WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 7, 1115-1125. Research Article ISSN 2277– 7105

ONE-POT SYNTHESIS OF 3, 4-TETRAHYDROPYRIMIDINE-5-CARBOXYLATE USING LANTHANUM (III) CHLORIDE ($LACL_3.7H_2O$) AS A CATALYST

C. Murugesan, M. Mohamed Sihabudeen*, and A. Asrar Ahamed

Department of Chemistry, Jamal Mohamed College (Autonomous), Tiruchirappalli TamilNadu, India.

Article Received on
25 April 2015,

Revised on 16 May 2015,
Accepted on 06 June 2015.

***Correspondence for Author**
M. Mohamed Sihabudeen
Department of Chemistry,
Jamal Mohamed College
(Autonomous),
Tiruchirappalli
TamilNadu, India.

ABSTRACT

A novel, efficient, and eco - friendly method for the synthesis of tetrahydropyrimidine by a one-pot three-component condensation of aldehydes, ethyl acetoacetate, dimedone and urea or thiourea, in the presence of a catalytic amount of Lanthanum (III) chloride ($LaCl_3.7H_2O$) under solvent conditions has been developed. The results showed that this heterogeneous catalyst has high catalytic activity and the desired products were obtained in good yield. After the reaction the catalyst was recovered easily and reused.

KEYWORDS: Lanthanum (III) chlorideone-spot synthesis Multicomponent synthesis 3, 4-tetrahydropyrimidine.

1. INTRODUCTION

Multicomponent reactions (MCRs) are very important for the construction of many heterocyclic compounds[1] and this strategy has been used effectively in the synthesis of many biologically active substances and natural products.[2] The synthesis of tetrahydropyrimidine has attracted the attention of chemists because of their highly potent antibacterial activity against many kinds of bacteria including *B. subtilis*, Escherichia coli.[3] Several methods have been reported for the synthesis of tetradihydropyrimidine from aromatic aldehydes, ethylacetoacetate, dimedone, urea, and thiourea involving the use of catalysts such as BF_3, $LiClO_4$, $ZrCl_3$,[4,5] $NiCl_2.6H_2O$,[6] $BiCl_3$,[7] $FeCl_3.7H_2O$,[8] $CeCl_3.7H_2O$. They can also be synthesized via Biginelli multicomponent reaction using cyclo-diketones[9] Many of the reported methods suffer from one or more disadvantages including harsh reaction conditions, long reaction times, poor yields and the use of hazardous and expensive

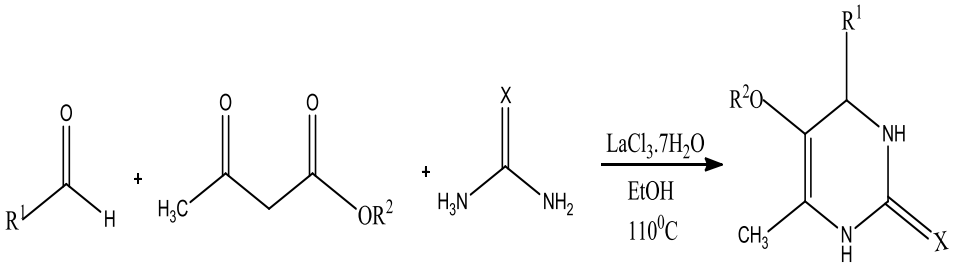
catalysts with limited reusability. Herein, we have attempted in this field, Lanthanum (III) chloride are very interesting since these mild Lewis acids are eco - friendly [$LaCl_3 \cdot 7H_2O$][10] and some of them can easily be recycled [$La(Of)_3$].[11] Nevertheless, many of these methods involve expensive reagents; therefore, we wish to report the direct synthesis of 3, 4-tetrahydropyrimidine-5-carboxylate using Lanthanum (III) chloride heptahydrate, one-step procedure from the Biginelli reaction under reflex condition an excellent yield in a ethanol solvent at temperature in the range of 80–110°C. The catalyst can be easily recovered and reused several times with good efficiency.

