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Tin(lV) catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones under solvent-free conditions

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One pot condensation of ethyl acetoacetate or methyl acetoacetate with various *para* and *ortho* substituted aromatic aldehydes and urea or thiourea by tin(IV) chloride affords twenty-one different substituted 3,4–dihydropyrimidin-2-(1*H*)-ones. Tin(IV) chloride has emerged as a powerful catalyst for the preparation of 3,4–dihydropyrimidin-2-(1*H*)-ones under simple and mild conditions. It is compatible with a wide variety of substituents in the aromatic aldehyde. Substituents at *para* position in aldehyde are more effective than the substituents at *ortho* position. Both the β–ketoesters, and urea or thiourea are equally effective towards an efficient 3,4–dihydropyrimidin-2-(1*H*)-one synthesis.

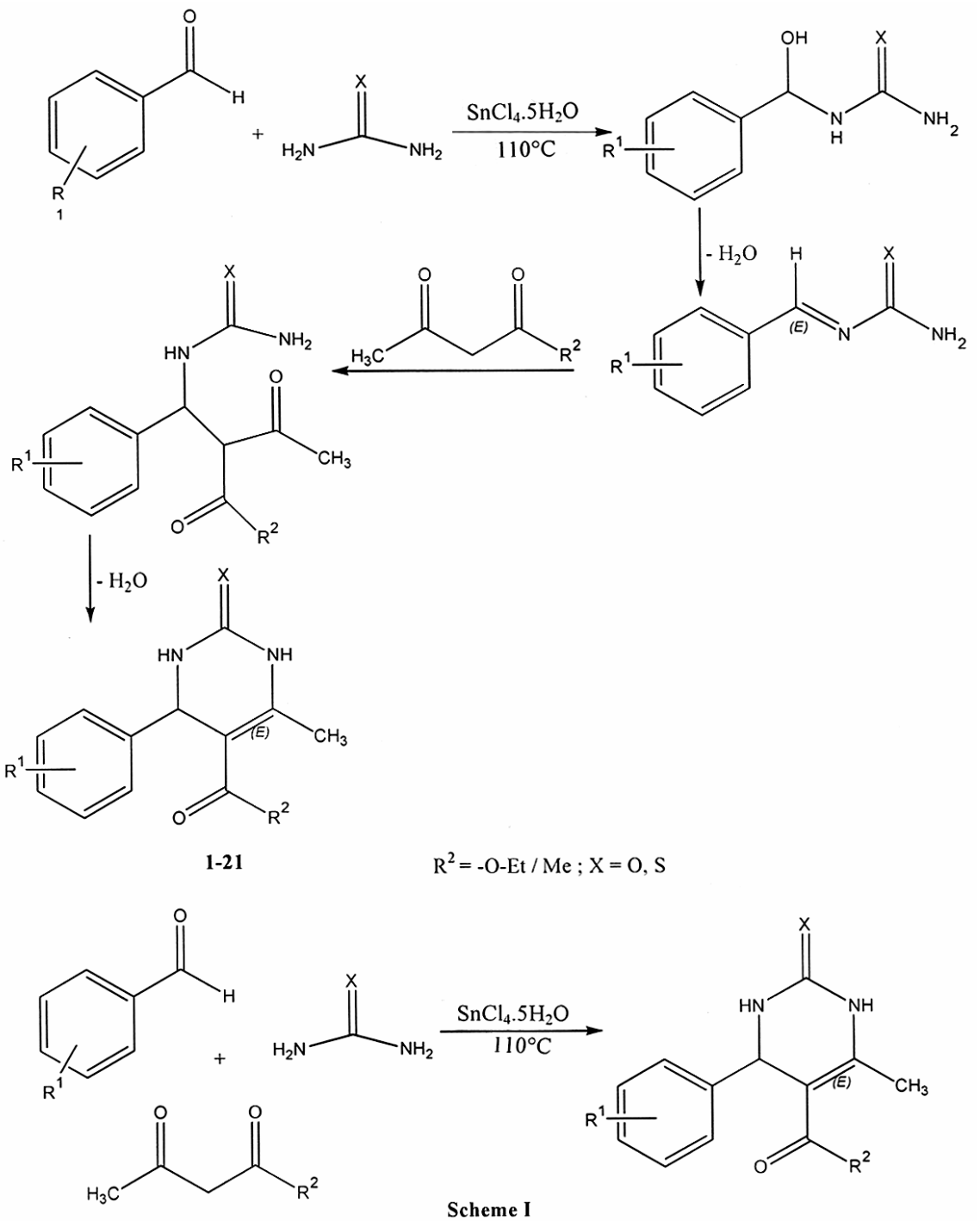
Keywords: Biginelli reaction, dihydropyrimidinones, tin(IV) chloride, solvent-free condition

