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$ZnCl_2$ Supported with Sand: An Efficient Synthetic Protocol for synthesis of Biginelli Products

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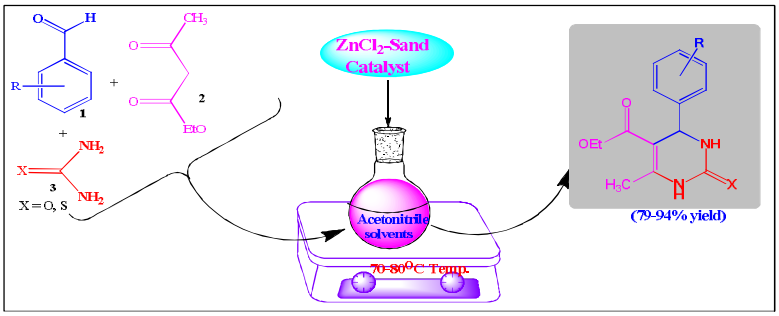
ABSTRACT

A highly efficient synthetic procedure was developed for the synthesis of pharmacologically useful 3,4-dihydropyrimidin-2-(1H)-ones/thiones using one-pot three component reaction of aromatic aldehyde, ethyl acetoacetate and urea/thiourea catalyzed by newly prepared heterogeneous catalyst ($ZnCl_2$ supported with Sand) in presence of ethanol solvent. Mild reaction conditions, excellent yields, operational simplicity, no tedious separation procedures, clean reaction profiles, energy-efficiency, and high atom-economy as well as the use of inexpensive and environmentally benign catalyst are the key advantages of the present method. All synthesized compounds were characterized by IR, ^{1}HNMR & ^{13}C NMR and mass spectral data

Graphical Abstract:



General synthesis of *Dihydropyrimidines using $ZnCl_2$-Sand Catalyst.*

Keywords: Heterogeneous Catalyst – ($ZnCl_2$ - Sand), Dihydropyrimidines, Biginelli Reaction, Eco-friendly Protocol.

INTRODUCTION

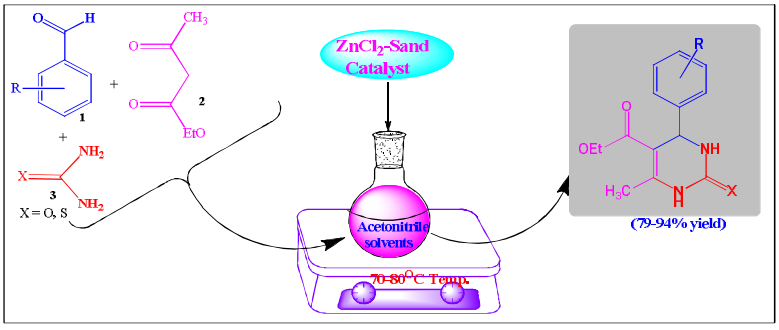
The prominent structural diversification and pharmacological properties exhibited by 3,4-dihydropyrimidin-2(1H)-ones as containing bioactive pyrimidine ring in central core nucleus [1]. This central ring as pyrimidine is basically important member of all the diazines having its presence in DNA

and RNA [2,3]. The scope of this pharmacophore further widened by their strong biological, pharmaceutical and industrial properties especially HIV gp-120-CD4 inhibitors [4] antihypertensive [5] anti cancer activity [6] calcium channel blockers [7] and α-1a-antagonists [8].Therefore wide applicability of these compounds encouraged the researchers, chemists and druggists to design and formulated efficient methods for the synthesis of bioactive dihydropyrimidines under the guidelines of principles of synthetic chemistry.

Multi-component reactions (MCRs) proved to be a highly valuable synthetic tool for building diverse and complex molecular structures through C–C and C-X (heteroatom) bond formation [9,10]. Multicomponent reaction can be considered as a subclass of domino processes as they are usually performed by putting all substrates in one-pot and undergo the transformations under similar reaction conditions Since several substrates are put together in only the molecular complexity that is built up very rapidly, but also the possibility of generating various analogues [11]. These offer significant benefits over conventional linear-type syntheses by virtue of their convergence, atom-economy, environ-mental concerns, productivity, facile execution and high yields [12, 13]. Thus the first successful effort for synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones, now popularly known as "Biginelli Product" was reported in eighteenth century (1893) for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones by involving one pot multicomponent condensation pathways [14].