2. EXPERIMENTAL

Unless specified, all chemicals were analytical grade and purchased from the Alfa aesar used without further purification. The known products were identified by comparison of their melting points and spectral data with those reported in the literature. The chemical reactions were monitored by TLC using silica gel SIL G/UV 254 plates[1] H NMR (400 or 300 MHz) and [13]C NMR (400 or 300 MHz) analyses were run on a Bruker Avance DPX-250 FT-NMR spectrometer. The chemical shifts (δ) have been reported relative to TMS, which was used as an internal reference. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.1. Experimental Procedure for Biginelli Reaction

A mixture of ethyl acetoacetate (0.002 mol), urea (0.004 mol) or thiourea (0.004 mol), aldehyde (002 mol), Lanthanum (III) chloride (0.02 mol, in 25%) and 12 M HCl acid (1 drop) in absolute EtOH (10 mL) was placed under refluxed conduction in EtOH for 18 h [12,13]. The reaction mixture was then cooled to r.t was poured into crushed ice and stirred for 5-10 min. The solution was stirred for 5 min until a solid appeared. The precipitate was then filtered and the solid was washed with cold H_2O (2 ×), then with an EtOH–H_2O mixture (1:1, 2 ×) and finally dried under vacuum. The crude product was then purified by recrystallization in absolute ethyl acetate (scheme 1).



Scheme 1. $LaCl_3 \cdot 7H_2O$ – Catalyzed synthesis of tetrahydropyrimidine

4a.ethyl-4-(4-ethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

C_{16} H_{22} N_2 O_4, m.w : 304.1, IR(KBr,cm^{-1}): 3436, 2976, 1717, 1281, 1177, 784, ^{1}H NMR (300 MHz, DMSO - d_6): 7.11-7.14 (d, J = 9.0 Hz, 2H), 6.87 - 6.84 (d, J = 9.8 Hz, 2H), 5.08 - 5.09 (s, J = 1.5 Hz ,1H), 5.07 (s, 2H, NH), 4.01 - 3.98 (m, J = 9.1 Hz, 2H), 3.96 - 34 (m, J = 6.1 Hz, 3H), 3.36 (s, 3H, CH_3), 2.5 - 2.23 (m, J = 6.5 Hz, 2H), 1.3 - 1.07 (m, J = 3.1 Hz, 3H); ^{13}C NMR (400 MHz, DMSO), 165, 158, 153, 145, 136, 131, 127, 115, 114, 63, 60, 5, 29, 18, 14, 14.

4b.ethyl-4-(4-ethoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

C_{16} H_{20} N_2 O_3 S, , m.w: 320.1, IR(KBr,cm^{-1}): 3311, 1668, 1254, 1185, 1115, 768, ^{1}H NMR(300 MHz, DMSO-d_6); 10.2 (s, NH, 1H, C=S), 7.1 - 7.09 (d, J = 2.1 Hz, 4H, ArH), 6.9 - 6.6 (d, J = 2.0 Hz, 4H, ArH), 5.10 - 5.09 (d, J = 1.5 Hz, 2H, NH), 4.49 - 4.45 (m, J = 12.0 Hz, 5H,CH_3), 4.01 - 3.98 (q, J = 9.0Hz, 5H, CH_2), 3.36 (s, 3H, CH_3), 2.23 (s, 2H, C=S), 1.3 - 1.2 (m, J = 9.1 Hz, 5H,CH_3), 1.1 - 1.0 (q, J = 6.1 Hz, CH_2), ^{13}C NMR (400 MHz, DMSO); 174, 155, 153, 145, 137, 136, 128, 114, 77, 76, 75, 40, 41, 29, 14, 14.1.

4c.ethyl-4-(3hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

C_{14} H_{16} N_2 O_4, m.w: 273.1, IR (KBr, cm^{-1}): 3346, 3124, 1686, 1369, 1292, 1136, 766; ^{1}H NMR(300 MHz, DMSO-d_6); 7.12 - 7.06 (m, J = 9.1 Hz, 2H, ArH), 6.69-6.65 (d, J = 1.2 Hz, 1H), 6.2 -6.1 (m, J = 3.0 Hz, 2H, ArH), 6.6 (s, 1H, NH), 6.1 - 6.0 (d, J = 3.0 Hz, 1H), 5.06 - 5.05 (d, J= 3.0 Hz, 1H, NH), 4.02 - 3.98 (m, J = 12.0 Hz, 3H), 3.38 (s, 3H), 1.14 - 1.16 (m, J = 9.0 Hz, 2H), ^{13}C NMR (400 MHz, DMSO); 156, 128, 116, 114, 113, 78, 77, 58, 40, 39, 39.2, 39.3, 38, 17, 13, 13.1.