Biginelli reaction is one of the most useful multicomponent cyclocondensation reactions. It is an acid catalyzed cyclocondensation reaction of a β-ketoester with an aldehyde and urea to yield 3,4–dihydropyrimidin-2-(1*H*)-ones (DHPMs) in quantitative amounts[1]. Various Lewis acids and protic acid promoters like $FeCl_3$ and HCl, BF_3-OEt_2, and ytterbium triflate[2], zirconium(IV) chloride[3], indium(III) bromide[4], lanthanum chloride[5], H_2SO_4 (Ref. 6), AcOH (Ref. 7), polypyrophosphate ester (PPE)[8], ammonium chloride[9], $CuCl_2.2H_2O$-HCl (Ref. 10) were used as catalysts. The currently accepted mechanism of this three component cyclocondensation is shown in **Scheme I**. The **Scheme I** depicts the formation of acyliminium ion intermediate by the condensation of aldehyde and urea or thiourea which upon nucleophilic substitution with 1,3-dicarbonyls give DHPMs (Ref. 11).

DHPMs represent heterocyclic systems of remarkable pharmacological efficacy and many exhibit antiviral, antitumor, antibacterial, anti-inflammatory activity. Several marine natural products containing the dihydropyrimidine-5-carboxylate core structure like the batzelladine alkaloids were found to be potent HIV gp-120-CD4 inhibitors[12]. Polyfunctional DHPMs are used as calcium channel blockers, anti-viral and anti-tumor agents, and α1a antagonists[13]. Owing to the immense therapeutic and medicinal significance of DHPMs, exploring convenient and efficient methods for their synthesis with readily available reagents is of prime importance. $SnCl_4$ is a strong Lewis acid. It is monomeric, highly soluble in organic solvents as well as in water, easy to handle and, therefore, an attractive alternative to many Lewis acids. It is extensively used as a catalyst in conjugate additions. It can bind to the electron withdrawing group in Michael acceptors or to the dienophile, lowering energy in Diels-Alder reactions. On perusal of the literature it was found that the water compatible reactive catalyst has not been employed in Biginelli reactions. Exploiting the inherent capacity of the Biginelli reaction to be promoted by acids, in this communication, is reported a simple and effective modification of the Biginelli reaction that produces high yields of dihydropyrimidinones using catalytic amounts of $SnCl_4.5H_2O$ while preserving the original one-pot strategy under solvent-free conditions.

Results and Discussion

The three component cyclocondensation reaction was carried out by heating a mixture of aromatic aldehyde (1 mmol), the β–ketoester (1 mmol), urea or thiourea (1.5 mmol) and $SnCl_4.5H_2O$ (0.4 mmol) for a period of 30 min to 90 min. This procedure is convenient, does not require cooling for crystallization and gives good yields (81%-91%). Thus, a series of DHPMs and a few thio analogues were prepared by employing different aldehydes following the above method, as shown in **Table I**. As



Scheme I

the reaction temperature was maintained between 110°C and 115°C, the water of hydration of $SnCl_4$ as well as the water resulting from the condensation reaction was lost as vapour, driving the reaction forward. Compounds **20** and **21** are reddish in colour while the remaining compounds are either colourless or faint yellow. As the reaction was carried out under solvent–free conditions, clean products are obtained. However, traces of impurities associated with the catalytic modification are removed either by recrystalisation from ethyl acetate and pet.ether mixture (1:3) or by column chromatography of the resulting crude material over silica gel (Merck 60-120 mesh) using ethyl acetate and pet.ether (1.5:8.5) as the mobile phase. The yields presented in **Table I** are the best results obtained with a 1:1:1.5:0.4 ratio of

