
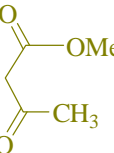
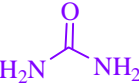
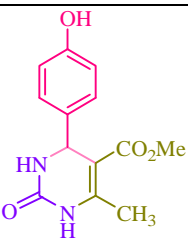
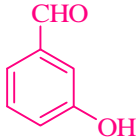
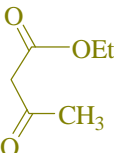
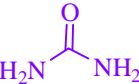
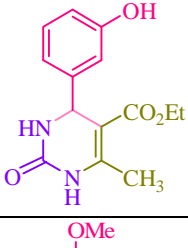
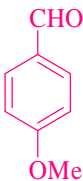
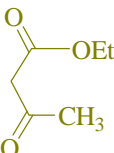
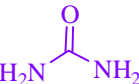
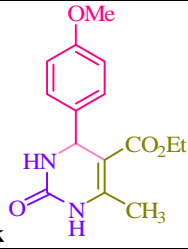
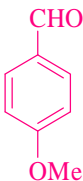
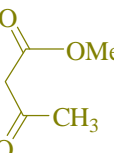
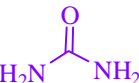
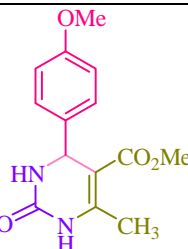
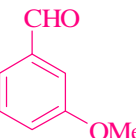
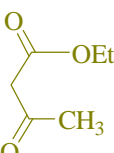
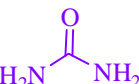
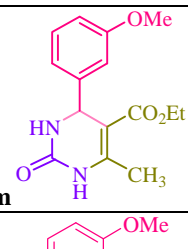
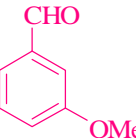
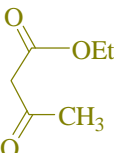
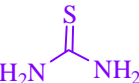
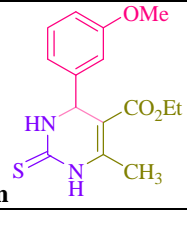
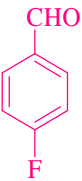
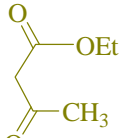
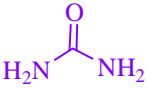
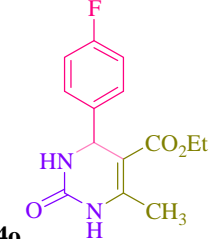
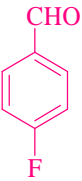
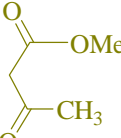
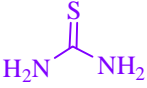
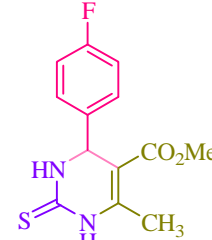
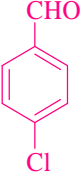
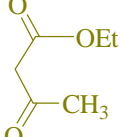
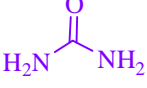
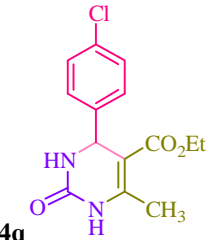
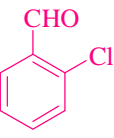
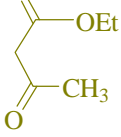
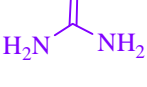
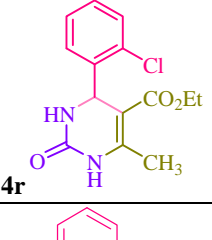
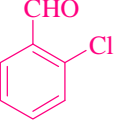
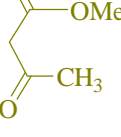
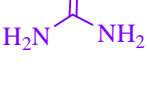
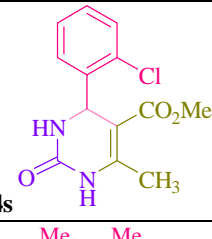
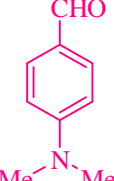
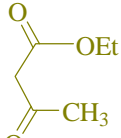
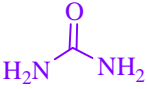
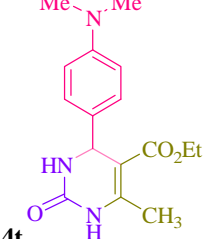
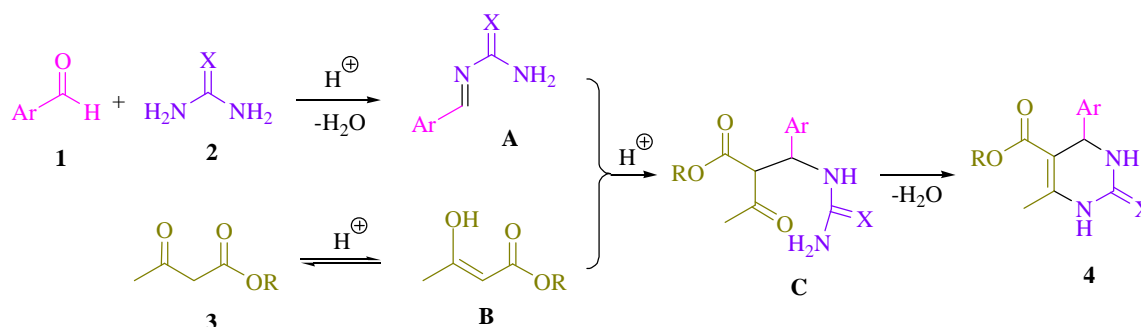
1	2	3	4	5	6	7	8	9
8				 4h	20	82	507–509	507–509 [20]
9				 4i	20	85	516–518	518–519 [15]
10				 4j	20	83	437–439	436–439 [19]
11				 4k	15	87	475–477	476–478 [21]
12				 4l	15	89	464–466	463–467 [19]
13				 4m	10	88	476–478	478–479 [15]
14				 4n	15	86	422–424	423–424 [15]