4d.ethyl-4-(3hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

C_{14} H_{16} N_2 O_3 S, m.w: 292.4, IR(KBr, cm^{-1}): 3308, 3118, 1666, 1369, 1259, 1194, 766, ^{1}H NMR (300 MHz, DMSO - d_6); 10.27 (s, 1H, C=S), 7.14 - 7.11 (m, J = 9.0 Hz, 2H, ArH), 6.67 (s, 1H), 6.65 (s, 2H, ArH), 5.10 (s, 1H), 4.06-4.01 (m, J = 15.1 Hz, 5H, CH_2), 3.34 (s, 1H, CH_3), 2.2 (s, 1H, C=S), 1.15 - 1.11 (m, J = 12.0 Hz, 5H, CH_3), ^{13}C NMR (400 MHz, DMSO); 156, 128, 116, 114, 113, 78, 77, 58, 40, 39, 39.2, 38, 17, 13.

4e.ethyl 6-methyl-2-thioxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate

C_{17} H_{22} N_2 O_3S, m.w : 365.1, IR(KBr,cm^{-1}): 3296, 3105, 1661, 1424, 1458, 1378, 1262, 785, ^{1}H NMR (300 MHz, DMSO - d_6); 10.3 (s, 1H, C=S), 6.51 (s, 1H), 5.157 - 1.150 (s, J = 2.1Hz, 1H, NH), 4.06 - 4.04 (m, J = 6.0Hz, 5H, CH_2), 3.36 (s, 3H, CH_3), 3.72 (s, 9H, OCH_3), 2.28 (s, 1H, NH, C=S), 1.16 - 1.13 (m, J = 6.1Hz, 5H, CH_3), ^{13}C NMR(400MHz, DMSO) ; 174, 160, 167, 152, 137, 104, 61, 60, 58, 14.

4f. 5-acetyl-4(4-ethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(H)-one

C_{15} H_{17} N_2 O_3, m.w : 274.5, IR(KBr,cm^{-1}): 3234, 2979, 1724, 1286, 1178, 792, ^{1}H NMR (300 MHz, DMSO - d_6); 7.65 (s, 2H, CH, ArH), 7.13 - 7.11 (d, J = 6.1 Hz, 4H, CH), 6.85 - 6.83 (d, J = 6.1 Hz, 1H, NH, C=O), 5.08 (s, 1H, NH), 4.002 - 3.95 (m, J = 15.6Hz, 5H, CH_2), 2.48 (s, 3H, CH, C=O), 2.23 (s, 3H, CH_3), 1.31 - 1.27 (m, J= 10.5Hz, 5H, CH_3), ^{13}C NMR (400 MHz, DMSO); 192, 157, 150, 145, 134, 125, 114, 27, 14.

4g.4-(5-chloro-2-hydroxyphenyl)-7,7-dimethyl–3,4,7,8-tetrahydroquinazoline-2,5 (1H,6H)-dione

C_{16} H_{17} N_2 O_3 Cl, m.w: 321.2, IR(KBr,cm^{-1}): 3408, 2956, 1630, 1477, 1377; ^{1}H NMR(300 MHz, DMSO - d_6); 7.6 - 7.3 (q, 1H), 7.1 - 7.0 (q, 2H, CH), 6.91 (d, 1H), 5.37 (s, 1H, NH), 2.4-2.2 (q, 1H, ArH), 1.92-1.04 (q, 1H, ArH), 0.98 - 0.90 (m, 6H, CH_3), ^{13}C NMR(400 MHz, DMSO); 198, 152, 150,146, 132, 128, 126, 50, 38, 32, 27, 26.

