

One pot synthesis of Biginelli 3,4-dihydro-1H-pyrimidin-2-ones and 1,2,3,4-tetrahydro pyrimidines

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Abstract

A simple and practical route for the Biginelli cyclocondensation reaction using anhydrous ZnCl₂ as a catalyst in n-heptane-toluene medium by reaction of substituted benzaldehydes, 1a-d (1a=2-ClC₆H₄-, 1b=2-BrC₆H₄-, and 1c=4-ClC₆H₄-, 1d=2-H₃CC₆H₄-) with 1, 3-dicarbonyl compounds, 2a-b (2a= ethyl acetoacetate and 2b= acetylacetone) and urea or thiourea, 3a-b to give the corresponding Biginelli 3,4-dihydro- 1H-pyrimidin-2-ones and 1,2,3,4-tetrahydro pyrimidines, 4a-d. The structures of the compounds 4a-d were confirmed by their ultraviolet, infrared, ¹H NMR, ¹³C NMR spectra and elemental analyses.

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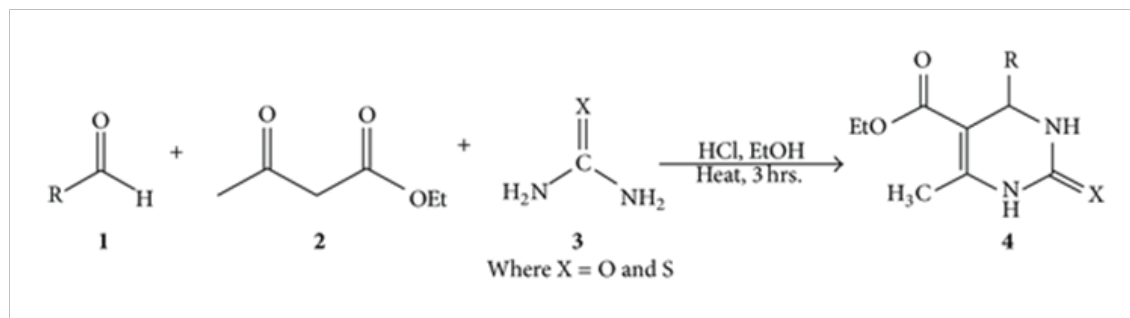
Introduction

The classical Biginelli condensation (Biginelli 1893) involving the reaction of an aldehyde, β-keto ester and urea or thiourea under strong acidic conditions to give 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) which exhibit widespread biological applications. A large number of catalysts, solvent systems have been developed in accelerating this reaction since then. DHPMs are well known for their wide range of bioactivity and their application as calcium channel blockers, α 1-1-a-antagonists, antihypertensive agents, inhibitors of the fatty acid transporter and mitotic kinesin inhibition (Rovnyak *et al.*, 1995; Van Zandt *et al.*, 2005). These compounds have also been found to possess antiviral, antitumor, anti-inflammatory and antibacterial properties (Tsuruo *et al.*, 1983; Kappe 1993, 2000). A huge number of reviews (Mirzaei *et al.*, 2001; Shaaban *et al.*, 2008; Cho *et al.*, 1989; Rajeshwari *et al.*, 2013) on synthesis and chemical properties of dihydropyrimidinones have already

been published. Several marine alkaloids with interesting biological activities also contain the dihydropyrimidinone-5-carboxylate core (Snider *et al.*, 1993). Most notably among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors (Snider *et al.*, 1996; Patil *et al.*, 1995). The anti-cancer agent monastrol (Fig. 1) has been shown to specifically affect mitosis *via* a new mechanism consisting of the specific and reversible inhibition of the motility of the motor protein mitotic kinesin (Dondoni *et al.* 2002; Laville *et al.*, 2009).

