

SNCL₂-CATALYZED SYNTHESIS OF DIHYDROPYRIMIDINONES UNDER SOLVENT-FREE CONDITIONS

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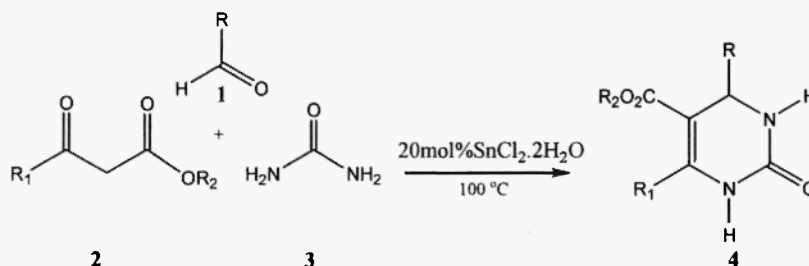
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Abstract : A simple, efficient and practical green synthetic route to the Biginelli cyclocondensation reaction using Stannous (II) Chloride Dihydrate as the catalyst is described under solvent free conditions to yield dihydropyrimidinones in high yields.

Key words: Dihydropyrimidines, Biginelli, Stannous chloride, Solvent-free.

Solvent-less catalytic reactions have received considerable attention in recent times in the area of green synthesis.^{1,2} On the other hand, dihydropyrimidinones and their derivatives have increasingly attracted the attention of synthetic chemists owing to their remarkable pharmacological properties such as calcium channel blockers, antiviral, antitumor, antibacterial, and anti-inflammatory activities.³ Moreover, the dihydropyrimidine-5-carboxylate core has been found in several marine natural products which are potent HIVgp-120-CD4 inhibitors.⁴ This prompted us to initiate a systematic investigation to look into the feasibility of solvent-free reactions towards development of green methodology for dihydropyrimidines. There have been many reports on the Lewis acid catalyzed Biginelli reactions to synthesize dihydropyrimidines.⁵

Stannous Chloride Dihydrate, which is cheap and commercially available, is known to be an efficient Lewis acid type precatalyst for carbon-carbon bond forming reactions and allylic addition of functionalized compounds to aldehydes and ketones.⁶ However, Sn(II)Cl₂.2H₂O, has not been carefully studied as a catalyst in heterocyclization and cyclocondensation reactions. In this report, we describe a simple and practical method for the synthesis of dihydropyrimidinones **4** by an improved Biginelli protocol using catalytic amount of stannous chloride under solvent-free conditions (Scheme-1).



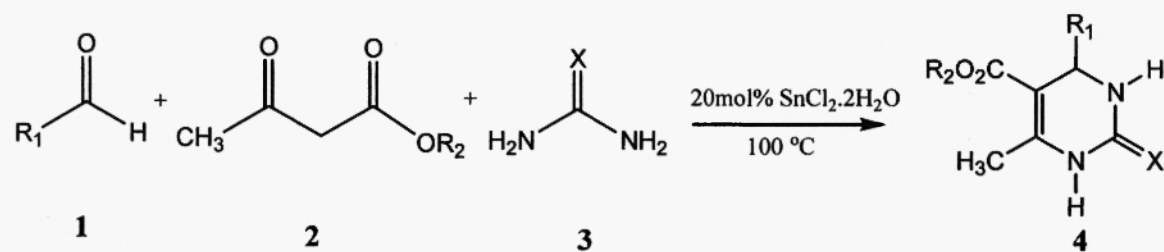
Scheme-1

Results and Discussion

The reaction of benzaldehyde (1.06 g, 10 mmol), ethylacetoacetate (1.30 g, 10 mmol) and urea (0.72g, 12mmol) was investigated previously using 20 mol% SnCl₂.2H₂O at 100°C for 20 minutes. The heterogeneous reaction mixture containing the solid stannous chloride was stirred rapidly. Stannous Chloride and urea dissolves gradually as the reaction proceeds and after 5 minutes the mixture turns to be clear oil. After 10 minutes of stirring, the oil starts solidifying and the solid mass was heated under the same temperature for 10 minutes (monitored by TLC). The resulting solid was crushed, washed with cold water (200 mL) and filtered under suction (water aspirator). The solid was dried and recrystallized from hot ethanol to afford the analytically pure product **4a** with 96% yield (Table-1). The same process was successfully extended to a wide range of structurally varied aldehydes, urea/thiourea, and β- dicarbonyl compounds (Table-1); the corresponding dihydropyrimidinones were obtained in excellent yields. Many of the pharmacological relevant substitution patterns on the aromatic ring could be introduced with high efficiency.

Aromatic aldehydes carrying either electron-donating substituents afforded high yields of products in high purity.

As an extensive investigation, we have elaborated the SnCl₂.2H₂O catalyzed one-pot Biginelli reaction under aqueous and acetonitrile mediums by taking the mixture of benzaldehyde, ethylacetoacetate and urea as a representative example. The corresponding dihydropyrimidinones were obtained in both the conditions in moderate to good yields. The aqueous condition requires refluxing and longer time (5h) of reaction which ended finally with 50% overall yield. Refluxing the same reaction mixture under acetonitrile affords good yield (92%). However, this condition also requires longer heating (4-5h) and the yields of dihydropyrimidines in both the conditions are found still lower than the solvent-free condition which needs only 20 minutes heating at 100 °C with a yield of 96%. The yields of the solvent-free condition were compared with other conditions such as under refluxing acetonitrile and water (Table-2). The products obtained under solvent-free conditions are of high purity and do not require any chromatographic separation. The solvent-free conditions are much better in terms of yields and shorter reaction times. In addition, the reactions are very clean, and no side product was obtained in any run.