4h.4-(5-chloro-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo–1,2,3,4,7,8-tetrahydroquinazoline-2,5 (1H,6H)-dione

C_{16} H_{17} N_2 O_3 Cl, m.w: 337.4, IR(KBr ,cm^{-1}): 3434, 2922, 1634, 1459, 1044, ^{1}H NMR(300 MHz, DMSO - d_6); 10.4 (s, 1H, C=S), 7.6 - 7.5 (m, 1H, ArH), 7.2-7.0 (q, 2H, CH), 6.9-6.6 (q, 2H, CH, ArH), 5.4 - 5.0 (m, 1H), 3.35 (s, 1H, ArH), 2.5 - 2.3 (m, 1H, ArH), 1.92 (s, 1H), 0.90 (s, 6H), $^{[13]}$C NMR (400 MHz, DMSO); 198, 174, 159, 152, 132, 128, 126, 117, 103, 50, 39, 33, 27, 26.

3. RESULTS AND DISCUSSION

To optimize the reaction conditions, we used Aldehyde, ethyl acetoacetate, and urea as substrates under various reaction conditions both in the absence and in the presence of Lanthanum (III) chloride (Table 1). In the absence of catalyst, the reaction failed to give the desired product at room temperature, even after prolonged reaction time (24 h,). Increasing

the temperature to 110 °C resulted in only a 40% yield of the desired product in the absence of catalyst. However, when 0.23 g of catalyst was added, the yield increased to 95% after a reaction time of only 18 h. Increasing the amount of catalyst and the reaction time did not improve the yield further, and decreasing the amount of catalyst and the reaction time reduced the yield. The reaction was also carried out in various other solvents (H_2O, CH_3OH, and EtOH) and under solvent-free conditions. Under these Conditions, the reactions were sluggish, and the formation of by products was observed. To evaluate the substrate scope of the reaction, we evaluated a variety of substituted aromatic aldehydes and alkyl acetoacetate esters under the optimal reaction conditions, and we obtained good to excellent yields of the corresponding tetrahydropyrimidine (Table 2).

Table 1: Effect of $LaCl_3.7H_2O$ Catalysis amount, solvent and temperature on model reaction

Entry	Catalyst (mol %)	Solvent	Temperature (^{0}C)	Time (hour)	yield (%)
1	0.002	H_2O	60	1	22
2	0.002	H_2O	70	3	42
3	0.002	CH_3OH	70	4	48
4	0.002	CH_3OH	90	5	55
5	0.002	EtOH	80	5	60
6	0.002	EtOH	110	8	62

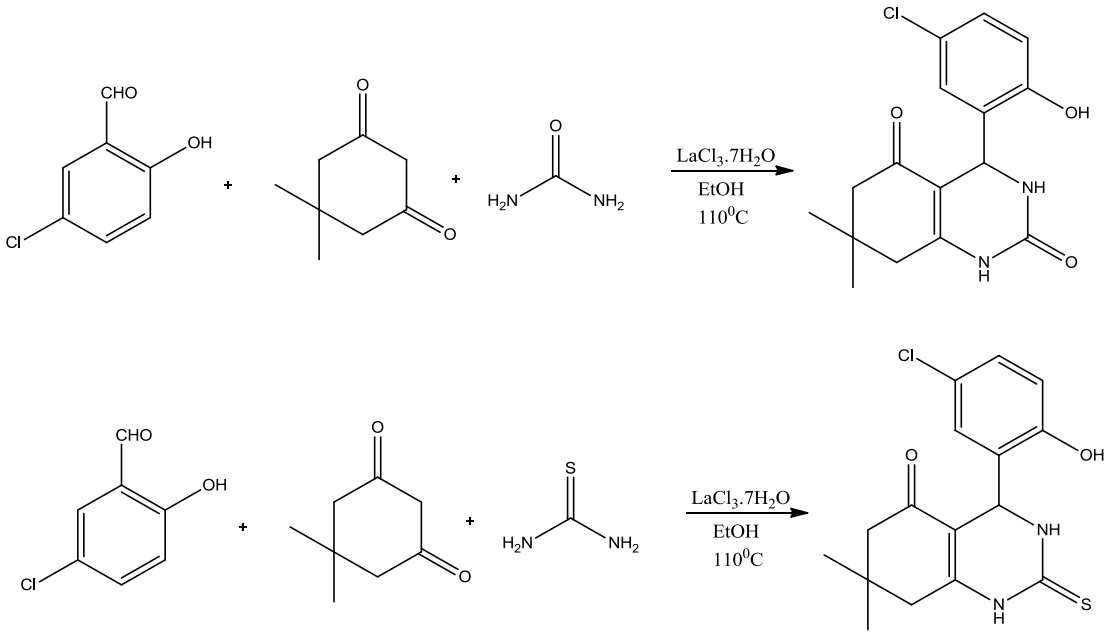
Reaction condition: Ethyl acetoacetate (0.002,) Aldehyde (0.002), and urea or thiourea (0.004), excellent yields

