Succinic Acid As a Green and Bio-Based Catalyst assisted solvent-free one-pot Biginelli synthesis of biologically active 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives

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ABSTRACT

Succinic acid as a bio-based green and versatile catalyst has been employed for one-pot facile three-component Biginelli synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones derivatives under solvent-free conditions with high to excellent yields and short reaction times. This sustainable procedure has notable benefits such as easy-to-handle, green, low-cost and non-toxic catalyst, materials available, simple work-up with no necessity of chromatographic purification steps, one-pot and solvent-free conditions. The products have been characterized by melting points and ^{1}H NMR spectroscopy.

Keywords: Succinic acid, 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives, Sustainable procedure, Biginelli condensation reaction, Solvent-free conditions.

INTRODUCTION

Succinic acid (C_4-dicarboxylic acid) (Figure 1) is a common metabolite in plants, animals and microorganisms and has been used widely in agricultural, food and pharmaceutical industries (Zeikus et al., 1999). This acid has holds good industrial applications and is used in industries such as, resins, polymer, paints, cosmetics and inks, etc (Vermuri et al., 2002). To date, the economically renewable resources used in succinic acid production reported are cheese whey

(Samuelov., 1999; Lee et al., 2000; Lee et al., 2003a; Wan et al., 2008), cane molasses (Agarwal., 2006; Liu et al., 2008), Jerusalem artichoke (Zheng et al., 2010), wheat flour (Du et al., 2008), wood hydrolysate (Lee., 2003b; Kim et al., 2004; Hodge et al., 2009) and corn straw hydrolysate (Zheng et al., 2009).

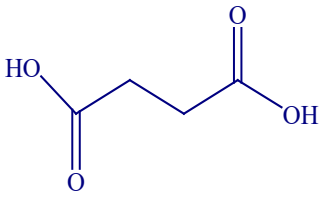


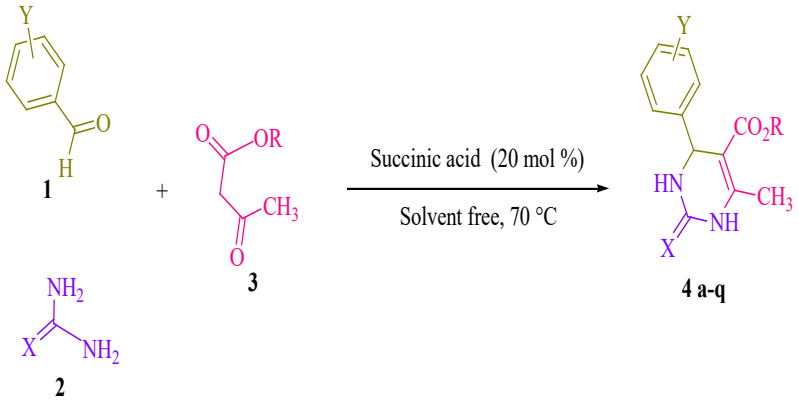
Figure 1. Structure of succinic acid.

One of the dominating factors in recent organic synthetic routs is green chemistry. Atom economy, reduction in byproduct, number of steps in organic synthesis, energy cost, produced waste, use of non-hazardous reagents in catalytic protocols are one of the most important goals of green chemistry. Furthermore, organic reactions under solvent-free conditions for green and clean synthesis of organic compounds have attracted much interest in organic chemists. And herein, our recent studies focused on developing of green catalyst (Mohamadpour, 2018a; Mohamadpour et al., 2018b; Mohamadpour et al., 2018c) in multi-component reactions (Mohamadpour et al., 2016; Mohamadpour et al., 2017; Lashkari et al., 2018).

Pyrimidinone derivatives are a common structural motif in variety of natural and non-natural products. Their derivatives 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 (Prakash et al., 2008), mitotic kinesin Eg5 inhibition (Kapoor et al., 2000), anti cancer (Mal3-101) (Wisen et al., 2008), anti HIV agent (Heys et al., 2000), antibacterial and antifungal (Ashok et al., 2007), antiviral (Hurst et al., 1961), antioxidative (Magerramow et al., 2006). The representatives such as batzelladines, ptilomycalines and crambescidines exhibit many biological activities such as anticancer, antifungal, anti HIV etc (Bewley et al., 2004).