In order to improve the efficiency of Biginelli reaction coupled with the biological study of synthesized compounds many catalysts have been developed such as zirconium(IV) chloride (Reddy *et al.*, 2002), indium(III) bromide (Fu *et al.*, 2002), ceric ammonium nitrate (CAN) (Yadav *et al.*, 2001), indium(III) chloride (Ranu *et al.*, 2000),

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Scheme 1. Traditional Biginelli reaction

lanthanum chloride (Lu *et al.*, 2000), Boric acid (Tu *et al.*, 2003), lithium bromide (Maiti *et al.*, 2003) silica/sulfuric acid (Salehi *et al.*, 2003), vanadium(III) chloride (Sabitha *et al.*, 2003), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (Lu *et al.*, 2000), zinc triflate (Xu *et al.*, 2003), trichloroacetic acid (Jaberi *et al.*, 2012), nanosilica-supported tin(II) chloride (Ghomi *et al.*, 2013), Bronsted acid (Anjaneyulu *et al.*, 2015), L-proline nitrate (Bahekar *et al.*, 2017), InBr_3 (Maskrey *et al.*, 2018) and $\text{Hf}(\text{OTf})_4$ (Kong *et al.*, 2019). Some of these catalysts are really very fascinating from a synthetic chemist's point. Despite their tremendous success, however, some drawbacks still remain. For example, some of the catalysts are expensive, complex or unavailable.

In the past 20 years, several one-pot methodologies for the synthesis of DHPM derivatives were developed and several modifications have been introduced. Most of them are based on Lewis acid-catalyzed reactions (Paraskar *et al.*, 2003; Sabitha *et al.*, 2005; Azizian *et al.*, 2006; Sadek *et al.*, 2010; Shapiro and Vigalok, 2008; Salim and Akamanchi, 2011; Chitra and Pandiarajan, 2009; Mandhane *et al.*, 2010) which permits the reaction to proceed under milder conditions and with higher yields, than those out-lined by *Biginelli* in the original procedure. Microwave irradiation has also proved beneficial (Pasunooti *et al.*, 2011). Natural acidic catalysts have been also utilized (Patil *et al.*, 2011).

Biginelli reaction has also been conducted under basic conditions. This involves the use of PPh_3 under solvent free conditions (Debache *et al.*, 2008), *t*-BuOK at 70°C (Shen *et al.*, 2010), chiral primary amines (Ding and Zhao, 2010) and ammonium carbonate in water (Tamaddon *et al.*, 2010). It is worth mentioning that many of these existing methods displayed drawbacks, such as environmental pollution caused by utilizing catalysts in stoichiometric quantities, exotic reaction conditions, unsatisfactory yields and complicated operations while others possess some advantages overcoming these drawbacks. Zinc chloride, a very inexpensive and easily available Lewis acid catalyst, has been widely used in organic

reactions, but it hasn't been carefully studied as a catalyst in Biginelli condensation until now, except for a few mentions in literature (Sun *et al.*, 2004).

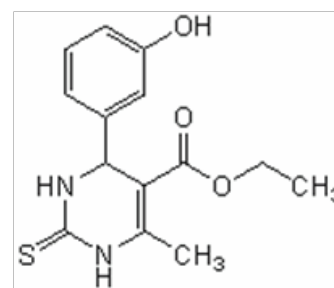
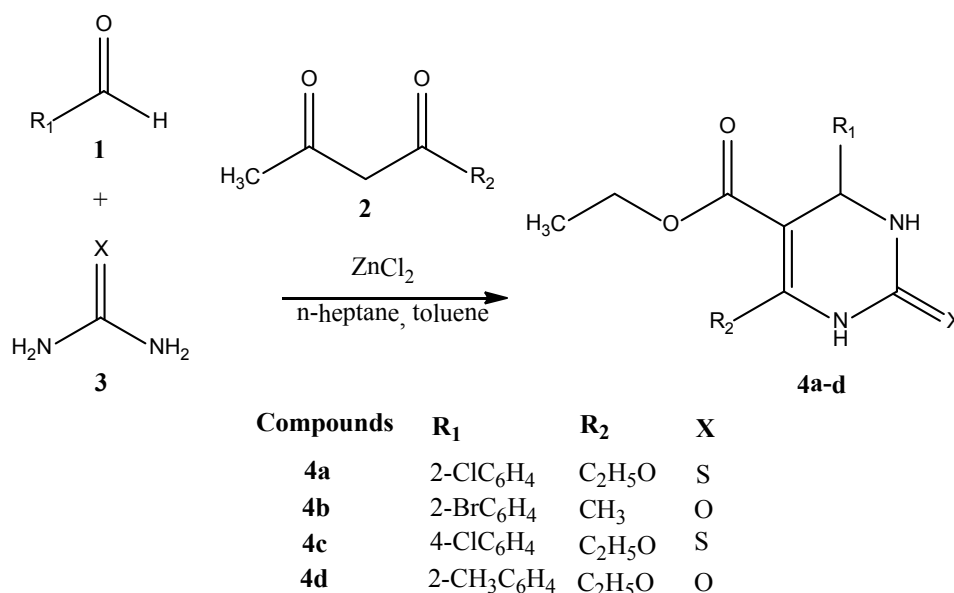


