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$HgCl_2$ PROMOTED ONE POT SYNTHESIS OF 3, 4-DIHYDROPYRIMIDIN-2 (1*H*)-ONES AND THIONES UNDER SOLVENT FREE CONDITIONS

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Abstract
A simple, efficient procedure for the one pot Biginelli condensation reaction of aldehydes, β-ketoester and urea/thiourea employing $HgCl_2$ as a novel catalyst under solvent free conditions is described. Compared to classical Biginelli reaction conditions, the present method has advantages of good yields, short reaction times and experimental simplicity. Further, comparative promoter efficiency of $SnCl_2.2H_2O$ and $HgCl_2$ in Multicomponent Biginelli Condensation reaction is also studied.

Keywords: Biginelli reaction, Dihydropyrimidinones, Solvent-free reactions, Tin (II) chloride, Mercury (II) chloride, Lewis acid

Introduction

The multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry [1]. The 3,4-dihydropyrimidin-2 (1 *H*)-ones are well known heterocyclic units in the realm of natural and synthetic organic chemistry due to their wide spectrum therapeutic and pharmacological properties [2] such as antiviral [3], antimitotic [4], anticarcinogenic [5], antihypertensive [6] and noteworthy, as calcium channel modulators [7]. Owing to the immense therapeutic and medicinal significance of DHPM's, exploring convenient and efficient methods for their synthesis with readily available reagents is of prime importance.

Solvent free organic reactions have been applied as a useful environmentally benign protocol in organic synthesis. Solvent free conditions often lead to short reaction times, increased yields, easier workup, match with green chemistry protocols, and may enhance the regio- and stereo selectivity of reactions [8,9]. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favorable procedure in chemistry [10]. Solid-state reactions occur more efficiently and more selectively than does the solution reaction, since molecules in the crystals are arranged tightly and regularly [11]. This work focuses on the synthesis of Biginelli compounds using $HgCl_2$ and $SnCl_2.2H_2O$ as Lewis acid catalysts under solvent free conditions at 40-50ºC temperature.

Biginelli reaction is an important multicomponent reaction for the condensation of DHPM's. The classical Biginelli reactions were conducted under strongly acidic conditions, which suffer from poor yields, and long reaction time and sensitive functional groups are lost during the reaction conditions. This has lead to the development of several new methodologies, which improve the yields compared to original procedure. These new strategies involve the combinations of Lewis acids and/or transition metal salts *e.g.* BF_3 –OEt_2, montmorillonite (KSF), polyphosphate esters and reagents like $InCl_3$ [12], LiBr [13], TMSCl/NaI [14], $LaCl_3$.$7H_2O$ [15], $CeCl_3$.$7H_2O$ [16], $Mn(OAc)_3$.$2H_2O$ [17] , InBr [18] , $FeCl_3$ and HCl [19] , ytterbium triflate [20] , Iodine [21], $ZnCl_2$ [22], $CoCl_2$ [23] *etc* . But the practical application of these methods suffers from disadvantages like use of mineral acids, expensive reagents such as lanthanide triflate, indium halides, zirconium tetrachloride as well as organic solvents, which are not environmentally benign. Therefore a need still exists for versatile and simple whereby DHPMS may be obtained under solvent free conditions.

To the best of knowledge, neither $SnCl_2.2H_2O$ nor $HgCl_2$ have been explored as a catalyst for Biginelli condensation reaction under solvent free conditions. There are few reports [24] on the synthesis of DHPM using of $SnCl_2.2H_2O$ in the presence of solvent but there is no report on its synthesis using $HgCl_2$ as Lewis acid catalyst. As per our ongoing efforts to synthesize privileged class of compounds [25] and our interest in Lewis acid applications for the biginelli reaction, herein we wish to report for the first time a novel, simple and efficient methodology for the synthesis of 3, 4-dihydropyrimidin-2 (1*H*)-ones and thiones in moderate to good yields (65-80%) by the reaction of aldehydes, β-ketoester and urea/thiourea using catalytic amount of $SnCl_2.2H_2O$ and $HgCl_2$ while preserving the original one pot strategy under solvent free conditions. Further, comparative promoter efficiency of $SnCl_2.2H_2O$ and $HgCl_2$ to catalyze biginelli condensation is also studied under neat conditions.