Recently, numerous protocols for the preparation of these compounds that is including various catalysts have been reported calcium fluoride (Chitra et al., 2009), copper(II)sulfamate (Liu et al., 2009), baker's yeast (Kumar et al., 2007), hydrotalcite (Lal et al., 2012), hexaaquaaluminium (III) tetrafluoroborate (Litvic et al., 2010), TBAB (Ahmad et al., 2009), copper (II) tetrafluoroborate (Kamal et al., 2007), Copper (II) acetate (Khodja et al., 2014), [Btto][*p*-TSA] (Zhang et al., 2015), triethylammonium acetate (Attri et al., 2017), *p*-dodecyl-

benzenesulfonic acid (Aswin et al., 2014) and TMSPTPOSA (Rao Jetti et al., 2017). Some of the limitations of these methodologies are low yields, toxic organic solvents and catalyst, harsh reaction conditions and expensive materials. Based on the above considerations and in continuation of our efforts to develop green methodologies, we reported herein succinic acid as a bio-based green catalytic system for the synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives via three-component Biginelli (Biginelli et al., 1893) reaction between *β*-keto esters, aldehyde derivatives and urea/thiourea under thermal and solvent-free conditions with high to excellent yields and short reaction times (Figure 1). One of the source of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purity the products. In this present work, the products were obtained through simple filtering with no need column chromatographic separation. The advantages of succinic acid as a bio-based, mild and green acidic catalyst in organic synthesis are eco-safe, highly efficient, easily to handle, and inexpensive.



(Ar)**1a**,=Ph; **1b, 1c**= 4-OH-C_6H_4; **1d**, **1e**= 2-Cl-C_6H_4; **1f**= 4-Me-C_6H_4; **1g, 1h**= 4-NO_2-C_6H_4; **1i, 1j**= 4-MeO-C_6H_4; **1k**= 4-Cl-C_6H_4; **1l**= 3-MeO-C_6H_4; **1m**= 4-F-C_6H_4; **1n**= N,N-di Me-C_6H_3; **1o**= 4-F-C_6H_4; **1p**= 3-MeO-C_6H_4; **1q**= Ph

(X) **2a**= O; **2b**= S

(R) **3a**= Et; **3b**= Me

Figure1. Synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives.

MATERIALS AND METHODS

General

Melting points all compounds were determined using an Electro thermal 9100 apparatus. ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with DMSO-d_6 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- q). 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 70 °C for appropriate time in the presence of succinic aicd **(**20 mol %). After completion of the reaction (by thin layer chromatography TLC) the mixture was cooled to rt and cold water was added and the precipitated was separated with filtration and recrystallized from ethanol to afford the pure products (4a- q). Spectra data of products are represented below:

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

Crystalline solid; Yield: 91%; M.p. 199-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H , t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 3.99 (2H, q, *J*=7.2 Hz, CH_2O), 5.15 (1H, s, CHN), 7.26 (3H, d, *J*= 7.2 Hz, ArH), 7.33 (2H, t, *J*=7.2 Hz, ArH), 7.76 and 9.21 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 81%; M.p. 232-234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.50 (3H, s, CH_3), 3.98 (2H, q, *J*=9.2 Hz, CH_2O), 5.04 (1H, s, CHN), 6.68-7.04(4H, m, ArH), 7.64 and 9.13 (2H, 2s, 2NH), 9.35 (1H, s, OH).

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

Crystalline solid; Yield: 85%; M.p.251-253 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.31 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 5.62 (1H, s, CHN), 7.28-7.34 (3H, m, ArH), 7.42 (1H, d, *J*=7.2 Hz, ArH), 7.72 and 9.36 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 82%; M.p. 220-222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.00 (3H , t, *J*= 9.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J*=9.2 Hz, CH_2O), 5.63 (1H, s, CHN), 7.25-7.34 (3H, m, ArH), 7.41 (1H, d, *J*=8.8 Hz, ArH), 7.73 and 9.29 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 92%; M.p.212-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.28(3H, s, CH_3), 3.55 (3H, s, OCH_3), 5.28 (1H, s, CHN), 7.52 (2H, d, *J*= 8.4Hz, ArH), 7.22 (2H, d, *J*= 8.8Hz, ArH), 7.93 and 9.40 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 90%; M.p. 206-208 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H, t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 2.28(3H, s, CH_3), 3.99 (2H, q, *J*=9.2 Hz, CH_2O), 5.27 (1H, s, CHN), 7.50-7.53 (2H, m, ArH), 7.23 (2H, d, *J*= 9.2Hz, ArH), 7.92 and 9.38 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 84%; M.p.205-207°C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 9.6 Hz, $\underline{CH_3}CH_2$), 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, CHN), 6.89 (2H, d, J= 8.4Hz, ArH), 7.15 (2H, d, *J*= 8.8Hz, ArH), 7.70 and 9.18 (2H, 2s, 2NH).

