Environmentally Friendly and Facile Synthesis of 2-oxo- and Thioxo-1,2,3,4-tetrahydropyrimidines Catalyzed by Formic Acid as a Natural Green and Bio-based Catalyst under Solvent-Free Conditions

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ABSTRACT

A green synthetic route to the facile Biginelli synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines have been developed using formic acid as a natural green and bio-based catalyst under solvent-free reaction conditions. All reactions are completed in a short period of times and the products are obtained in high to excellent yields. The salient features of this green approach are simple work-up with no necessity of chromatographic purification steps, absence of hazardous organic solvents, use of safe, non-volatile, noncorrosive and readily green catalyst, solvent-free conditions, one-pot reaction, eco-friendly and clean synthesis.

Keywords: Formic acid, Natural green and Bio-based catalyst, 2-oxo- and Thioxo-1,2,3,4-tetrahydropyrimidines, Solvent-free conditions

INTRODUCTION

Synthesis of heterocyclic compounds has attracted great interests due to their wide applicability in life and nature. The compounds with pyrimidinone derivatives are reported as, such 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).

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. Due to, our recent studies focused on developing of green catalyst in multi-component reactions (Mohamadpour et al., 2016; Mohamadpour et al., 2017; Lashkari et al., 2018; Mohamadpour., 2018a; Mohamadpour et al., 2018b; Mohamadpour et al., 2018c; Mohamadpour., 2019).

In recent decades, a number of methodologies for the preparation of these compounds have been reported that is including various catalysts such as calcium fluoride (Chitra et al., 2009), copper(II)sulfamate (Liu et al., 2008), 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*-dodecylbenzenesulfonic acid (Aswin et al., 2014), TMSPTPOSA (Rao Jetti et al., 2017), hierarchical zeolite (Shahid et al., 2017), bismuth(III)nitrate or PPh_3 (Slimi et al., 2016), lanthanum oxide (Kuraitheerthakumaran et al., 2016) and dendrimer-PWA (Safaei-Ghomi et al., 2018). Some of these methodologies have limitations such as difficult work-up, toxic and expensive catalysts, low yields, the use of strongly acidic conditions and long time reactions. As part of our ongoing research program on the development of green methodologies, herein, we report a green and facile one-pot synthesis of synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines *via* three-component Biginelli (Biginelli et al., 1893) reaction between *β*-keto esters, aldehyde derivatives and urea/thiourea in the presence of catalytic amount of formic acid under thermal and solvent-free conditions. The advantages of formic acid as a mild, natural green and bio-based acidic catalyst (Thompson et al., 1997) in organic synthesis are environmentally friendly, highly efficient and non-toxic. It is noted that, formic acid as a catalyst shows superior properties like commercially available. It is inexpensive and can be easily handled. The merits of this acidic catalyst does not end here, in this present work, the products were obtained through simple filtering with no need column chromatographic separation. Furthermore, high to excellent yields, short reaction times and eco-friendly procedure that makes our protocol alternative in comparison to some of the earlier reported methods.

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

instrument 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 2-oxo- and thioxo-1,2,3,4 tetrahydropy-rimidines (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 formic acid (10 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 by filtration and recrystallized from ethanol to afford the pure products (**4a- q**).

Spectra data some of known products are represented below:

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

Yield: 87%; 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, $H_{benzylic}$), 7.50-7.53 (2H, m, H_{Ar}), 7.23 (2H, d, *J*= 9.2Hz, H_{Ar}), 7.92 and 9.38 (2H, 2s, 2NH).

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

Yield: 80%; m.p. 250-252 °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, $H_{benzylic}$), 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).

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

Yield: 86%; m.p. 202-204°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, $H_{benzylic}$), 6.89 (2H, d, *J*= 8.4Hz, H_{Ar}), 7.15(2H, d, *J*= 8.8Hz, H_{Ar}), 7.70 and 9.18 (2H, 2s, 2NH).