Fig. 1. Monostrol

In continuation of our interest in the synthesis of fused pyrimidines (Akhter *et al.*, 2015), we report herein a simple and practical route for the Biginelli cyclocondensation reaction using ZnCl_2 as a catalyst in *n*-heptane-toluene medium. This is a novel, one pot combination that not only preserves the simplicity of Biginelli's one pot reaction but also consistently produce excellent yields of the di (or tetra) hydropyrimidinones, 4a-d (Scheme 2). The compounds 4a-d do not seem to be available in the literature.

Materials and methods

All chemicals were purchased from E. Merck. Thin layer chromatography (TLC) was carried out on plates percolated with silica gel 60 F254 and spots were detected with iodine vapour. Melting points were determined on an Electro thermal micro melting-point apparatus and uncorrected. The Ultraviolet spectra of the samples were recorded on a Shimadzu UV-160A spectrometer with a scanning range of 800-200 nm using methanol as solvent. IR spectra were recorded with Shimadzu IR 470A spectrophotometer in the range 4000-400 cm^{-1} . The ^1H NMR and ^{13}C NMR spectra of



Scheme 2. Synthesis of the compounds, 4a-d

the samples were recorded on a Bruker 400 MHz spectrophotometer using DMSO-d₆ as solvent with Tetramethylsilane (TMS) as an internal standard.

General procedure

A mixture of a benzaldehyde (10 mmol), a 1,3-dicarbonyl compound (10 mmol), urea or thiourea (15 mmol) and ZnCl₂ (273 mg, 2mmol) was refluxed in heptane-toluene (30mL, 1:1) medium under magnetic stirring for 4 hours. Upon completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, poured onto 30 ml of water. The resulting solid was filtered under suction and successively washed with H₂O (30 ml) and petroleum ether-EtOAc (5:1, 30 ml). The crude product was then purified by re-crystallization (acetone-ethanol mixture) to give pure product. Compounds obtained according to this procedure were characterized and identified by their melting points, UV, FT-IR, ¹H-NMR, ¹³C-NMR and elemental analyses.

4-(2-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, 4a:

Yield 78%; white crystalline solid; mp 164-165°C; R_f value in TLC 0.85 (Ethyl acetate: Chloroform,1:4); UV (λ_{max} in nm): 305 (π→π*/n→π* of C=O); IR (KBr) (ν_{max} cm⁻¹): 3180 (N-H stretching), 1708 (C=O), 1654 (C=C in conj. with C=O),

1444 (C=S stretching), 1089 (Aromatic-Cl); ¹H NMR δ (in ppm): 8.81 (s, 1H, N-H, 1-H), 7.67 (s, 1H, N-H, 3-H), 7.36 (d, 1H, J=7.8 Hz, 3'-H), 7.24-7.20 (m, 3H, 4', 5' & 6'-H), 5.89 (d, 1H, J=3.0 Hz, 4-H), 4.01 (q, 2H, J=7.2, CH₃CH₂COO-), 2.43 (s, 3H, CH₃-C=C₅-), 1.05 (t, 3H, J=4.8 Hz, CH₃CH₂COO-); ¹³C NMR δ (in ppm): 174.02 (C-2), 164.82 (CH₃CH₂COO-), 144.62 (C-6), 138.50 (1'), 132.51(2'), 129.78(3'), 129.57(6'), 128.51(4'), 127.60(5') (6C-aromatic), 100.73 (5-C), 60.26 (CH₃CH₂COO-), 52.56 (4-C), 17.74 (CH₃-C=C₅-), 13.79 (CH₃CH₂COO-). Anal. Found: C, 54.20; H, 4.90; N, 8.98; Calc. for C₁₄H₁₅ClN₂O₂S: C, 54.10; H, 4.86; N, 9.01%.