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

Crystalline solid; Yield: 89%; M.p.210-212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.11 (3H , t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, CH_3), 4.02 (2H, q, *J*=7.2 Hz, CH_2O), 5.19 (1H, s, CHN), 7.23 (2H, d, *J*=7.2 Hz, ArH), 7.28 (1H, t, *J*=7.2 Hz, ArH), 7.36 (2H, t, *J*=7.2 Hz, ArH), 9.68 and 10.36 (2H, 2s, 2NH).

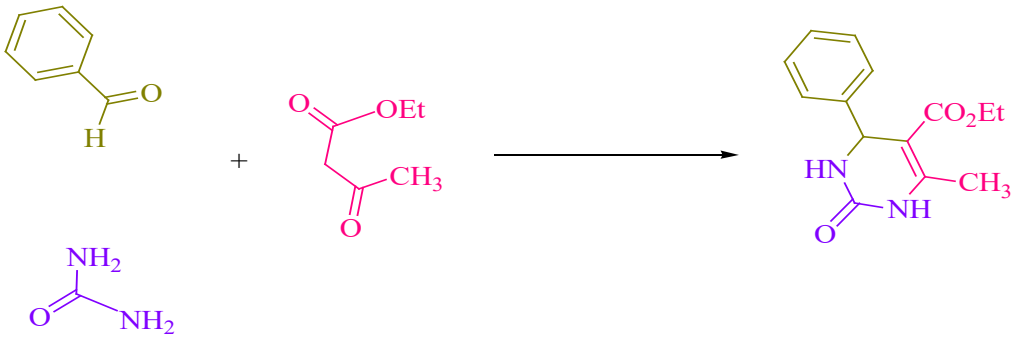
RESULTS

Initially, we chose benzaldehyde (1.0 mmol), urea (1.5 mmol) and ethyl acetoacetate (1.0 mmol) as the standard substrates to search for suitable reaction conditions in the presence of different molar catalyst under solvent-free conditions at 70 °C. We tested several molar of catalyst for this multi component

synthesis. When 5, 10, 15 and 20 mol% of succinic acid were used, the yields were 31, 55, 76 and 91 %, respectively (Table 1, entries 2-5). Therefore, 20 mol% of succinic acid were convenient (Table 1, entry 5) and excessive amount of succinic acid did not increase the yields significantly (Table 1, entry 10). Various temperatures from rt to 80 °C were optimized for this reaction. When the systematic screening was made, we found that, in the presence of 70 °C, substrates were transformed into the desired product **4a** in an excellent yield (Table 1, entry 5). With these optimized conditions in hand, we examined the scope of this multi-component process by using various easily available starting materials. As revealed in Table 2, a range of invaluable 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives can be synthesized in high to excellent yields.

Herein we reported the use of succinic acid as an efficient and bio-based green catalyst for eco-safe and convenient preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives using a multi-component reaction of aryl aldehyde derivatives (**1**, 1.0 mmol), urea/ thiourea (**2**, 1.5 mmol) and ethyl/ methyl acetoacetate (**3**, 1.0 mmol) under solvent-free conditions (Figure 1).

Table 1. Optimization of the reaction condition on the synthesis of **4a** [a]



Entry	Succinic acid (mol %)	Temperature (^{0}C)	Time (min)	Isolated Yields (%)
1	Catalyst free	70	240	Not product
2	5	70	65	31
3	10	70	45	55
4	15	70	30	76
5	**20**	**70**	**20**	**91**
6	20	rt	240	Not product
7	20	40	60	38
8	20	60	35	71
9	20	80	20	92
10	25	70	20	92

Note: [a] Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5mmol) and succinic acid was heated under various temperatures for the appropriate time.