Table-1 : $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -catalyzed synthesis of dihydropyrimidinones under solvent-free conditions

Entry	R ₁	R ₂	X	Yield (%)	Mp (°C) found	Mp (°C) reported
4a	C ₆ H ₅	C ₂ H ₅	O	96	208-209	209-210 ^{6a}
4b	4-CH ₃ C ₆ H ₄	C ₂ H ₅	O	95	221-222	221-222 ^{6d}
4c	4-CH ₃ O C ₆ H ₄	C ₂ H ₅	O	95	200-202	199-201 ^{6b}
4d	4-HO C ₆ H ₄	C ₂ H ₅	O	92	237-238	236-238 ^{6b}
4e	4-Cl C ₆ H ₄	C ₂ H ₅	O	95	215-216	216-217 ^{6b}
4f	4-Me ₂ N C ₆ H ₄	C ₂ H ₅	O	90	253-254	256-258 ^{6c}
4g		C ₂ H ₅	O	90	174-175	177 ^{6d}
4h		C ₂ H ₅	O	86	260-262d	-
4i		C ₂ H ₅	O	92	189-190	187 ^{6d}
4j		C ₂ H ₅	O	89	248-250	247 ^{6d}
4k	4-Cl C ₆ H ₄	C ₂ H ₅	S	86	208-210	209-210 ^{6e}
4l	4-CH ₃ C ₆ H ₄	C ₂ H ₅	S	90	214-215	-

Table 2 Biginelli reaction of benzaldehyde, ethylacetoacetate and urea catalyzed by $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ under different conditions

Entry	Solvent	Catalyst (mol%)	Time	Yield of 4a (%)
4a	Water	20	5h	50
4a	Acetonitrile	20	4h	92
4a	No solvent	20	20min	96

In summary, a broad range of structurally diverse 1,3-dicarbonyl compounds, aldehydes, and urea/thiourea are subjected under the one-pot Biginelli cyclocondensation catalyzed

by Stannous Chloride under solvent-free conditions to produce the corresponding dihydropyrimidinones. In view of the simplicity, environmentally friendly nature and high yields, the present procedure of the synthesis of dihydropyrimidin-2 (1H)-ones provides a simple, efficient, cost-effective, and green modification of the Biginelli's reaction.

Experimental

The IR spectra were recorded on a Shimadzu FT-IR-8400S spectrometer in KBr pellets with absorption given in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded on a Varian EM-390 (300MHz) spectrometer in $\text{DMSO}-d_6$ with tetramethylsilane as internal standard. The Chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to internal tetramethyl silane (TMS). Mass measurements were carried out with Jeol JMSD-300 spectrometer from CDRI, Lucknow, India. Elemental analyses were performed on a Heraeus CHN-O-Rapid Analyzer.

Preparation of 4a under water reflux. Benzaldehyde (1.06 g, 10 mmol), and urea (0.72 g, 12 mmol) was suspended in water (15 mL) along with ethyl acetoacetate (1.30 g, 10 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.45 g, 20 mol %), and the heterogeneous mixture was refluxed for 5 h (monitored by TLC). The reaction mixture after being cooled to room temperature was poured cold water (100 mL). The solid separated was filtered under suction (water aspirator), dried, and then recrystallized from hot ethanol to afford pure product (50%).

Preparation of 4a under acetonitrile reflux. A solution of ethyl acetoacetate (1.30 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and urea (0.72 g, 12 mmol) in acetonitrile (20 mL) was heated under reflux in the presence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.45 g, 20 mol %) for 4 h (monitored by TLC). The reaction mixture (after being cooled to room temperature) was poured onto cold water (100 mL) and stirred for 5-10 min. The solid separated was filtered under suction (water aspirator), washed with ice-cold water (100 mL), and then recrystallized from hot ethanol to afford pure product (92%).

General procedure for $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ catalyzed Biginelli reactions under solvent –free conditions: To a mixture of aldehyde **1** (10 mmol), β -dicarbonyl compound **2** (10 mmol) and urea or thiourea **3** (12 mmol) was added $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2 mmol, 20 mol %) at room temperature. After it was stirred for 5 min, the resulting mixture was heated at 100 °C in a preheated oil bath for 20 –30 min (monitored by TLC). The reaction mixture was

brought to room temperature, crushed and 100 mL of cold water was added and stirred for 5-10 min. The solid was filtered under suction, washed with ice-cold water (100 mL), and then recrystallized from hot ethanol to afford pure product. Spectral and analytical data of selected compounds are given below:

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

^1H NMR: δ 1.15 (t, J = 7.1 Hz, 3H), 2.30 (s, 3H), 4.00 (q, J = 7.1 Hz, 2H), 7.20-7.25 (m, 2H), 8.40-8.58 (m, 2H), 9.00 (brs, 1H, NH), 9.40 (brs, NH); ^{13}C NMR: δ 13.7, 17.7, 49.6, 59.9, 106.4, 124.7, 124.8, 139.3, 146.6, 150.8, 156.8, 165.2. IR (KBr): 3290, 1712, 1679, 1589 cm^{-1} . Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.70; H, 5.63; N, 16.28.

5-Ethoxycarbonyl-4-(methylphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione

(4l): ^1H NMR: δ = 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.33–2.35 (m, 6H, $2\times\text{CH}_3$), 4.10 (m, 2 H, OCH_2), 5.36 (d, J = 2.4 Hz, 1 H), 7.02 (br. s, 1 H, NH), 7.12–7.26 (m, 4 H, ArH), 7.58 (br. s, 1 H, NH). MS (EI): m/z = 290 $[\text{M}^+]$. Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C 62.04, H 6.25, N 9.65. Found C 62.44, H 6.53, N 9.70.

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