Table 2 (continued)

1	2	3	4	5	6	7	8	9
15					10	95	449–451	447–449 [18]
16					10	91	480–482	481–483 [18]
17					20	82	488–490	487–488 [16]
18					15	84	493–495	493–496 [14]
19					15	85	522–524	521–523 [14]
20					15	87	529–531	527–529 [20]

Notes: ^a isolated yield; ^b reaction conditions: benzaldehyde (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and salicylic acid (15 mol %) was heated at 343 K.



Scheme 2. Proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones

Table 3

Comparison of catalytic ability of some catalysts reported in the literature for synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives^a

Entry	Catalyst	Conditions	Time/Yield, %	References
1	Bakers' yeast	Room temperature	24h/84	[15]
2	Hydrotalcite	Solvent-free, 353 K	35 min/84	[16]
3	[Al(H ₂ O) ₆](BF ₄) ₃	MeCN, Reflux	20 h/81	[17]
4	Cu(BF ₄) ₂ .xH ₂ O	Room temperature	30 min/90	[19]
5	[Btto][<i>p</i> -TSA]	Solvent-free, 363 K	30 min/96	[21]
6	Triethylammonium acetate	Solvent-free, 343 K	45min/90	[22]
7	<i>p</i> -Dodecylbenzenesulfonic acid	Solvent-free, 353 K	3 h/94	[23]
8	Salicylic acid	Solvent-free, 343 K	10 min/91	This work

Note: ^a based on the three-component reaction of benzaldehyde, ethyl acetoacetate and urea.

4. Conclusions

In summary, we have demonstrated that a bio-based, natural and efficient catalyst, salicylic acid, can be used for the eco-safe, one-pot and facile Biginelli synthesis biologically active 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives via one-pot three-component reaction of aldehydes, urea/thiourea and ethyl/methyl acetoacetate under thermal and solvent-free conditions with high to excellent yields and short reaction times. Use of the inexpensive and easy to handle salicylic acid as a bio-based, versatile and natural catalyst, straightforward work-up, absence of hazardous organic solvents, eco-safe and one-pot procedure are the notable advantages of this simple protocol.

Acknowledgements

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САЛІЦИЛОВА КИСЛОТА ЯК ПРИРОДНИЙ І УНІВЕРСАЛЬНИЙ БІО-КАТАЛІЗАТОР ДЛЯ ОДНОСТАДІЙНОГО “ЗЕЛЕНОГО” СИНТЕЗУ У ВІДСУТНОСТІ РОЗЧИННИКА ПОХІДНИХ 3,4-ДИГІДРОПІРИМІДИН-2-(1H)-ОНУ/ТІОНУ

Анотація. Розроблено одностадійний «зелений метод» синтезу у відсутності розчинника екологічно безпечних, біологічно активних похідних 3,4-дигідропіримідин-2-(1H)-ону/тіону за допомогою трикомпонентної реакції конденсації Біджінеллі β-кетоестерів (метил або етил ацетоацетат), ароматичного альдегіду (похідна бензальдегіду) і сечовини або тіосечовини з використанням саліцилової кислоти як природного та універсального біо-катализатора. Показано, що перевагами такого синтезу є природний, простий у використанні, «зелений» біо-катализатор, легкий процес оброблення, відсутність шкідливих органічних розчинників, високі виходи, одностадійність та короткий час реакції. Для одержаних продуктів визначено температури топлення і проведено ¹H ЯМР аналіз.

Ключові слова: саліцилова кислота, природний біо-катализатор, похідні 3,4-дигідропіримідин-2-(1H)-ону/тіону, реакція конденсації Біджінеллі, відсутність розчинника.