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MICROWAVE ASSISTED RAPID SYNTHESIS OF 3, 4-DIHYDROPYRIMIDINE-2-(1H)-ONES/THIONES USING LSA AS A CATALYST UNDER SOLVENT FREE CONDITIONS

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ABSTRACT

Lignin Sulphonic Acid (LSA) was found to be an efficient catalyst for the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones/thiones from the multicomponent condensation reaction of aromatic aldehyde, ethyl acetoacetate and urea / thiourea in solventfree condition on microwave at 180 W.

Key words: LSA, Ethyl acetoacetate, Dihydropyrimidines.

INTRODUCTION

Over the past few decades, multicomponent reactions (MCRs) have gained considerable interest in both academia and industry owing to exceptional synthetic efficiency, intrinsic atom economy, high reactivity, and procedural simplicity[1,2]. MCRs have great contribution towards convergent synthesis of complex and important biologically active molecules from readily available starting materials, and have emerged as powerful tool for drug discovery[3,4]. These all multicomponent reactions are shown by Hantzsch[5,6]. Knoevenagel[7-11], Biginelli[12-14]. Italian chemist Biginelli reacted same two components in equimolar ratio *viz.* acetoacetic ester, aldehyde and third component as urea in double amount in acidic alcoholic solution to obtain a new compound, the now well-known 3, 4-dihydropyrimidin-2(1*H*)-ones or Biginelli compounds[15,16], which are obvious aza-analogues of the Hantzsch dihydropyridines. Biginelli did not detect any Hantzsch dihydropyridines[5,6] as byproducts[17].

Subsequently to these academic developments, the Biginelli scaffold was shown due to their pharmacological, therapeutic properties, and biological activities of several marine alkaloids which contain the dihydropyrimidine nucleus[18-21] from a pharmaceutical point of

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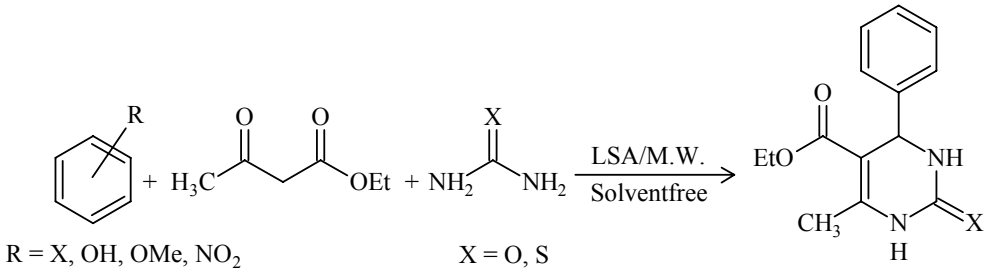
view; because of this importance, investigations were very fast, and virtually every major journal was flooded with papers on the Biginelli reaction[22-36]. As a result, there were nearly five hundred research publications, mostly involving catalyst changes. Major emphasis being based on mainly Lewis acid such as $Yb(OTf)_3$[18], BF_3xOEt_2[19], $La(OTf)_3$[37], $LaCl_3$[38], $BiCl_3$[39], LiBr[40] $LiClO_4$[41], cerium ammonium nitrate[42], $FeCl_3X.6H_2O$, $NiCl_2X6H_2O$[43], silica sulfuric acid[44], VCl_3[45] etc., and protic acids such as H_2SO_4, HOAc, Conc. HCl[46-48]. Many methods based on microwave irradiation, ionic liquids and clay[49] are reported. However, all these methods have some limitations such as harsh reaction condition, tedious work up procedure, use of solvents, long reaction time etc. and therefore, to overcome these limitations and in continuation of our ongoing work[50,51] we have developed a new method for the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones/thiones using LSA as a strong acid catalyst from the condensation of aldehyde, acetoacetic ester and urea or thiourea (1 : 1 : 2) **(Scheme 1)**.



Scheme 1: Synthesis of 3, 4-dihydropyrimidine-2-(1H)-ones/thiones

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka and Aldrich fine chemicals and used as received. Melting points were observed in open capillary tubes in a circulating oil melting point apparatus. Products were characterized by comparison of their spectral and physical data with authentic samples. IR spectra were obtained using a Shimdzu FT-IR spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument. ^{1}H NMR spectra were recorded on a Bruker Advance Dpx-250.