Table I — Tin(IV) catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs)*

Under solvent-free conditions

Compd	R^1	R^2	X	Time[#] (min)	Yield[@] (%)	Colour	m.p. (°C) Found	m.p. (°C) Lit.
1	C_6H_5	OEt	O	65	91	Colorless	200-02	201-03 (Ref. 14)
2	4-CH_3	OEt	O	30	90	Red	170-72	169-71 (Ref. 3)
3	2-Cl	OEt	O	90	82	Colorless	215-17	216-18 (Ref. 9)
4	4-Cl	OEt	O	65	84	Pale yellow	209-11	210-12 (Ref. 14)
5	4-F	OEt	O	80	90	Pale yellow	184-86	185-87 (Ref. 17)
6	4-NO_2	OEt	O	80	87	Pale yellow	206-08	207-09 (Ref. 14)
7	2-NO_2	OEt	O	90	83	Pale yellow	207-09	206-08 (Ref. 16)
8	4-OMe	OEt	O	30	86	Red	199-01	199-201 (Ref. 14)
9	4-OH	OEt	O	65	81	Red	226-28	226-28 (Ref. 15)
10	C_6H_5	OMe	O	65	90	Colorless	205-07	207-09 (Ref.14)
11	4-CH_3	OMe	O	30	89	Red	169-70	—
12	2-Cl	OMe	O	90	82	Pale yellow	252-53	252-53 (Ref. 9)
13	4-Cl	OMe	O	65	85	Pale yellow	203-05	204-06 (Ref. 17)
14	4-NO_2	OMe	O	80	84	Pale yellow	233-35	235-37 (Ref. 14)
15	4-OCH_3	OMe	O	30	88	Red	192-94	191-93 (Ref. 14)
16	C_6H_5	OEt	S	65	89	Colorless	204-06	205-07 (Ref. 8)
17	4-Cl	OEt	S	65	84	Pale yellow	208-10	209-11 (Ref. 18)
18	4-NO_2	OEt	S	80	84	Pale yellow	200-02	—
19	2-NO_2	OEt	S	90	83	Pale yellow	201-03	—
20	4-OCH_3	OEt	S	30	85	Red	150-52	150-52 (Ref.19)
21	4-OH	OEt	S	65	82	Red	191-93	193-94 (Ref. 3)

[#]Reaction time (min)
[@]Isolated yield
*The IR and NMR data of the pure products were identical to those of the authentic samples.

aromatic aldehyde:β–ketoestors:urea or thiourea: $SnCl_4$. The stannic chloride mediated cyclo-condensation is inexpensive and requires short reaction times varying between 0.5 hr to 1.5 hr. Longer reaction times neither improved the yield of DHPMs nor increased the side products. The reaction times are considerably less when compared to ammonium chloride – 3 hr; Proline–OMe– HCl – 18 hr; $InBr_3$ – 7 to 24 hr in THF/EtOH; LiBr – 3 to 4 hr; Zinc Sulphamate – 2 to 5 hr; Silica H_2SO_4 – 6 hr; Zeolite – 8 hr in EtOH; VCl_3 – 2 hr; $InCl_3$ – 7 hr in THF or $SnCl_2.2H_2O$, LiCl – 6 to 8 hr in EtOH.

The structure of all the dihydropyrimidinones prepared are characterized by IR and ^{1}H NMR and are well correlated with the available literature data[17]. From the mass spectrum it is observed that once the M^+ ion is produced, the aryl fragment at C_4 in all pyrimidine systems departs to give a common fragment at *m/z* 183. This indicates that the dihydropyrimidones prepared are structural analogs which have common fragmentation under electron impact. Similarly, the *m/z* 183 fragment cleaves to eliminate 28 amu, CH_2=CH_2 unit, in all the cases and finally all the compounds prepared with urea or thiourea have a base peak at *m/z* 43 further confirming the structure of dihydropyrimidinones.

Electron donating groups in *para* position readily give the DHPMs as compared to the electron withdrawing groups in the respective position of the aromatic aldehyde. However, *para* hydroxy group is an exception and the corresponding DHPM is obtained in poor yield. This may probably be due to the incompatibility of the –OH group with $SnCl_4$. It was also noticed that irrespective of the nature of the substituent, the *ortho* substituents in aromatic aldehyde afford less amount of DHPMs and require more time to form the product than its respective *para* isomer thus imparting regioselectivity to the Biginelly reaction. No difference could be observed either in the yield of DHPMs or in the duration of reaction when the methyl acetoacetate replaced the ethyl acetoacetate as β-ketoester or thio urea replaced the urea.

Experimental Section

Melting points were determined on a Polomon melting point apparatus (model no. M.P-96) and are uncorrected. IR spectra of the samples were recorded on a spectrum GX instrument (Perkin Elmer, USA) using KBr pellet. ^{1}H NMR spectra were recorded in

DMSO-d_6 employing Varian Gemini 200 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on VG Micromass 7070 H spectrometer operating at 70 eV.