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

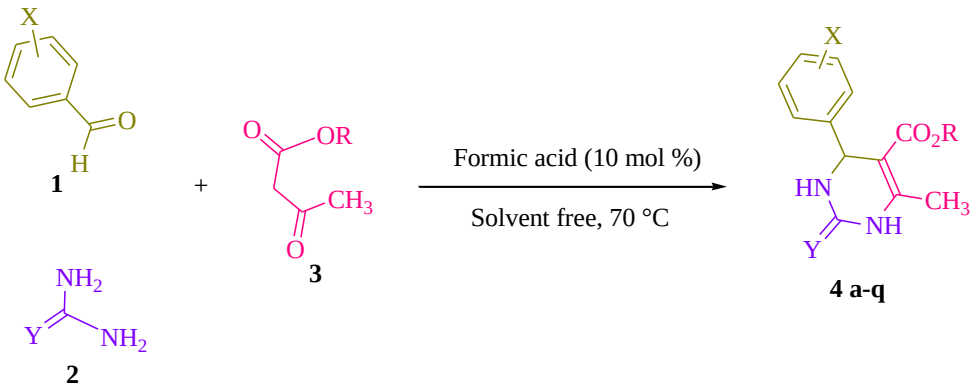
Yield: 86%; m.p. 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.10 (3H, t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, CH_3), 3.99 (2H, q, *J*=7.2 Hz, CH_2O), 5.15 (1H, s, $H_{benzylic}$), 7.26 (3H, d, *J*= 7.2 Hz, H_{Ar}), 7.33 (2H, t, *J*=7.2 Hz, H_{Ar}), 7.76 and 9.21 (2H, 2s, 2NH).

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

Yield: 85%; m.p. 209-211 °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, $H_{benzylic)}$, 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).

RESULTS

At the beginning, we performed three-component condensation of benzaldehyde (1.0 mmol), urea (1.5 mmol) and ethyl acetoacetate (1.0 mmol) in the presence of formic acid (10 mol%) under solvent-free at 70 °C, the product **4h** was found in 86%, which was confirmed by ^{1}H NMR spectroscopy. Encouraged by this result, we have chosen this reaction as a model reaction to study the reaction conditions further for the synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines (**4a-q**). The catalyst plays an important role in the success of the reaction in terms of the rate of the reaction and yields. In order to optimize the reaction conditions, quantity of the catalyst required was determined. No product could be detected in the absence of the catalyst even after 10 h (Table 1, entry 1). Then, 5 mol% formic acid was used to perform the reaction. But it requires slightly longer reaction time and low yields (Table 1, entry 2). Therefore, the loading of catalyst was gradually increased from 5 mol% to 15 mol% (Table 1). It was found that 10 mol% of formic acid are optimal to carry out the reactions in a short duration (Table 1, entry 3). The use of excess of catalyst did not alter either reaction time or yield of the product. Thus, the use of 10 mol% formic acid is ideal to achieve the desired product in high yields. We also investigated different temperatures for the model reaction (Table 1). It was observed that fast reaction occurred on raising the temperature from rt to 80 °C and the yield of preferred production increased significantly (Table 1). We were satisfied to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 70 °C to afford the desired product (**4h**) in 86% yields within 20 min (Table 1, entry 3). A further increase in the temperature did not affect the product yield (Table 1, entry 8). Having optimized reaction conditions, we synthesized a series 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines *via* aryl aldehyde derivatives (**1**, 1.0 mmol), urea/ thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) (**4a-q**) using 10 mol% formic acid as the catalyst under solvent-free conditions at 70 °C (Scheme 1) and the results are summarized in Table 2.