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

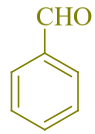
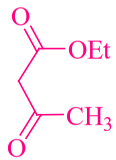
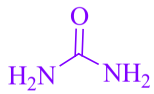
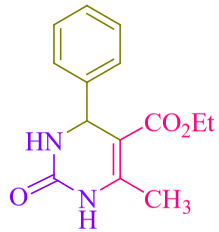
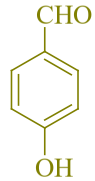
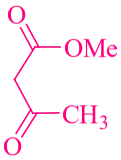
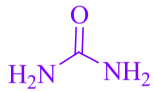
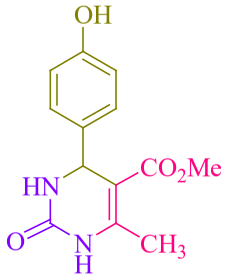
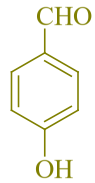
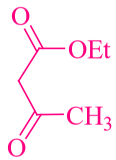
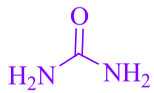
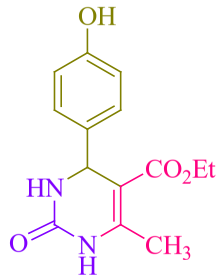
Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	M.p.˚C	Lit. M.p.˚C
1				 **4a**	20	91	199-200	200-202 (Liu et al., 2009)
2				 **4b**	30	83	246-248	245-246 (Kumar et al., 2007)
3				 **4c**	35	81	232-234	234-236 (Khodja et al., 2014)

Table 2. Cont.

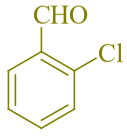
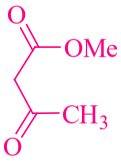
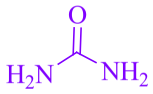
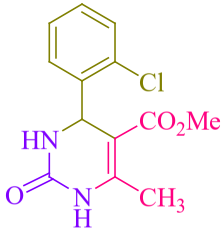
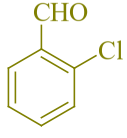
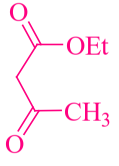
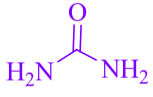
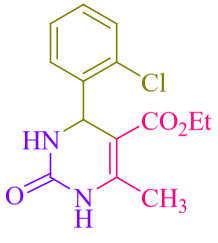
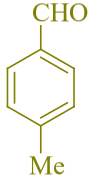
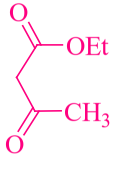
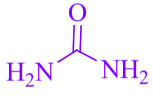
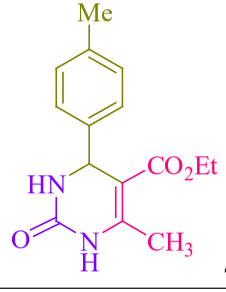
Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	M.p.˚C	Lit. M.p.˚C
4				 **4d**	30	85	251-253	248-252 (Liu et al., 2009)
5				 **4e**	30	82	220-222	220-223 (Liu et al., 2009)
6				 **4f**	20	91	203-205	204-205 (Kumar et al., 2007)

Table 2. Cont.

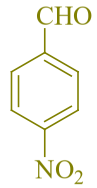
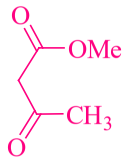
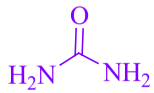
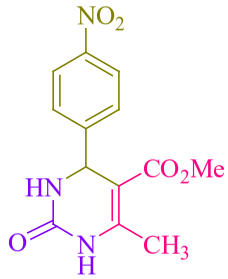
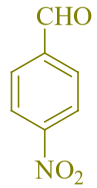
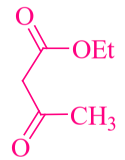
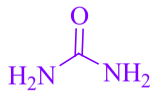
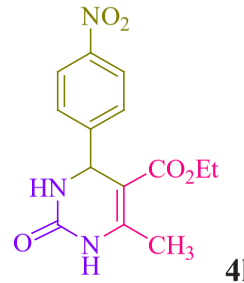
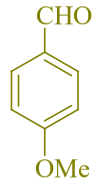
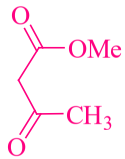
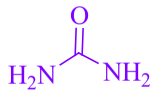
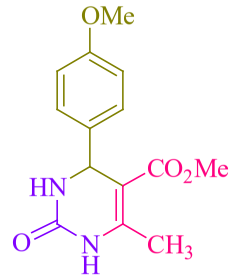
Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	M.p.˚C	Lit. M.p.˚C
7				 **4g**	20	92	212-214	214-216 (Liu et al., 2009)
8				 **4h**	20	90	206-208	207-209 (Liu et al., 2009)
9				 **4i**	25	83	191-193	190-194 (Kamal et al., 2007)