General procedure for the synthesis of dihydropyrimidinones

A mixture of aromatic aldehyde (2 mmol), ethyl acetoacetate/methyl acetoacetate (2 mmol), urea or thiourea (3 mmol) and $SnCl_4.5H_2O$ (0.8 mmol) was taken in a 50 mL R.B. flask and heated between 110°C and 115°C for 30 min to 90 min. After cooling to RT, the reaction mixture was diluted with cold water to dissolve the excess of urea and then filtered. The solid mixture was either recrystallized from ethyl acetate:pet.ether (1:3) or run over a short column of silica gel to afford the pure product.

5-Ethoxycarbonyl-6-methyl-4-(4-florophenyl)-3,4-dihydropyrimidin-2-(1*H*)-one, 5. m.p. 174-76°C. IR (KBr): 3244, 3122, 1727, 1699, 1650 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.10 (3H, t, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, CH_2), 5.25 (1H, s, CH), 7.50 (2H, d, *J*=7.4Hz, arom.), 7.67 (1H, s, NH with D_2O exchangeable), 8.00 (2H, d, *J*=7.4Hz, arom.), 9.01 (1H, s, NH with D_2O exchangeable); EIMS: *m/z* (%) 278 (20) M^+, 183 (48), 155 (46), 43 (100).

5-Ethoxycarbonyl – 6 - methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2-(1*H*)-one, 6. m.p. 206-08°C. IR (KBr): 3215, 1728, 1707, 1645 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.07 (3H, t, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, CH_2), 5.33 (1H, s, CH), 7.50 (2H, d, *J*=7.3Hz, arom.), 7.67 (1H, s, NH with D_2O exchangeable), 8.20 (2H, d, *J*=7.3Hz, arom.), 9.33 (1H, s, NH with D_2O exchangeable); EIMS: *m/z* (%) 305 (12) M^+, 183 (46), 155 (53), 142 (100), 43 (50).

5 - Ethoxycarbonyl - 6 - methyl - 4 -(4 - methoxy phenyl)-3,4-dihydropyrimidin-2-(1*H*)-one, 8. m.p. 199-201°C. IR(KBr): 3310, 3231, 3108, 2983, 1700, 1645, 1459 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.09 (3H, t, CH_3), 2.25 (3H, s, CH_3), 3.71 (3H, s, OCH_3) 3.98 (2H, q, CH_2), 5.12 (1H, d, *J*=2.9Hz, CH), 6.88 (2H, d, *J*=7.8Hz, arom.), 7.15 (2H, d, *J*=7.8Hz, arom.), 7.71 (1H, s, NH with D_2O exchangeable), 9.12 (1H, s, NH with D_2O exchangeable); EIMS: *m/z* (%) 290 (10) M^+, 183 (20), 155 (30), 142 (50), 43 (100).

5 - Ethoxycarbonyl-6 - methyl - 4 -(4- hydroxy - phenyl)-3,4-dihydropyrimidin-2-(1*H*)-one, 9. m.p. 226-28°C. IR (KBr): 3374, 3280, 3103, 2980, 1686, 1638, 1515 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.08 (3H, t, CH_3), 2.23(3H, s, CH_3), 3.97 (2H, q, CH_2), 5.05 (1H, s, CH), 7.01 (2H, d, arom.), 7.05 (2H, d, arom),7.63 (1H, s, NH), 9.12 (1H, s, NH) 9.33 (1H, s, OH); EIMS: *m/z* (%) 276 (33) M^+, 183 (57), 155 (45), 142 (65), 43 (100).

5 - Ethoxycarbonyl -6 - methyl - 4 - (4- hydroxy-phenyl)-3,4-dihydropyrimidin-2-(1*H*)-thione, 21. m.p. 191-93°C. IR (KBr): 3187, 3016, 1687, 1469 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.09 (3H, t, CH_3), 2.26 (3H, s, CH_3), 3.97 (2H, q, CH_2), 5.12 (1H, s, CH), 6.79 (2H, d, arom.), 7.19 (2H, d, arom.), 7.62 (1H, s, NH), 9.19 (1H, s, NH), 9.76 (1H, s, OH); EIMS: *m/z* (%) 292 (20) M^+, 155 (20), 142 (40), 43 (100).

Conclusion

The present Tin(IV) chloride catalysed procedure provides an efficient and improved method for the Biginelli reaction. It is an important supplement to the existing methods for the synthesis of dihydropyrimidinones under solvent – free and mild conditions with improved yields. This method has also been found to have the ability to tolerate a wide variety of substituents.

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