Table 2: Synthesis of Dihydropyrimidine under solvent free conditions Catalyzed by $LaCl_3.7H_2O$

Entry	R^1	R^2	X	Product	yield	Melting point
1	4-Eeo-C_6H_4	OC_2H_5	O	4a	84	274 - 275
2	4-Eeo-C_6H_4	OC_2H_5	S	4b	86	278 - 279
3	3-HO-C_6H_4	OC_2H_5	O	4c	87	280 - 281
4	3-HO-C_6H_4	OC_2H_5	S	4d	95	282 - 283
5	3,4,5-OMe C_6H_2	OC_2H_5	S	4e	95	248 - 249
6	4-Eeo-C_6H_4	CH_3	O	4f	90	270 - 271

Reaction conditions: Aldehyde (0.002 mol), dicarbonyl combound (0.002 mol), urea or thiourea (0.004), EtOH 10 ml, $LaCl_3.7H_2O$ 0.14g, 110 ^{0}C, 18h, excellent yield.

To further explore the substrate scope of the reaction, we replaced ethyl acetoacetate or dimedone. As expected, these cyclic substrates also underwent smooth, one-pot conversion to give the corresponding tetrahydropyrimidine in good yields (Scheme 2). In all cases, the pure product was isolated by simple filtration. To explore the advantages and drawbacks of this Lanthanum (III) chloride - catalyzed reaction, we compared the results we obtained under the optimized conditions with results reported in the literature for Biginelli reactions mediated by other catalysts (Table 3). The yield of the catalyzed ($LaCl_3.7H_2O$) reaction was comparable to or higher than the yields obtained with all but one of the other catalysts listed in Table 3. However, all the other catalysts required longer reaction times (Scheme 2). According to the mechanism suggested by Yamamoto,[14] we have a Brønsted acid-assisted Brønsted acid catalyst catalytic system (HOAc + $LaCl_3.7H_2O$), and this catalyst system showed higher activity than the other catalysts listed in Table 3.

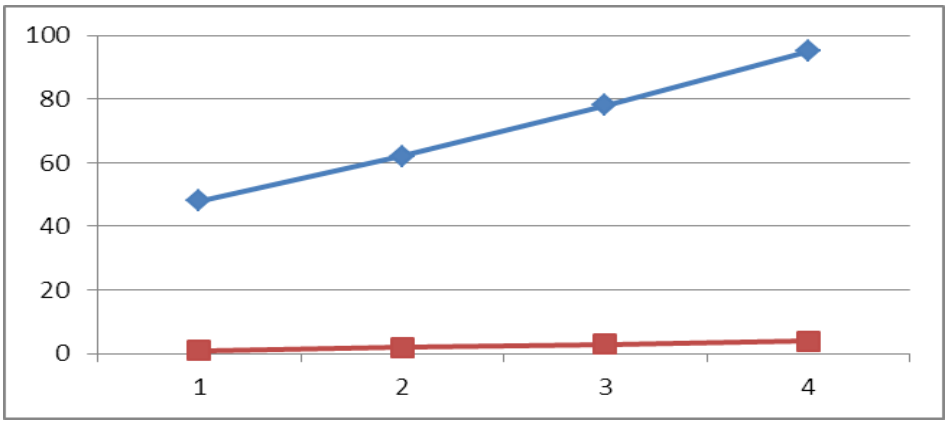


(4g-4h)