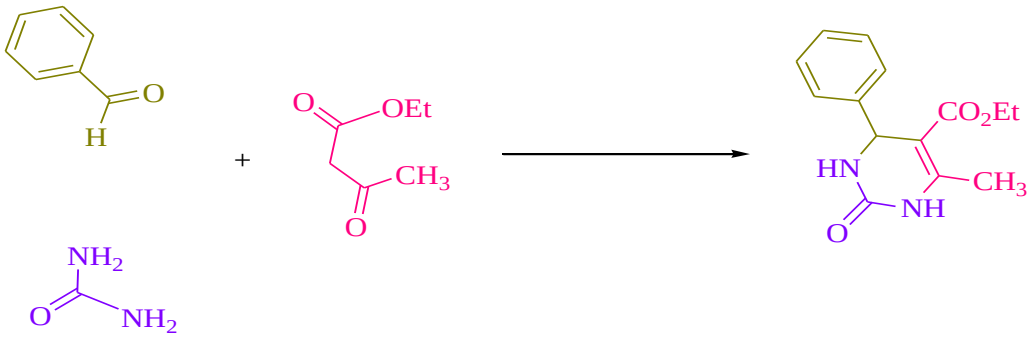
(Ar)**1a**,=4-NO_2-C_6H_4; **1b**= 4-OH-C_6H_4; **1c**= 2-Cl-C_6H_4; **1d**= 4-OH-C_6H_4; **1e**= 3-OMe-C_6H_4; **1f**= 4-Me-C_6H_4; **1g**= 4-OMe-C_6H_4; **1h**= Ph; **1i**= 4-NO_2-C_6H_4; **1j**= 2-Cl-C_6H_4; **1k**= Ph; **1l**= 4-F-C_6H_4; **1m**= 4-Me-C_6H_4; **1n**= 4-F-C_6H_4; **1o**= 3-OH-C_6H_4; **1p**= 2-$NO_2C_6H_4$; **1q**= N,N-diMe-C_6H_4

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

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

Figure 1. Synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines.

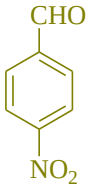
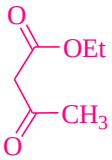
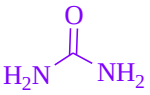
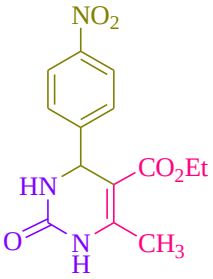
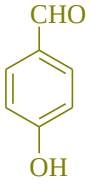
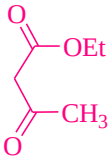
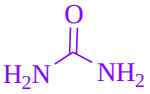
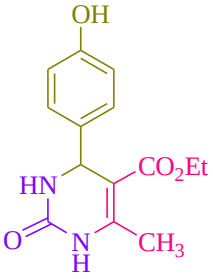
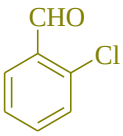
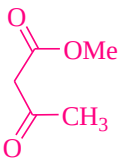
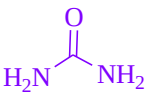
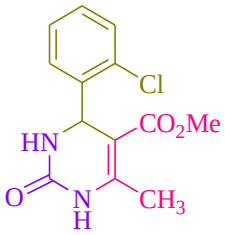
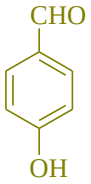
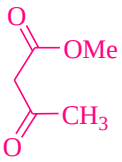
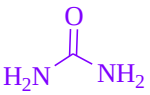
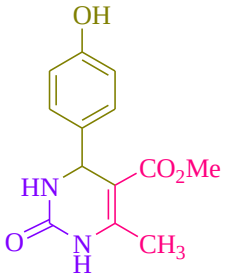
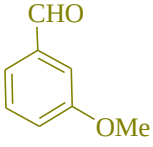
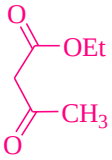
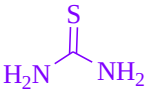
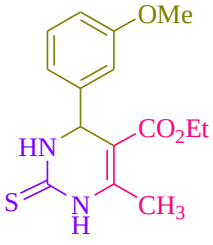
Table 1. Optimization of the reaction condition on the synthesis of **4h** [a].



Entry	Formic acid (mol %)	Temperature (^{0}C)	Time (min)	Isolated yields (%)
1	Catalyst free	70	600	No product
2	5	70	35	61
3	**10**	**70**	**20**	**86**
4	10	rt	600	No product
5	10	40	75	25
6	10	50	45	42
7	10	60	30	67
8	10	80	20	86
9	15	70	20	88