5-Acetyl-4-(2-bromophenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one, 4b:

Yield 70%; Off white crystalline solid; mp 224-226°C; R_f value in TLC 0.44 (Neat Chloroform); UV (λ_{max} in nm): 301 (π→π*/n→π* of C=O); IR (KBr) (ν_{max} cm⁻¹): 3252 (N-H stretching), 1705 (C=O), 1624 (C=C in conj. with C=O), 1026 (Aromatic-Br); ¹H NMR δ (in ppm): 9.27 (s, 1H, N-H, 1-H), 7.67 (s, 1H, N-H, 3-H), 7.59 (d, 1H, J=8.4 Hz, 3'-H), 7.35 (d, 1H, J=7.8 Hz, 5'-H), 7.25 (d, 1H, J=7.2 Hz, 6'-H), 7.19 (d, 1H, J=7.8 Hz, 4'-H), 5.61 (d, 1H, J=3.0 Hz, 4-H), 2.32 (s, 3H, CH₃CO-), 2.03 (s, 3H, CH₃-C=C₅-); ¹³C NMR δ (in ppm): 201.26 (CH₃CO-), 160.83 (C-2), 139.56 (C-6), 145.22 (1'), 122.80 (2'), 130.56 (3'), 129.46 (6'),

128.17 (4'), 127.44 (5') (6C-aromatic), 105.41 (5-C), 51.92 (4-C), 26.22 ($\underline{\text{CH}}_3\text{CO-}$), 17.82 ($\underline{\text{CH}}_3\text{-C}_6\text{=C}_5\text{-}$). Anal. Found: C, 50.60; H, 4.32; N, 8.99; Calc. for $\text{C}_{13}\text{H}_{13}\text{BrN}_2\text{O}_2$: C, 50.50; H, 4.24; N, 9.06%.

4-(4-Chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, 4c:

Yield 38%; yellowish crystalline solid; mp 168-170°C; R_f value in TLC 0.52 (Neat ethyl acetate); UV (λ_{max} in nm): 285 ($\pi \rightarrow \pi^*/n \rightarrow \pi^*$ of C=O); IR (KBr) (ν_{max} cm^{-1}): 3276 (N-H stretching), 1750 (C=O), 1612 (C=C in conj. with C=O), 1415 (C=S stretching), 1084 (Aromatic-Cl); $^1\text{H NMR}$ δ (in ppm): 7.44 (s, 1H, N-H, 1-H), 7.41 (s, 1H, N-H, 3-H), 7.29 (d, 2H, J=7.8 Hz, 3' & 5'-H), 7.22 (d, 2H, J=8.4 Hz, 2' & 6'-H), 5.36 (d, 1H, J=2.49 Hz, 4-H), 4.08 (q, 2H, J=6.6, $\text{CH}_3\text{CH}_2\text{COO-}$), 2.34 (s, 3H, $\underline{\text{CH}}_3\text{-C}_6\text{=C}_5\text{-}$), 1.17 (t, 3H, J=7.2 Hz, $\underline{\text{CH}}_3\text{CH}_2\text{COO-}$); $^{13}\text{C NMR}$ δ (in ppm): 173.89 (C-2), 165.02 ($\text{CH}_3\text{CH}_2\text{COO-}$), 145.22 (C-6), 139.50 (1'), 128.52(2'), 129.88(3'), 128.58(6'), 130.51(4'), 129.90(5') (6C-aromatic), 101.61 (5-C), 59.96 ($\text{CH}_3\text{CH}_2\text{COO-}$), 52.12 (4-C), 17.77 ($\underline{\text{CH}}_3\text{-C}_6\text{=C}_5\text{-}$), 13.72 ($\underline{\text{CH}}_3\text{CH}_2\text{COO-}$). Anal. Found: C, 54.22; H, 4.82; N, 8.98; Calc. for $\text{C}_{14}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$: C, 54.10; H, 4.86; N, 9.01%.