Further, several combinatorial routes for 3,4-dihydropyrimidin-2-(1H)-ones/thiones synthesis have been reported in literature using solid phase techniques [15-17]. In general, large number of Lewis acids such as CaF_2 [18], Lanthanum chloride [19], ZnCl2-Silica [20], NaHSo4-Sand [21], Indium (III) halides [22], BF_3OEt [23] and Resins [24] were used as the catalyst. Notable among the catalysts used to drive the reaction are zeolites HZSM-5 and MCM-41 [25] ionic liquids [26] natural acid [27], Metal halides [28], TBAB [29] and a variety of Triflates [30-32] were also employed for Biginelli reactions. This reported synthetic methodologies has many drawbacks like use of Hazardous Chemicals (solvent and Catalyst), non-eco-friendly methodic application, prolong reaction times, very less yields with minimum purity of products and complex synthetic pathway.

In continuation of the current research from our laboratory to develop an efficient multicomponent reaction for the synthesis of bioactive pyrimidines via Biginelli reaction. We report here, to explore the efficient, simple and fast synthesis of highly functionalized new 3,4-dihydropyrimidin-2-(1H)-ones/thiones via one-pot three component reactions using heterogeneous catalyst ($ZnCl_2$ supported Sand) in presence of ethanol solvent (Scheme 1).



Scheme 1: General synthesis of *Dihydropyrimidines using $ZnCl_2$-Sand Catalyst.*

MATERIALS AND METHODS

Instrumentation: All chemicals used in this work were of analytical grade and were purchased from Merck and Loba Chemie (Mumbai)and used without further purification. $ZnCl_2$-Sand as heterogeneous Catalyst prepared in Laboratory. Deionized water is used during this procedure. All known compounds

were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/ UV 254 plates. Melting points were recorded on a Bauchi B-545 apparatus in open capillary tubes and are uncorrected. The products were characterized by IR spectra, 1H NMR. And Mass Spectroscopy IR spectra were recorded on Alpha-Eco-ATR BRUKER instrument, 1H NMR was recorded on MSL-300 instrument using TMS as an internal standard.

General Procedure

Method A: Preparation of $ZnCl_2$-Sand as Natural and Heterogeneous Catalyst for Synthesis of Dihydropyrimidines: To a well stirred (commercially available) Red sea Sand (5 g, mesh size-100-200) in Benzene/DCM (40 mL) taken in 100 ml round bottom flask, (2g) of anhydrous $ZnCl_2$ was added slowly to it initially at room temperature, the reaction mixture was refluxed for 7 h, After stirring for another 30 min at room temperature, the solvent was removed to dryness. further dried in oven at 100-130^{o}c for 6-8 h, The heterogeneous catalyst as Sand (basically silica) -chloride was obtained as free powder, the catalyst prepared was used in the reaction procedure and the catalyst if stored properly in sealed vessel could be used till 4-6 months without loss of catalytic activity.

Method B: Synthesis of Dihydropyrimidines by the use of $ZnCl_2$-Sand Catalyst: The mixture of an aldehyde (10mmol), ethyl acetoacetate / acetyl acetone (10mmol), Urea/ thiourea (15mmol) and $ZnCl_2$-Sand Catalyst (1g, 20 mol%), solvent ethanol (10mL) were mixed thoroughly at stirrer taken in round bottom flask over oil bath at 70-80^{0}c for a period of 2.5 h and reaction was monitored by TLC (hexane/ethyl acetate 8:2). After the completion of the reaction, the reaction mixture was poured in crushed ice (10mL) with continuous stirring to remove excess urea or thiourea, after proper solidification, the crude product was filtered, dried and than recrystallized by (70%) ethanol and further purification has been done by short column chromatography on silica gel.

Spectroscopic data of selected compounds

5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyramidin-2(1H)-one (PG_1): Light Yellow Color, Yield: 88%, M.P: 205-207^{o}C; IR (KBr,cm^{-1}): 3313, 3103, 1698, 1611, 1412,1296 and 1011; ^{1}H NMR (500 MHz, DMSO-d_6): δ:8.01(s,1H,NH), δ:7.26(m, 5H$_{aromatic}$), δ:5.33(s,1H,CH), δ: 3.98(q, *J* 7.1Hz, 2H), δ: 2.35(s,3H), δ:1.13(t, 3H); MS (EI,70 eV): m/z=303 (M^+), 227, 180, 149, 141, 41.

5-ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyramidin-2(1H)-one (PG_3): Light Yellow Color, Yield: 89%, M.P:189-193^{o}C; IR; (KBr,cm^{-1}): 3301, 3211, 1716,1674 1510,1398 and 1112; ^{1}H NMR (500 MHz, DMSO-d_6): δ:8.0(s,1H,NH), δ: 7.10 (m, 5H,aromatic), δ: 5.13(d, 1H,CH), δ:3.75(q *J*6.9 Hz,2H), δ:2.21(s,3H), δ:1.21(t,*J*7.1 Hz, 3H), MS (EI,70 eV): m/z=299 (M^+), 256, 232, 198, 153, 131.