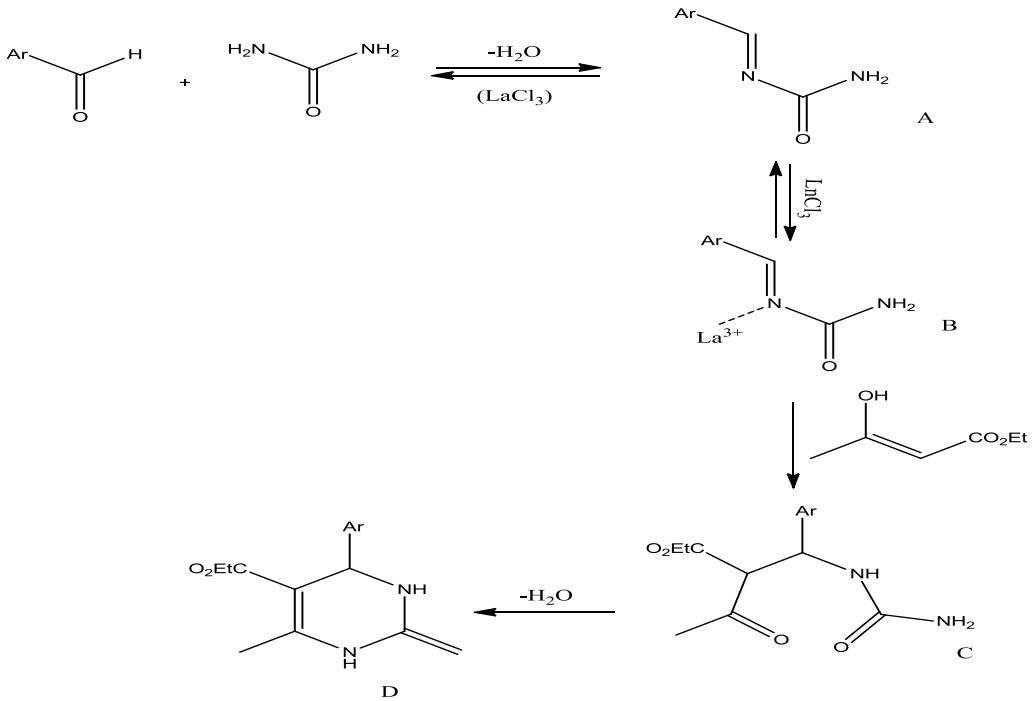
Scheme 2: $LaCl_3.7H_2O$- Catalyzed condensations of aldehyde, cyclic 1,3-dicarbonayl compounds, and urea or thiourea.

We also evaluated the feasibility of reusing the Lanthanum (III) chloride catalyst. We allowed aldehyde, ethyl acetoacetate, and urea or thiourea to react under the optimized

reaction conditions and then filtered the reaction mixture, washed the collected solid catalyst with hot EtOH, dried it in air, and reused it in a second reaction with the same substrates. We were able to reuse the $LaCl_3.7H_2O$ catalysis four times any appreciable loss in its catalytic activity (Fig.1).



The mechanism of the Biginelli reaction has recently been revised by Kappe.[15] Based on this work we suggest the following mechanism for the Lanthanum (III) chloride -catalyzed Biginelli reaction (Scheme 3). The first step is the acid-catalyzed condensation of aldehyde and urea (or thiourea). The formation of *N*-acyl imine intermediate **A** is the rate-limiting step of the reaction. The intermediate **A** is complexed by Lanthanum chlorides, giving **B**, which acts as an electrophile for the nucleophilic addition of the ketoester enol. The resulting adduct **C** undergoes condensation with the urea-NH_2 to give the cyclized product **D**.



Scheme 3. Mechanism for Lanthanum (III) chloride- catalyzed biginelli reaction

Table 3: Comparison of the $LaCl_3.7H_2O$- Catalyzed reaction mediated by other catalysts

Catalyst	Temperature (^{0}C)	time (h)	yield (%)	Ref
Con.H_2SO_4	100	5	48	16
Con.HCl	80	5	58	17
$CuCl_2$. $2H_2O$	95	6	72	18
$SnCl_2.2H_2O$	100	6	68	19
$LaCl_3.7H_2O$	110	7	95	this work