Results and Discussion

Initially, we have studied the Biginelli one pot condensation reaction of benzaldehyde(1a), ethylacetoacetate(2a) and urea(3a) using $SnCl_2.2H_2O$ and $HgCl_2$ as promoter agents in acetonitrile at 50-60ºC temperature. To establish the optimal conditions, we carried out a set of experiments varying solvents, the reaction times, and molar ratio of the reagents. The best yield was obtained when 0.5 equivalents of $SnCl_2.2H_2O$/ $HgCl_2$, 1eq of both benzaldehyde and ethylacetoacetate and 2 eq. of urea were magnetically stirred in water/ethanol for 45-55 minutes at 50-60ºC temperature. It seems that water is a much better solvent in $SnCl_2.2H_2O$ catalyzed reaction whereas ethanol/toluene is better in $HgCl_2$ promoted reaction in terms of yields than all other tested solvents **(Table-1).** However, under solvent free conditions reaction was fast and 65-80 % yield of DHPM was obtained in 30-35 minutes **(Table-2).** Encouraged by these results, and due to increasing demand in modern organic processes of avoiding expensive purification techniques and large amount of solvents, we examined the reactivity of our catalysts under solvent free conditions. A mixture of aromatic aldehyde **1**, ethyl acetoacetate **2**, urea/thiourea **3** and catalytic amount of $SnCl_2.2H_2O$/ $HgCl_2$ was magnetically stirred at 40-50ºC for 30-35 minutes. To check promoter efficiency of catalyst and reproducibility of the reaction, different aldehydes were reacted with urea/thiourea to give 21 different compounds. The use of large amount of catalyst does not increase the yields. It was found that catalysts employed differed in their efficiency in terms of yields and purity. As indicated in **Table-2**, catalyzing the reaction by

$SnCl_2.2H_2O$ gave superior results over the $HgCl_2$ both in terms of yields and purity **(Table-2).** From this observation we conclude that Lewis acid character of $HgCl_2$ and $SnCl_2.2H_2O$ to catalyze condensation reaction follows the order: $SnCl_2.2H_2O$ (71-78%) > $HgCl_2$ (67-74%)