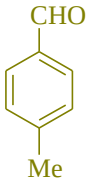
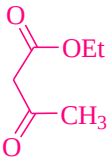
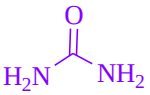
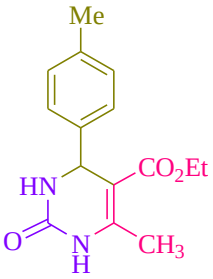
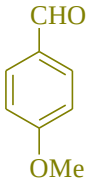
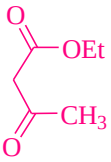
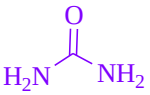
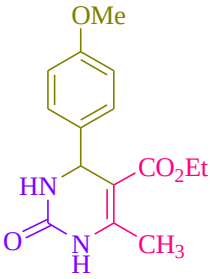
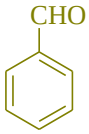
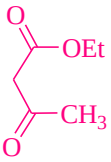
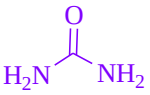
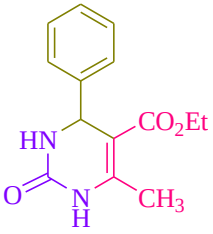
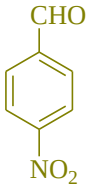
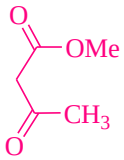
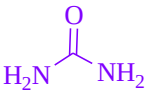
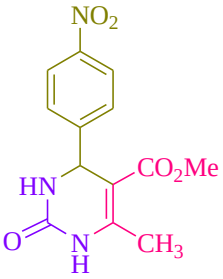
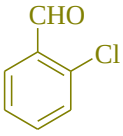
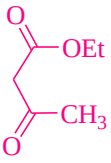
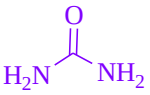
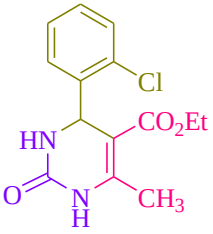
Note: [a] Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5mmol) and formic acid was heated under various temperatures for the appropriate time.

Table 2. Synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines.

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.˚C	Lit. m.p.˚C
1				 **4a**	20	87	206-208	207-209 (Liu et al., 2009)
2				 **4b**	35	73	231-233	234-236 (Khodja et al., 2014)
3				 **4c**	25	80	250-252	248-252 (Liu et al., 2009)
4				 **4d**	30	75	246-248	245-246 (Kumar et al., 2007)
5				 **4e**	30	84	151-153	150-151(Kumar et al., 2007)

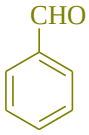
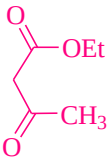
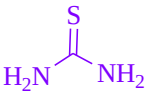
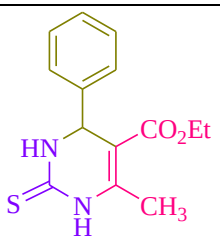
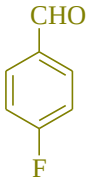
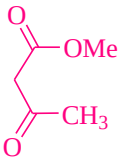
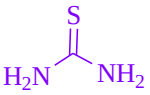
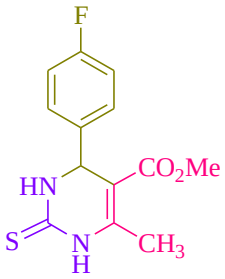
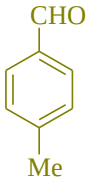
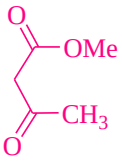
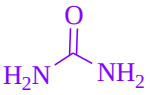
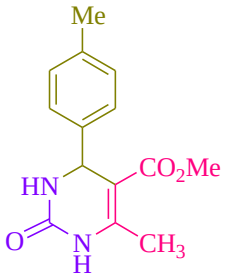
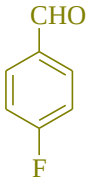
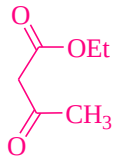
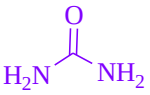
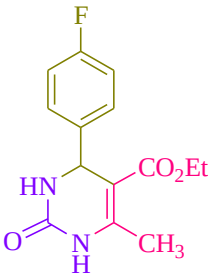
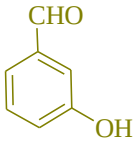
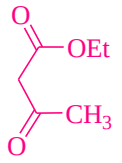
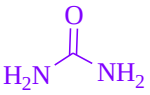
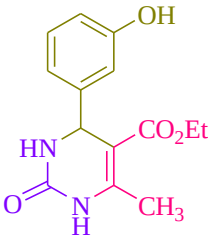
Note: [a] Isolated yield. [b] Reaction conditions: Aryl aldehyde derivatives (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and formic acid (10 mol %) was heated at 70 °C.