*Classical Biginelli conditions

4. ANTIMICROBIAL ACTIVITY

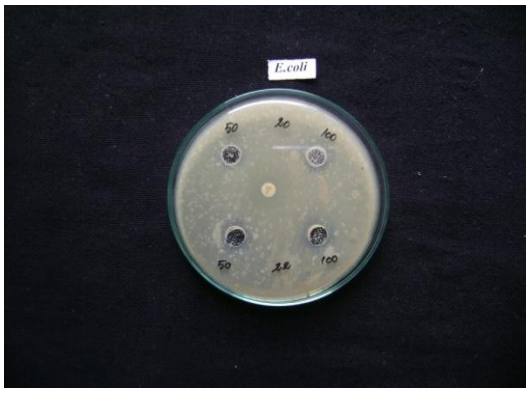
The result of in vitro of antimicrobial activity of biginelli reaction against of two species Gram - ve *(E,Coli, B. subtilis*) Gram +ve (*Moraxilla, Enterobacter*), and two fungal species (A.niger, Trychopyton) are reported in Table (IV). Compounds 4a, 4b, 4e, and 4g have shown excellent antibacterial activity against *E, Coli* and *B. subtilis*. They inhibited the bacterial growth up 85 – 90% at 100 ppm concentration where as 4c, 4d, 4h and 4f were found to have moderate antibacterial activity in the range of 80 – 85% at 100 ppm concentration and the remaining compounds have medium antibacterial activity. Antifungal activity compounds were moderately active against both the fungal species *A. Niger* and *Trychopyton*. (Figs. 2)

This procedure was repeated for each Petri plates then the petriplates were incubated at 37^{0}C for 24 h. After incubation the plates were observed for zone of inhibition (*E, Coli, B. subtilis), (A.niger, Trychopyton).* The antimicrobial activity was investigated against Gram –ve (E, Coli, *B. subtilis*) Gram +ve bacteria *(Enterobacter, Moraxilla)* fungi *A.niger* and *Trychopyten* by Auger cup borer method using *ofloxacin* as a standard for bacterial and fungal culture respectively. The minimum inhibitory Concentration (MIC) study was carried out at different concentration such as 50, 100 ppm, but the zone of inhibition (100 ppm) was selected as (MIC). A test tub containing sterile nutrient ager medium (Nutrient plates) and allowed to solidify for 5 min. The cup borer was sterilized by dipping into absolute ethanol and flaming it and then allowed to cool down with the help of sterile cup- borer this cup in the agar were marked and were injected with 0.1 ml of respective test sample solution of concentration 100 ppm in DMSO solvent 0.1 ml standard *ofloxacin* (100 ppm) solution in distilled water and 0.1 ml of DMSO respectively. Then the test tube was allowed to differ for 1 hr in refrigerator at 45^{0}C. The plates were incubated in upright position at 37^{0}C for 24h and

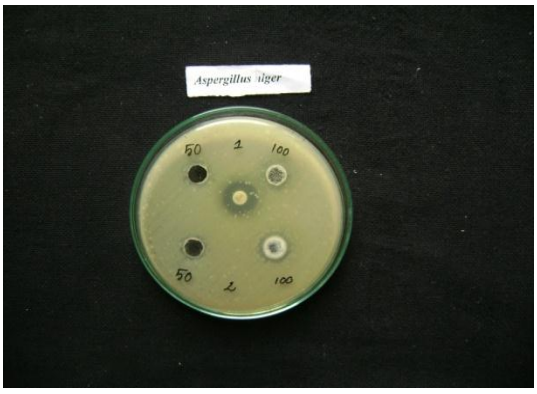
on the next day the zone of inhibition surrounding each cup was observed. The data for antifungal activity in terms of zone of inhibition

Table. IV. Data of antimicrobial activity of compounds (4a-h)