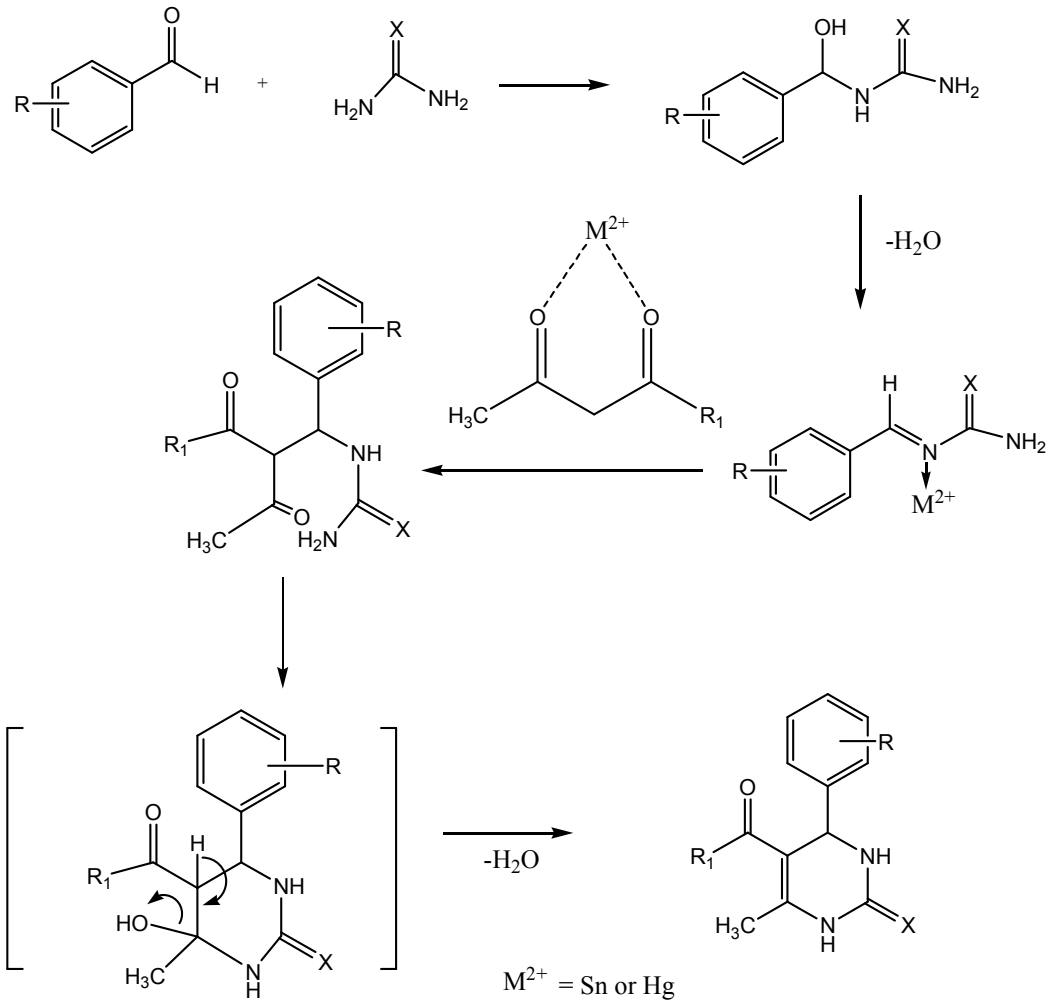
In all cases studied, the three-component reaction proceeded smoothly to give the corresponding DHPM's in satisfactory yields. Most importantly, aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well to give the corresponding DHPM's with high purity in moderate to good yields. Another important feature of this procedure is the tolerance of various functional groups such as methoxy, halides, nitro, hydroxy, etc., to the reaction conditions. Thiourea has been used with similar success to provide corresponding S-dihydropyrimidinones analogues, which are also of interest due to their biological activities.

It should be noted that $SnCl_2.2H_2O$ or $HgCl_2$ was used as the sole promoter agent in neutral media while for others previously reported [23] hydrates of metal halides such as Fe (III), Ni (II) and Co (II) a catalytic amount of conc. HCl was needed as a Bronsted acid co-catalyst. Reaction proceeded without using any additional proton source. All compounds were obtained in good to excellent yields. Melting points of all compounds were found to be much closer to reported substances indicating high purity of the compounds (Table-2).

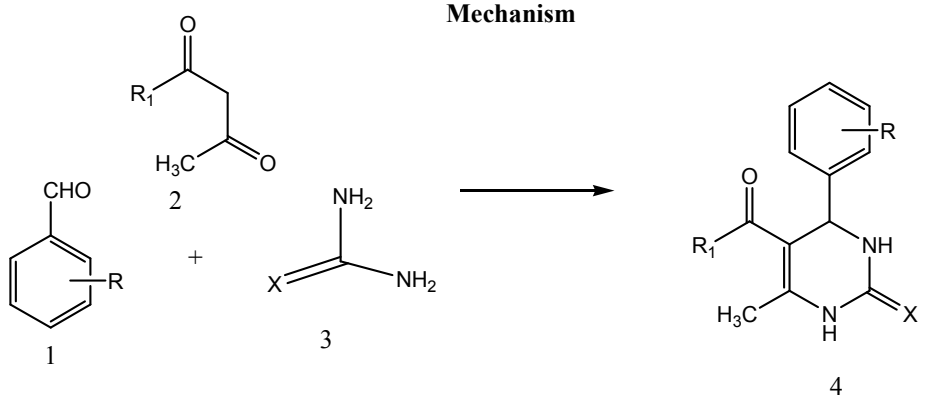
The structure of all the dihydropyrimidinones prepared is characterized by IR and ^{1}HNMR and are well correlated with the available literature data.