6-Methyl-2-oxo-4-o-tolyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid ethyl ester, 4d:

Yield 70%; white crystalline solid; mp 207-208°C; R_f value in TLC 0.72 (Ethyl acetate: Chloroform, 1:1); UV (λ_{max} in nm): 292 ($\pi \rightarrow \pi^*/n \rightarrow \pi^*$ of C=O); IR (KBr) (ν_{max} cm^{-1}): 3235 (N-H stretching), 1700 (C=O), 1643 (C=C in conj. with C=O); $^1\text{H NMR}$ δ (in ppm): 8.43 (s, 1H, N-H, 1-H), 5.81 (s, 1H, N-H, 3-H), 7.24-7.20 (m, 4H, 3', 4', 5' & 6'-H), 5.64 (bs, 1H, 4-H), 3.97 (q, 2H, J=7.2, $\text{CH}_3\text{CH}_2\text{COO-}$), 2.41 (s, 3H, Ar- $\underline{\text{CH}}_3$), 2.35 (s, 3H, $\underline{\text{CH}}_3\text{-C}_6\text{=C}_5\text{-}$), 1.05 (t, 3H, J=7.2 Hz, $\underline{\text{CH}}_3\text{CH}_2\text{COO-}$); $^{13}\text{C NMR}$ δ (in ppm): 153.13 (C-2), 165.64 ($\text{CH}_3\text{CH}_2\text{COO-}$), 141.40 (C-6), 146.82 (1'), 132.59 (2'), 130.66 (3'), 127.86 (6'), 127.17 (4'), 126.84 (5') (6C-aromatic), 100.64 (5-C), 59.89 ($\text{CH}_3\text{CH}_2\text{COO-}$), 52.18 (4-C), 18.92 ($\underline{\text{CH}}_3\text{-C}_6\text{=C}_5\text{-}$), 18.45 (Ar- $\underline{\text{CH}}_3$), 14.04 ($\underline{\text{CH}}_3\text{CH}_2\text{COO-}$). Anal. Found: C, 65.61; H, 6.70; N, 10.11; Calc. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$: C, 65.68; H, 6.61; N, 10.21%.

Results and discussion

The one-pot synthesis of di (or tetra) hydroypyrimidines 4a-d were synthesized by the three component condensation of substituted benzaldehydes 1a-d, with corresponding β -dicarbonyl compounds 2a-b and urea or thiourea 3a-b in presence of anhydrous zinc chloride in heptane-toluene under

refluxing conditions in an analogous manner reported previously (Akhter *et al.*, 2015). The structures of the compounds 4a-d were confirmed based on their UV, FT-IR, $^1\text{H NMR}$, $^{13}\text{C NMR}$ and elemental analyses.

The compounds 4a-d agree well to the expected λ_{max} values in their UV spectra. The absorption bands in the range 305-285 nm may be assigned to the $\pi \rightarrow \pi^*$ of C=O in these compounds. The weak $n \rightarrow \pi^*$ absorption bands in the cases of these compounds due to C=O were probably masked within the $\pi \rightarrow \pi^*$ absorption range.

The IR data of the compounds 4a-d showed sharp as well as broad bands in the range (ν_{max}) 3276-3180 cm^{-1} indicating the presence of N-H group. The absorption bands at 1750-1700 cm^{-1} indicate the presence of non-conjugated C=O stretching including the pyrimidine moieties. The bands at 1654-1612 cm^{-1} were assigned to C=C of aromatic rings in conjugation with C=O and 1444-1415 cm^{-1} for C-S stretching of compounds 4a and 4c. Additional bands were observed at 1089-1026 cm^{-1} due to presence of halogenated aromatics of compounds 4a, 4b and 4c.

In their $^1\text{H NMR}$ spectra of compounds 4a-d, the N-H protons were relatively deshielded (δ 9.27-7.44) and appeared as singlet due to anisotropy and presence of electronegative atoms attached to this group. The proton at position 4 appeared as a doublet (or broad singlet) gave signals at δ 5.89-5.36 due to the vicinal coupling with the proton at position 3. The methylene protons (4a, 4c and 4d) appeared as quartet being attached to a methyl in one side and an ester on the other side further deshielded due to direct link with one oxygen of ester group and gave peaks at δ 4.08-3.97 ppm. The methyl protons in these compounds attached to an alkene carbons gave peaks at δ 2.43-2.03 ppm and another methyl protons (4b) attached to carbonyl group gave peaks at δ 2.32 ppm as singlet. The aromatic methyl of compound 4d appeared as singlet and gave signal at δ 2.41 ppm. The methyl protons of ester group (4a, 4c and 4d) appeared as triplets and gave signals at δ 1.17-1.04 ppm. All aromatic protons have shown peaks in their expected positions.