General procedure

To a mixture of aldehyde **(1)** (2 mmol), β-keto ester **(2)** (2 mmol), urea or thiourea **(3)** (2 mmol), catalytic amount of lignin sulphonic acid (5 mol. %) was added in 100 mL beaker and the contents were covered with petri dish. The beaker was irradiated with M.W. at 180 W with 10 sec. gap for corresponding time (Table 1). After completion of the reaction as monitored by TLC, ice-cold water was added to the reaction mixture and stirred for

10-15 minutes. The contents of the flask were then filtered, washed with cold water (20 mL) to remove excess urea. Ethyl acetate was added to the solid residue and filtered to separate insoluble solid acid catalyst. The solvent was evoporate to get the corresponding 3, 4-dihydropyrimidin-(2H)-one. It was then recrystallized by hot ethanol to get the pure product (**Scheme 1**).

RESULTS AND DISCUSSION

Lignin sulphonic acid (LSA) is presented as an effective heterogeneous catalyst for Biginelli condensation reaction from 1 equivalent *p*-chlorobenzaldehydes, 1 equivalent ethyl acetoacetate and 2 equivalents of urea in presence of LSA (10 mol. %) under solvent free condition using Microwave power at 180 W. During the course of optimization of reaction condition, the reactions were generally completed in 2-5 min. Meanwhile, experimental data indicated that the reaction was complete when reaction time was less than 10 min. However, no increase in yield was observed, when the reaction time was prolonged with respect to solvent as per optimization reaction. The optimized reaction conditions for the reaction were found to be LSA 10 mol % under M.W at 180 W for 2-5 min. Therefore, for the study of generality and scope of the reaction, the reactions with different aromatic aldehydes were carried out under similar reaction conditions (Table 1) and it was found that aromatic aldehydes with electron donating substiuent give higher yield as compared to electron withdrawing substituent. Both are giving more than 90% yield. The mild reaction conditions, high yields, low cost, easy preparation and handling of the polymeric catalyst are the attractive features of the present methodology.

Spectral data of selected compounds

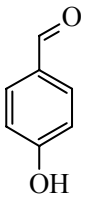
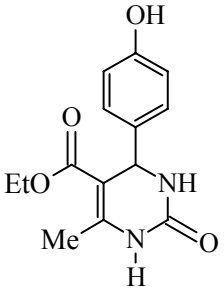
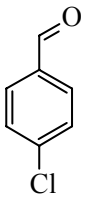
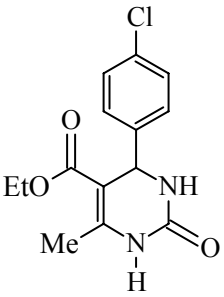
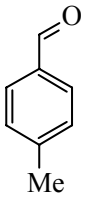
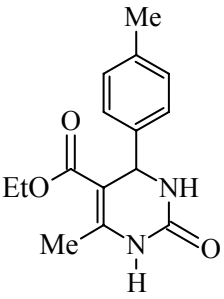
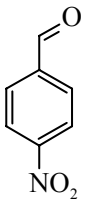
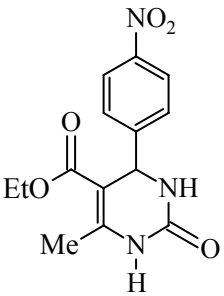
(1) 4-(4-Hydroxyphenyl)-6-ethyl-5-methoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one

White solid; yield 90% mp: 240°C; IR (KBr, V_{max} cm^{-1}): 3264, 3227, 3110, 2976, 1686, 1663, 1605, 1511, 1455; ^{1}H NMR ($CDCl_3$, ppm)*:* δ 9.32 (s, 1H, OH), 9.11 (s, 1H, NH), 7.61 (s, 1H, NH), 5.91 (s, 1H), 5.37 (d, *J* = 2.9 Hz, 1H), 4.09 (s, 3H), 2.33 (m, 2H), 1.17 (t, *J*) 7.4 Hz, 3H); MS *m*/*z* = 275 (M^+); Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276): C = 60.86%; H = 5.84%; N, 10.14%, O = 23.16%; Found: C = 56.74%; H = 5.70%; N = 10.05%, O = 23.10%.