Table 1. Effect of catalyst under different reaction conditions for condensation of benzaldehyde, ethylacetoacetate and urea (4a).

Entry	Solvent	Catalyst	Time (Min.)	Yield (%)
1	EtOH	$SnCl_2.2H_2O$	50	67
2	CH_3CN	$SnCl_2.2H_2O$	55	63
3	H_2O	$SnCl_2.2H_2O$	50	72
4	Toluene	$SnCl_2.2H_2O$	50	69
5	EtOH	$HgCl_2$	50	61
6	CH_3CN	$HgCl_2$	55	60
7	H_2O	$HgCl_2$	50	60
8	Toluene	$HgCl_2$	50	61



Mechanism



Scheme I-Reagents and conditions: $SnCl_2.2H_2O$, $HgCl_2$

R=H,4-OCH_3;4-OH;4-Cl;3-OCH_3;2,4-Dimethyl;3-OH,4-OCH_3;3-OCH_3,4-OH;3,4-dimethoxy; 2-OH;2-Cl;3-NO_2;3,4,5-trimethoxy ; X = O, S ; R1 = OMe, OEt

Table 2. Physical characterization data of compounds 4a-t

Entry	R	R_1	X	$SnCl_2.2H_2O$ Yield (%)	$HgCl_2$ Yield (%)	M.P. (°C) Found	Reported (Lit.)	Color
4a	H	OEt	O	78	74	202-204	202-203[27]	Colorless
4b	H	OMe	O	77	73	207-209	210-212[28]	Colorless
4c	H	OEt	S	75	71	204-206	206-208[27]	Colorless
4d	H	OMe	S	75	72	220-222	223-226[29]	Colorless
4e	4-OCH_3	OEt	O	76	72	194-196	199-201[30]	Yellow
4f	4-OCH_3	OMe	O	74	69	183-185	192-193[30]	Red
4g	4-OH	OEt	O	78	69	221-223	231-233[27]	Red
4h	4-OH	OEt	S	78	72	190-195	----	Pale yellow
4i	4-OH	OMe	O	75	69	228-230	231-232[31]	Colorless
4j	4-Cl	OEt	O	75	70	205-207	210-212[32]	Colorless
4k	4-Cl	OEt	S	76	68	175-177	180-182[33]	Colorless
4l	3-OCH_3	OEt	O	72	70	214-216	220-221[34]	Yellow
4m	3-OCH_3	OMe	O	75	68	210-212	----	Pale Yellow
4n	3-OCH_3	OMe	S	78	70	208-210	----	Pale Yellow
4o	2,4-Dimethyl	OEt	O	78	72	198-200	-----	Pale Yellow
4p	3-OH, 4-OCH_3	OEt	O	75	71	225-228	230-232[27]	Red
4q	4-OH, 3-OCH_3	OEt	O	75	70	227-230	233-235[27]	Yellow
4r	3- OCH_3, 4-OCH_3	OEt	O	71	67	149-151	152-153[27]	Colorless
4s	2-OH	OEt	O	76	73	199-202	202-203[35]	Pale Yellow
4t	3-OCH_3, 4- OCH_3, 5-OCH_3	OEt	O	74	68	214-216	216-218[33]	Colorless

In the plausible mechanism catalyzed by tin chloride, the initial step is the formation of imine. The Sn/Hg ion co-ordinates with the nitrogen atom of imine to give an intermediate complex which activates the C=N bond towards nucleophile. Further, complexation of ß-ketoester with Sn/Hg ion increases the nucleophilicity of a-carbon of enolate, facilitating the attack on imine carbon. Attack of free amidic group to ß-carbonyl carbon, results in the formation of six-membered heterocyclic intermediate which on dehydration gives the desired DHPM's. This is in harmony with the mechanism proposed by kappe et al [26].