The structures of the compounds 4a-d were further confirmed by their $^{13}\text{C NMR}$ spectra. The chemical shifts of carbonyl carbon at 2-C were found to be deshielded in the range of δ 174.02-153.13. The chemical shifts of $\underline{\text{CH}}_3\text{CO-}$ of compound 4b was further deshielded (δ 201.26). The chemical shift values for $\text{-COOCH}_2\text{CH}_3$ in compounds 4a, 4c and 4d were observed at (δ 165.64-164.82). The chemical shifts of 6-C were similarly deshielded (δ 145.22-139.56). The 5-C of the compounds showed chemical shift values at δ 105.40-100.64. The chemical shift values for 4-C in these compounds were

observed at δ 52.56-51.92. The chemical shift values for methyl carbon attached to alkene ($C_6=C_3$) in these compounds were observed at δ 18.92-17.74. The chemical shift values for $-\text{COOCH}_2\text{CH}_3$ and $-\text{COOCH}_2\text{CH}_3$ in compounds 4a, 4c and 4d were observed at δ 60.26-59.89 and 14.04-13.71 respectively. The chemical shift values for $\text{CH}_3\text{CO}-$ in compound 4b and aromatic methyl carbon in compound 4c were observed at δ 26.22 and 18.45 respectively. The ^{13}C NMR chemical shifts for the carbons of aromatic rings were found in their expected positions.

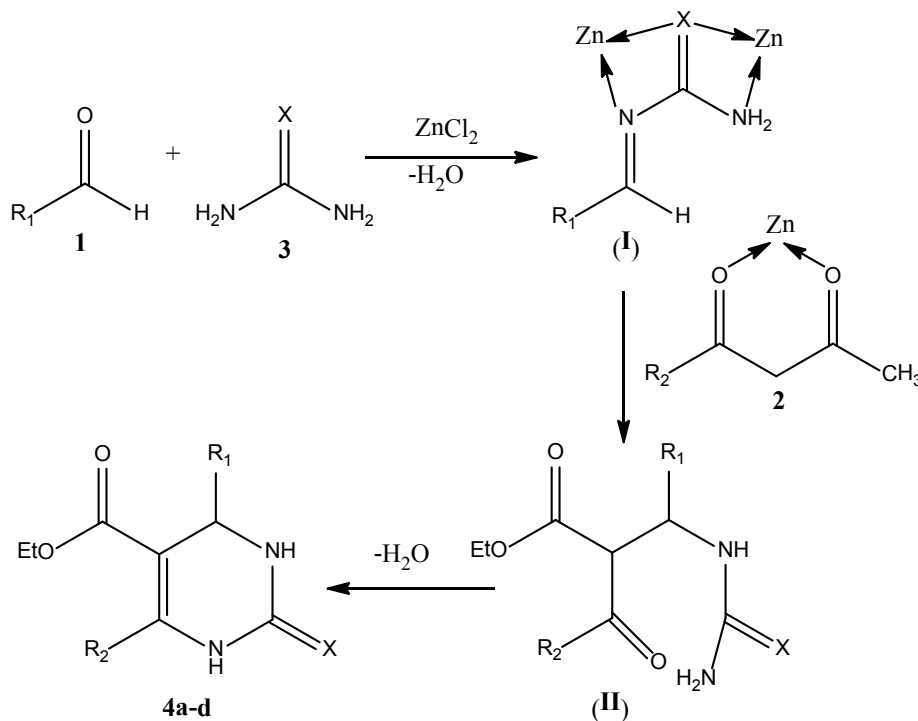
Although different mechanistic pathways have been proposed previously (Tamaddon *et al* 2010), we believe that the reaction may proceed through an initially formed imine intermediate [I] from the reaction of the aldehyde, 1 and urea or thiourea, 3 (Scheme-3). The co-ordination of the lone pair of the nitrogen atom with the Lewis acid could lead to the *in situ* formation of iminium ion [II] which is sufficient electrophile to react with the enol form of ethyl acetoacetate, 2 affording finally intramolecular cyclization with loss of H_2O molecule, producing di (or tetra) hydropyrimidines, 4a-d.

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Where R_1 = Subs. phenyl, R_2 = $-\text{CH}_3$ or $-\text{OCH}_2\text{CH}_3$ and X = O or S

Scheme 3. A plausible reaction mechanism for 4a-d

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