Table 2. Cont.

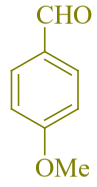
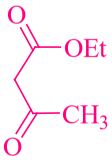
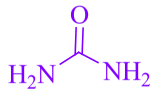
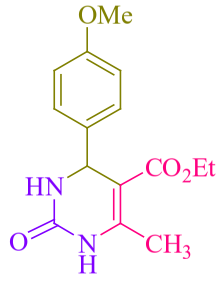
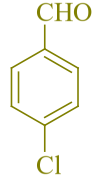
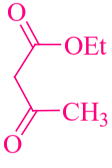
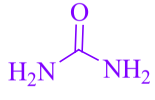
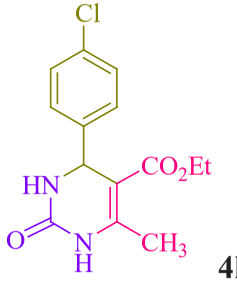
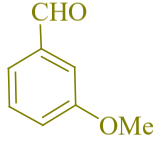
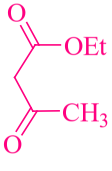
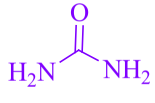
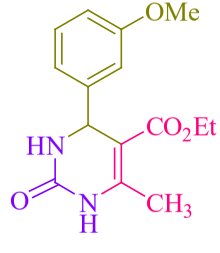
Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	M.p.˚C	Lit. M.p.˚C
10				 **4j**	25	84	205-207	203-205 (Zhang et al., 2015)
11				 **4k**	30	78	215-217	214-215 (Lal et al., 2012)
12				 **4l**	25	87	206-208	205-206 (Kumar et al., 2007)

Table 2. Cont.

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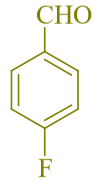
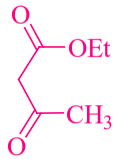
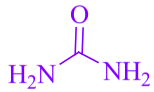
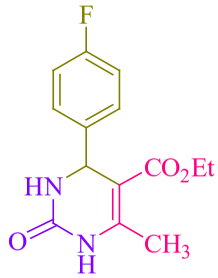
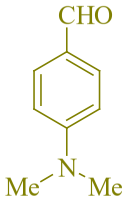
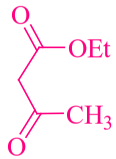
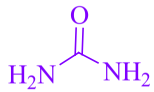
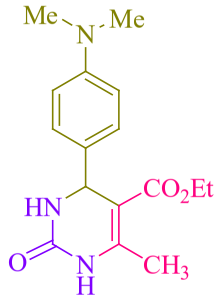
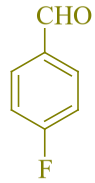
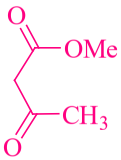
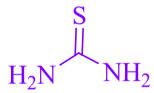
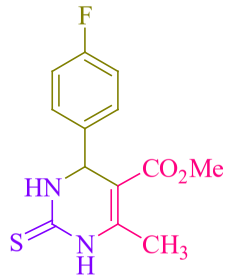
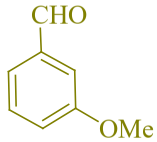
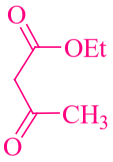
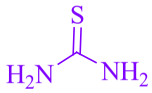
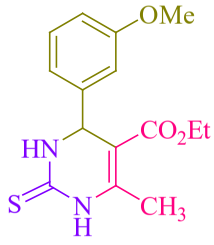
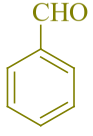
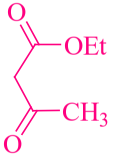
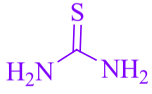
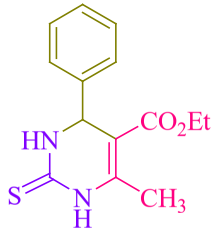
13				 **4m**	15	92	173-175	174-176 (Ahmad et al., 2009)
14				 **4n**	25	86	252-254	254-256 (Khodja et al., 2014)
15				 **4o**	20	90	209-211	208-210 (Ahmad et al., 2009)

Table 2. Cont.