Table 2. Cont.

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.˚C	Lit. m.p.˚C
6				 **4f**	20	88	200-202	204-205 (Kumar et al., 2007)
7				 **4g**	25	86	202-204	203-205 (Zhang et al., 2015)
8				 **4h**	20	86	198-200	200-202 (Liu et al., 2009)
9				 **4i**	20	86	212-214	214-216 (Liu et al., 2009)
10				 **4j**	25	78	220-222	220-223 (Liu et al., 2009)

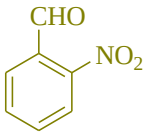
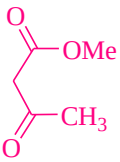
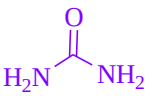
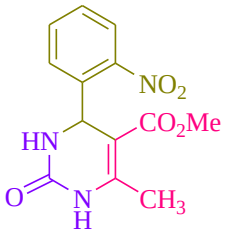
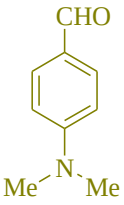
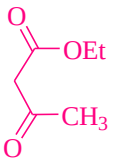
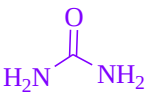
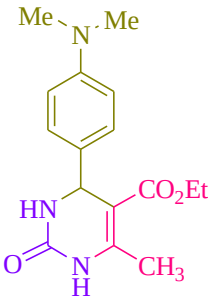
Note: [a] Isolated yield. [b] Reaction conditions: Aryl aldehyde derivatives (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and formic acid (10 mol %) was heated at 70 °C.

Table 2. Cont.

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.˚C	Lit. m.p.˚C
11				 **4k**	20	85	209-211	208-210 (Liu et al., 2009)
12				 **4l**	25	86	206-208	208-210 (Ahmad et al., 2009)
13				 **4m**	20	84	201-203	200-203 (Kamal et al., 2007)
14				 **4n**	20	89	176-178	174-176 (Ahmad et al., 2009)
15				 **4o**	35	78	165-167	163-166 (Kamal et al., 2007)

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 formic acid (10 mol %) was heated at 70 °C.

Table 2. Cont.

Entry	Substrate	Substrate	Substrate	Product [a]	Time (min)	Yield % [b]	m.p.°C	Lit. m.p.°C
16				 **4p**	20	89	276-278	274-277 (Kamal et al., 2007)
17				 **4q**	30	84	255-257	254-256 (Khodja et al., 2014)

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 formic acid (10 mol %) was heated at 70 °C.

DISCUSSION

Although different mechanistic pathways have been previously proposed (Kamal et al., 2007; De Souza et al., 2009; Alvim et al., 2014; Rao Jetti et al., 2017; Safaei-Ghomi et al., 2018), we believe that the reaction may proceed through an initial *N*-acylimine **B** formed from aldehyde **3** and urea **2** (Figure 2). The coordination of the lone-pair of the nitrogen atom in the *N*-acylimine **B** with the formic acid could lead to the *in situ* formation of an *N*-carbamoyliminium ion **C**, which is sufficiently electrophilic to react with the enol form of ethyl acetoacetate **A** affording the open chain intermediate **D**. Further intramolecular cyclization, with elimination of H_2O, produce the 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines **4**.