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyramidin-2(1H)-one (PG_8): Light Yellow Color, Yield: 85%, M.P: 203-206^{o}C; IR (KBr,cm^{-1}): 3323, 3216, 1687, 1627, 1387,1270 and 1122; ^{1}H NMR (500 MHz, DMSO-d_6): δ:7.81(s,1H,NH), δ:7.2(m, 5H$_{aromatic}$), δ:5.11(s,1H), δ: 3.87(q, *J* 6.3Hz, 2H), δ: 2.24(s,3H), δ:1.10(t, 3H); MS (EI,70 eV): m/z=306 (M^+), 218, 190, 147, 136, 46.

5-ethoxycarbonyl-6-methyl-4-(4-methoxylphenyl)-3,4-dihydropyramidin-2(1H)-one (PG_4): Light Yellow Color, Yield: 89%, M.P: 199-201^{o}C; IR (KBr,cm^{-1}): 3299, 3232, 1721, 1622, 1388,1274 and 1088; ^{1}H NMR (500 MHz, DMSO-d_6): δ:7.88(s,1H,NH), δ:7.14(m, 5H$_{aromatic}$), δ:5.16(s,1H,CH), δ: 3.86(q, *J* 6.6Hz, 2H), δ: 2.23(s,3H), δ:1.08(t, 3H); MS (EI,70 eV): m/z=298 (M^+), 214, 187, 141, 143, 38.

5-ethoxycarbonyl-6-methyl-4-(2,4-dinitrophenyl)-3,4-dihydropyramidin-2(1H)-one (PG6): Light Yellow Color, Yield: 93%, M.P: 210-213^{o}C; IR (KBr,cm^{-1}): 3363, 3203, 1718, 1621, 1442,1276 and

1016; ^{1}H NMR (500 MHz, DMSO-d_6): δ:7.76(s,1H,NH), δ:7.28(m, 5H$_{aromatic}$), δ:5.21(s,1H), δ: 3.79(q, *J* 7.0Hz, 2H), δ: 2.17(s,3H), δ:1.02(t, 3H); MS (EI,70 eV): m/z=302 (M^+), 228, 178, 143, 144, 43.

5-ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyramidin-2(1H)-one (PG_2): Light Yellow Color, Yield: 94%,M.P: 194-193^{o}C; IR (KBr,cm^{-1}): 3337, 3243, 1699, 1600, 1401,1216 and 1015; ^{1}H NMR (500 MHz, DMSO-d_6): δ:7.69(s,1H,NH), δ:7.12(m, 5H$_{aromatic}$), δ:5.13(s,1H,CH), δ: 3.78(q, *J* 6.9Hz, 2H), δ: 1.99(s,3H), δ:098(q, 3H); MS (EI,70 eV): m/z=288 (M^+), 217, 176, 141, 138, 38.

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyramidin-2(1H)-one(PG_7): Light Yellow Color, Yield: 86%, M.P: 213-216^{o}C; IR (KBr,cm^{-1}): 3393, 3244, 1728, 1651, 1422,1286 and 1101; ^{1}H NMR (500 MHz, DMSO-d_6): δ:7.83(s,1H,NH), δ:7.41(m, 4H$_{aromatic}$), δ:5.88(s,1H,CH), δ: 3.73(m,2H) , δ: 2.38(s,3H), δ:0.79(t, 3H); MS (EI,70 eV): m/z=300 (M^+), 231, 176, 152, 138, 46.

RESULTS AND DISCUSSION

Progressive and potential approach for Biginelli reaction with regard to synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones having high pharmacologic value is off great interest in organic synthetic area. There has been a growing interest over the past few years to carry out organic reactions over heterogeneous catalysts, because of simple experimental and procedural set ups, lesser chemical degradation, higher product purity, less use of hazardous chemicals and easy recovery as well reusability of catalyst. The model multi-component condensation reaction of substituted benzaldehyde 1 (10 mmol), ethyl acetoacetate 2 (10 mmol), urea/ thioura 3 (15 mmol) and catalyst as $ZnCl_2$ supported Sand (20 mole %) was heated to reflux (70-80^{o}C) on oil bath in the presence of ethanol as solvent gave the high yield of products (79-94%). The synthetic results showed that the presence of different electron donating and electron withdrawing substituted benzene reacts well under similar reaction conditions giving the corresponding dihydropyrimidine derivatives with good yields (Table 2).

The reported literature reveals that no earlier reports of $ZnCl_2$ supported Sand as catalyst for Biginelli reaction. $ZnCl_2$ supported Sand a combination of mild acid and natural supporting agent showed promising results in terms of yield for producing the desired product with procedural simplicity, reusability and easy recovery of catalyst. Experimental investigation showed the suitability of catalyst for the selective construction of heterocyclic ring system, especially for the synthesis of 3,4-dihydropyrimidin-2(1H)-thiones (Table 1, entry 6). The presence of $ZnCl_2$ supported catalyst enhanced the rate of reaction tremendously and the reactions proceeded with good yields and compounds were obtained in solid form. The synthesized compounds were purified by column chromatography. Reactions were monitored by TLC regularly for the final product synthesis as 3,4-dihydropyrimidin-2-(1H)-ones/thiones.