Conclusions

We have developed simple and efficient procedure for the one pot synthesis of 3,4dihydropyrimidinones and thiones, employing $HgCl_2$ as a novel promoter under solvent free conditions. Moreover, Tin (II) chloride is found to be superior catalyst over mercury (II) chloride both in terms of yields and purity of Biginelli compounds.

Experimental Section

General. Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a Toshniwal apparatus. The spectral analyses of synthesized compounds have been carried out at SAIF, Punjab University, Chandigarh. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, e.g. benzene: ethyl acetate (9:1), benzene: ethyl acetate: Methanol (8.5:1.4:0.1). IR spectra were recorded in KBr on a Perkin Elmer Infrared RXI FTIR spectrophotometer and ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer using DMSO-d_6 and $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard.

General procedure for the synthesis of dihydropyrimidinones 4a-u:

A mixture of an aromatic aldehyde (10mmol), ethylacetoacetate (10mmol), urea (20 mmol), tin chloride/mercury chloride (5 mmol) were mixed in R.B. flask and the mixture was magnetically stirred at 40-50ºC for the time needed to complete the reaction (as monitored by TLC). The initial syrupy reaction mixture solidifies within 30-35 minutes. After completion, the reaction mixture was cooled to room temperature and poured onto crushed ice, filtered and recrystallized by using either ethanol or ethyl acetate and pet ether (1:3) to afford pure product 4.The obtained products were identified by comparison with authentic samples (synthesized by conventional process) and from their spectral (^{1}H NMR and IR) data and their melting points.

For comparison sake, 4a was synthesized similarly by stirring at 60-70ºC in various solvents e.g. ethanol, toluene, water and acetonitrile for 45-55 min. by using both tin and mercury chloride as Lewis acid catalysts. Results are summarized in Table 1

Spectral data of some selected compounds is given below:

Ethyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidin-5-carboxylate (4a) m.p. 202-204 ºC; IR (KBr): 3242, 3117, 2980, 1722, 1645, 1600,1462,1388,1091,781 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.12 (t, 3H, $OCH_2C\mathit{H}_3$), 2.27 (s, 3H, CH_3), 4.02 (q, 2H, $OC\mathit{H}_2CH_3$), 5.11 (s, 1H, CH), 7.18-7.28 (m, 5H, aromatic), 7.31 (s, 1H, N-H), 9.37 (s, 1H, N-H) ppm.

Methyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidin-5-carboxylate (4b) m.p. 207-209 ºC; IR (KBr): 3246, 3117, 2980, 1732, 1664, 1600,1462,1388,1091,781 cm^{-1}; ^{1}H NMR

(DMSO-d_6): 2.19 (s, 3H, CH_3), 3.87 (s, 3H, -$COOCH_3$), 5.02 (d, 1H, CH), 7.18-7.28 (m, 5H, aromatic), 7.64 (s, 1H, N-H), 9.15 (s, 1H, N-H) ppm.

Ethyl-6-methyl-2-thioxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidin-5-carboxylate (4c) m.p. 204-206 ºC; IR (KBr): 3240, 3117, 2980, 1720, 1640, 1595,1530,1388,1091,781 cm^{-1}; ^{1}H NMR (DMSO-d_6): 1.12 (t, 3H, OCH_2CH_3), 2.29 (s, 3H, CH_3), 4.12 (q, 2H, OCH_2CH_3), 5.16 (d, 1H, CH), 7.50-7.53 (m, 5H, aromatic), 7.81 (s, 1H, N-H), 9.41 (s, 1H, N-H) ppm.

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