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	M.p.˚C	Lit. M.p.˚C
16				 **4p**	25	85	148-150	150-151 (Kumar et al., 2007)
17				 **4q**	20	89	210-212	208-210 (Liu et al., 2009)

Note: [a] Isolated yield. [b] Reaction conditions: Aryl aldehyde derivatives (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and succinic acid (20 mol %) was heated at 70 °C.

DISCUSSION

Proposed mechanistic route of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones synthesis in the presence of succinic acid are shown in Figure 2. In this probable mechanism, the succinic acid catalyzed Biginelli condensation via acylimin intermediate (A) is presented in Figure 2. 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).

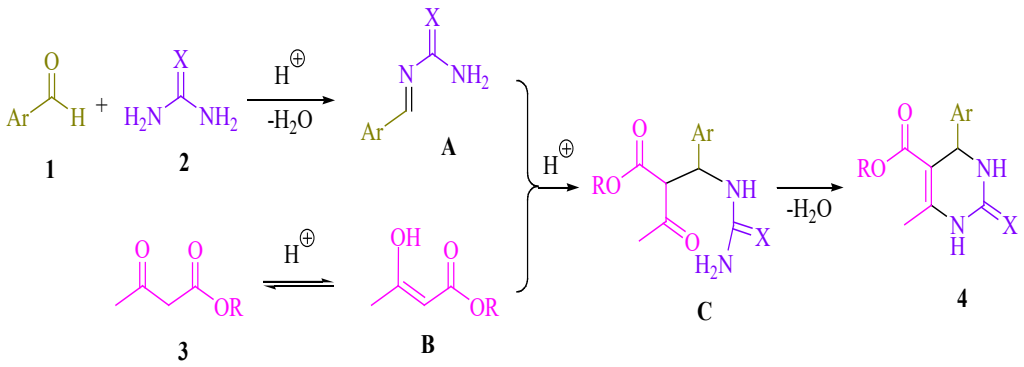


Figure 2. Proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives are shown in Table 3. This study reveals that succinic acid has shown its extraordinary potential to be an alternative green, bio-based, readily, highly efficient and inexpensive 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 this eco-safe and simple procedure.

Table 3. Comparison of catalytic ability some of 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	(Kumar et al., 2007)
2	Hydrotalcite	Solvent-free, 80 °C	35 min/84	(Lal et al., 2012)
3	$[Al(H_2O)_6](BF_4)_3$	MeCN, Reflux	20 h/81	(Litvic et al., 2010)
4	$Cu(BF_4)_2.xH_2O$	Room temperature	30 min/90	(Kamal et al., 2007)
5	[Btto][*p*-TSA]	Solvent-free, 90 °C	30 min/96	(Zhang et al., 2015)
6	triethylammonium acetate	Solvent-free, 70 °C	45min/90	(Attri et al., 2017)
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80 °C	3 h/94	(Aswin et al., 2014)
8	TMSPTPOSA	EtOH/Reflux	3 h/95	(Rao Jetti et al., 2017)
9	**Succinic acid**	**Solvent-free, 70 °C**	**20 min/91**	**This work**

Note: [a] Based on the three-component reaction of benzaldehyde, ethyl acetoacetate and urea.

CONCLUSION

In summary, the use of succinic acid as a bio-based green and mild catalyst for facile preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives *via* one-pot three-component Biginelli condensation of aryl aldehydes, urea/thiourea and ethyl/methyl acetoacetate is studied. The use of readily, easily to handle, non-toxic and inexpensive catalyst, simple work-up and solvent-free conditions provides a sustainable procedure compared to conventional methods.

ACKNOWLEDGEMENTS

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