This advance protocol designed for synthesis of dihydropyrimidines has shown notable improvement in overall synthetic reaction efficiency with the utility of newly prepared heterogeneous catalyst as $ZnCl_2$-Sand (Sand is basically SiO_2compositioned natural supporter), with the decrease of production of chemical waste without using highly toxic reagent for Biginelli product. The support applied catalyst to enhance rate of reaction is by forming the bonds as Si-Cl easily available to give rise Lewis acid centers on silica. More ever the extent of chlorination of the silica (Sand) surfaces is increased by the use of required amount of $ZnCl_2$ and immobilization of Chloride on surfaces of silica has been significantly increased by this mild Lewis acid. Our studies have shown that Zinc chloride is a satisfactory chlorinating agent for silica, when diluted with dry benzene, good numbers of silanol groups were replaced by chlorine.

To investigate the effectiveness of different solvents like MeOH, EtOH, H_2O, Chloroform, DMSO and CAN as well change in amount of catalyst used for the enhancement of rate of reaction with increase in product yield of 3,4-dihydropyrimidin-2-(1H)-ones/thiones, many trials have been done, but investigation exhibits that out of many solvent used, ethanol worked almost best by keeping the effective amount of

catalyst as 110 mg (Constant) to get high yield of product in minimum time duration (94 % yield of product) compared to other solvents and also helped to get products easily separated from solvent used after reaction, similarly, variation in the amount of catalyst to get better yield were 50 mg, 70 mg , 90 mg , 110 mg, 130 mg,150 mg and 67 %, 71% , 81%, 94% , 88%, 81% respectively, best results were obtained with the use of 110 mg of $ZnCl_2$-Sand as catalyst shown by observations in order to increase the rate of reaction for the synthesis of 3,4-dihydropyrimidin-2(1H)- thiones to get good yield of end product. Further to show the merits of the catalyst $ZnCl_2$-s and used in our experiment has been compared to other reported catalysts, also reveals the advantage of $ZnCl_2$-Sand loudly (Table 1).

Table 1: Comparison of ZnCl2-Sand as Catalyst with some reported Catalysts
For the synthesis of 3, 4-dihydropyrimidin-2(1H)-one/thiones

Entry	**Catalyst**	**Reaction time**	**Yield % [ref]**
1	Zeolite-HZSM-5	8h	83[25]
2	CaF_2	7h	78[18]
3	$ZnCl_2$-Silica	6.4h	84[20]
4	Bi $(NO_3)_3$	6h	80[33]
5	H_3PMoO_{40} (2%)	5h	75[34]
6	$ZnCl_2$-S and	2.5h	94 This work

Table 2: Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones catalysed by $ZnCl_2$-S and as Catalyst.

Entry	**R**	**X**	**Time hours**	**Yield %**	**M.P ^oC**
PG_1	C_6H_5	O	2.5	89	205-207
PG_2	Cl - C_6H_4	O	3.1	94	190-193
PG_3	4-OH- C_6H_4	O	2.3	89	189-193
PG_4	4-OCH3- C_6H_4	O	2.2	89	199-201
PG_5	4-$N(CH_3)_2$-C_6H_4	O	3.5	79	251-254
PG_6	2,4-NO2- C_6H_4	O	3.2	93	210-213
PG_7	OH- C_6H_4	O	2.5	86	213-216
PG_8	4-CH3- C_6H_4	O	2.4	85	203-206
PG_9	C_6H_5	S	3.1	85	204-207
PG_{10}	OH-C_6H_4	S	2.4	91	202-205
PG_{11}	4-OCH3- C_6H_4	S	2.5	88	161-164
PG_{12}	Cl - C_6H_4	S	3.3	90	191-193
PG_{13}	2,4-NO2- C_6H_4	S	3.4	90	202-205

APPLICATIONS

The prepared heterogeneous catalyst $ZnCl_2$-Sand have advantages such as inexpensive, natural, non-toxic and reusable to get results as per design of methodology.

CONCLUSIONS

Summarizing the whole work in conclusion, our work discloses a simple and efficient modification of the Biginelli 3,4-dihydropyrimidin-2-(1H)-ones/thiones synthesis, with excellent product yields with high purity, activated reaction rates compatibility with various functional groups, eco-friendly procedure and time saving process. The prepared heterogeneous catalyst $ZnCl_2$-S and have advantages such as inexpensive, natural, non-toxic and reusable to get results as per design of methodology. This procedure

will offer an easy access to substituted 3,4-dihydropyrimidin-2-(1H)-ones/thiones and thiones with different substitution patterns in high to excellent yields.

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