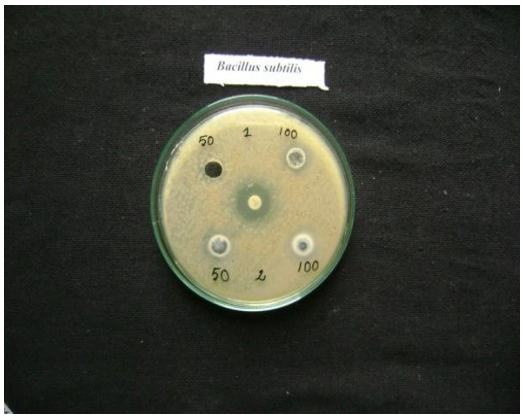
Compounds	Zone of inhibition(mm)					
	Gram positive bacteria		Gram negative bacteria		Fungi	
	Enterobacter	*Moraxilla*	*E.coli*	*B. subtilis*	*A.niger*	*Trychophyton*
4a	12	13	14	15	14	15
4b	15	21	15	19	16	18
4c	16	11	12	16	10	12
4d	17	19	15	20	16	15
4e	16	24	20	20	25	21
4f	16	27	20	18	23	22
4g	16	18	16	16	16	16
4h	13	15	19	16	18	16
***Ofloxacin*(10µg/ml)**	20	22	20	20	20	18



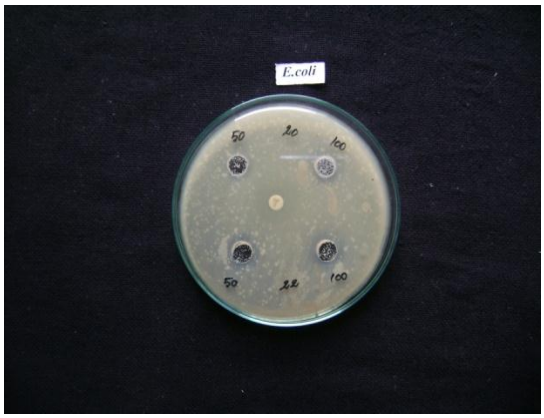
E, Coli



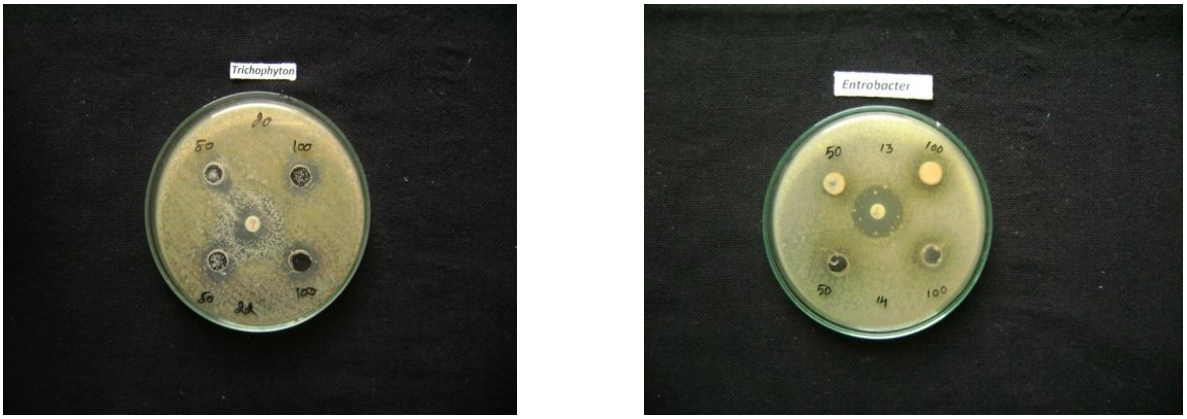
A.niger



B. subtilis



E, Coli



Trychophyton ***Enterobacter***

Figure 2. Antibacterial and antifungal activity

5. CONCLUSION

We developed a very simple and efficient method for the direct preparation of Substituted tetrahydropyrimidine by a multicomponent reaction of ketoesters, aldehydes and urea or thiourea in the presence of a Lanthanum (III) chloride heptahydrate as a catalyst in with readily available starting materials. All the compounds were evaluated for their in vitro antibacterial and antifungal activity. The activity data revealed that the compounds have maximum zone of inhibition.

ACKNOWLEDGEMENT

The authors are thankful to the Principal and the Head of the department of Chemistry Jamal Mohamed College for providing necessary facilities to do our work. SAIF - Punjab for the analytical support and the Eumic Analytical Laboratory and Research institute, Tiruchirappalli for their help in antimicrobial susceptibility testing

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