(2) 4-(4-Chlorophenyl)-6-ethyl-5-methoxycarbonyl-3,4-dihydropyrimidin-2(1H)-one

White solid; yield 95%; mp 210°C; IR (KBr, V_{max} cm^{-1}): 3241, 3119, 2980, 1720, 1647; ^{1}H NMR ($CDCl_3$, ppm): δ 8.14 (s, 1H), 7.37 (m, 4H), 5.91 (s, 1H), 5.37 (d, *J* = 2.9 Hz, 1H), 4.09 (s, 3H), 2.33 (m, 2H), 1.17 (t, *J*) 7.4 Hz, 3H); MS (*m*/*z*, %): 293 (M^+); elemental analysis Calcd for $C_{14}H_{15}N_2O_3Cl$ (294.08): C = 57.05%; H = 5.13%; N = 9.50%, O = 16, 29%, Found: C = 56.94%; H = 5.03%; N = 9.40%, O = 16. 20%.

Table 1: Synthesis of 3, 4-dihydro pyrimidines using LSA

S. No.	Aldehyde	Product	Time (min)	Yield[a] (%)	M.P. (°C)
1			3	90	240
2			3	95	210
3			4	90	200
4			3	90	208

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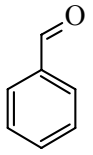
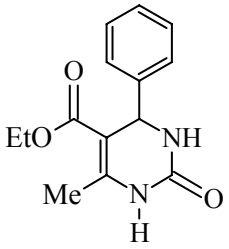
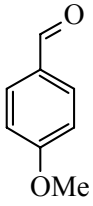
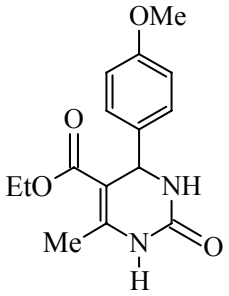
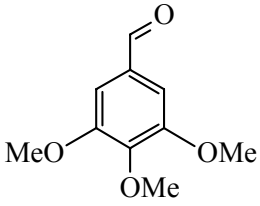
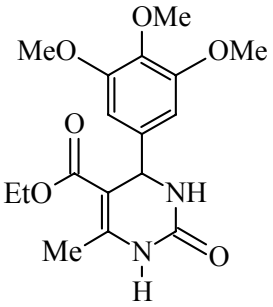
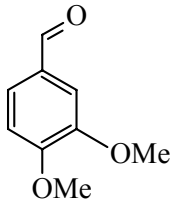
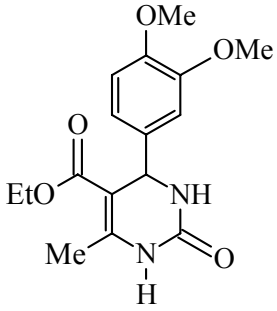
S. No.	Aldehyde	Product	Time (min)	Yield[a] (%)	M.P. (^{o}C)
5			3	95	201
6			3	90	202
7			4	90	234
8			4	88	234

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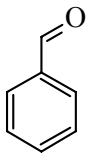
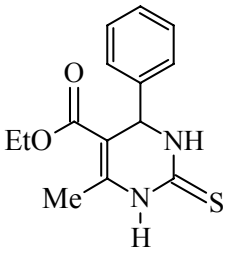
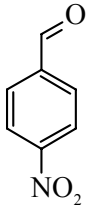
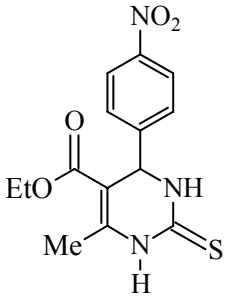
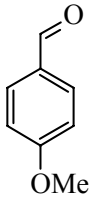
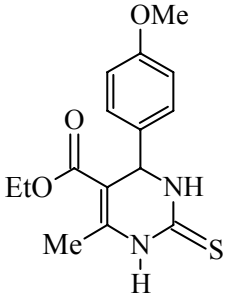
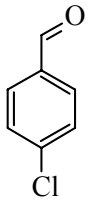
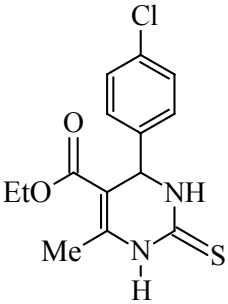
S. No.	Aldehyde	Product	Time (min)	Yield[a] (%)	M.P. (^oC)
9			4	92	207
10			3	89	234
11			3	85	152
12			3	87	180

[a]All yields refer to pure isolated products, characterized by mp, IR and ^{1}H NMR

CONCLUSION

Medicinally important 3,4-dihydropyrimidine-2(1H)-ones were synthesized using LSA as a catalyst by microwave irradiation conditions through multicomponent Biginelli reaction. Importantly, heterogeneous nature of LSA catalyst permits easy work up procedure with its recovery and reuse.

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