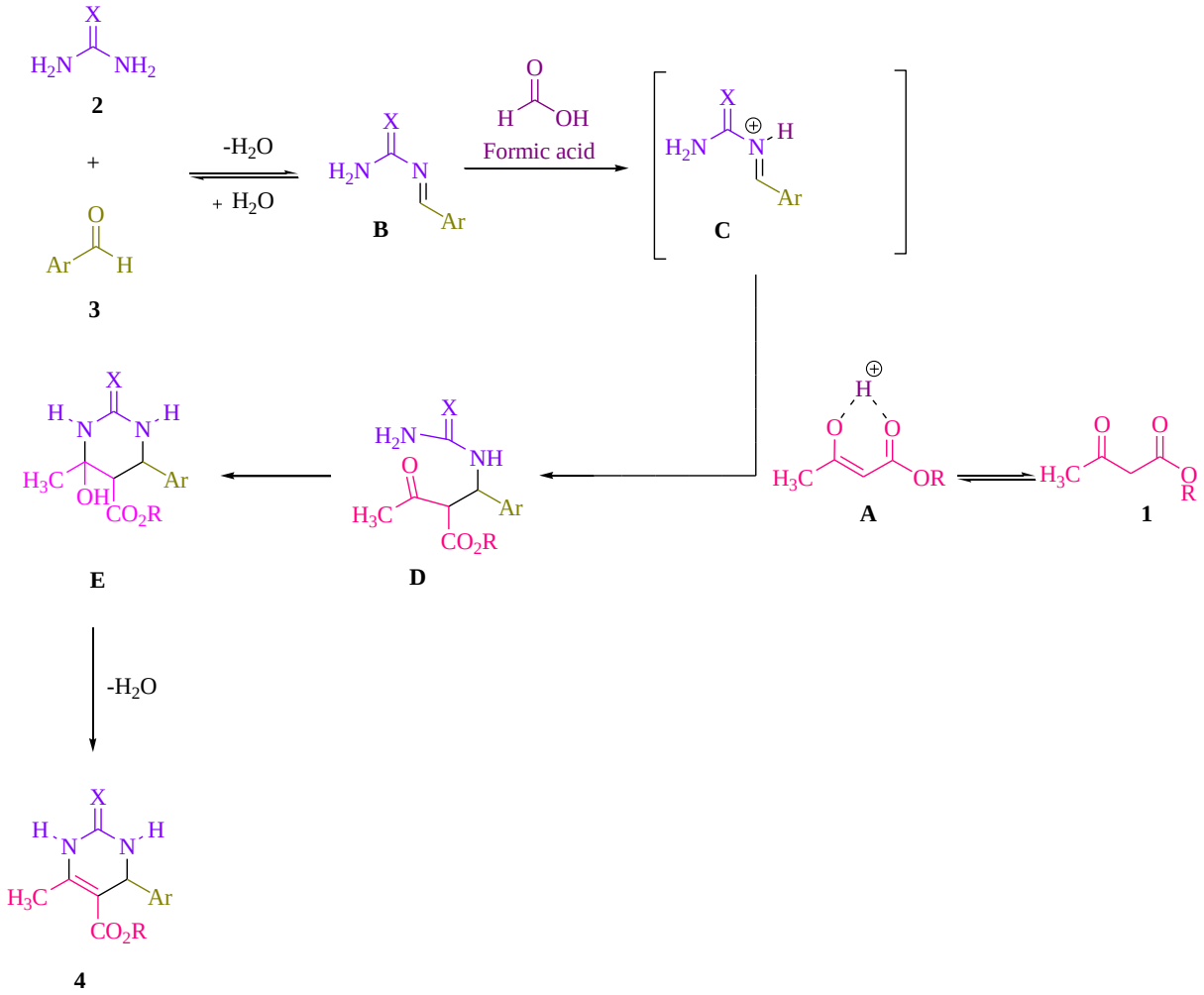


Figure 2. Proposed mechanistic route for the synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines are shown in Table 3. This study reveals that formic 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 green and simple procedure.

Table 3. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines[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	Formic acid	Solvent-free, 70 °C	20 min/86	This work

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

CONCLUSION

In summary, a natural green, highly efficient and bio-based acidic catalyst, *i.e.* formic acid was developed and exploited for clean, facile and economical one-pot synthesis of 2-oxo- and thioxo-1,2,3,4-tetrahydropyrimidines from starting materials under solvent-free conditions. This method gave an insight on the credibility of pathway followed by the aforementioned green and bio-based catalyst in aiding the heterocyclic compound formation. Cleaner reaction profile, simple column-free work up condition, shorter reaction times, high to excellent yields, solvent-free conditions, eco-friendly and high catalytic activity make this present procedure an interesting alternative to multistep approach.

ACKNOWLEDGEMENTS

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