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An Efficient One-Pot Multicomponent Synthesis Of 1, 2, 3, 4-Tetrahydropyrimidin-2(1H)-Thiones Catalyzed By Lew's Acid Catalyst

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ABSTRACT:

This study reports on the solvent-free, one-pot multicomponent synthesis of heterocyclic 1,2,3,4-tetrahydropyrimidin-2-(1H)-thiones (THPMs) using $ZrOCl_2$. The versatile and an efficient method is described for the solvent free synthesis of 1,2,3,4-tetrahydropyrimidin-2(1H)-ones proceed through one-pot multi component condensation of ethyl acetoacetate, an aryl aldehydes, and thiourea promoted by $ZrOCl_2$as a Lew's acid catalyst. The titled derivatives can be evaluated by advance spectroscopic data such as IR, ^{1}HNMR, ^{13}CNMR and LCMS. The present methodology enhances majority of advantages such as high yields, relatively short reaction times, mild reaction condition, and easy work up. The experimental design method is used to optimize variables like temperature, catalyst quantity, and reaction time.

KEYWORDS:

Ethyl acetoacetate, Aryl aldehydes, Thiourea, 1, 2, 3, 4-tetrahydropyrimidin-2(1H)-ones, $ZrOCl_2 8H_2O$

1. INTRODUCTION:

Multi-component reactions are enhancement of an importance in organic and medicinal chemistry and they offer the role significant advantages over conventional linear-type syntheses, including high selectivity, good yields, milder reaction conditions and simple work-up. Thus, a several number of diverse compounds can be obtained in parallel syntheses. New, efficient methods for rapid construction of potentially bio-active compounds are required, and multi component reactions allow the construction of several bonds in a single operation. They are this gaining in importance as powerful technique for synthesizing complex as well as diverse molecules.

A robust technology for the quick synthesis of biologically significant, diverse, and complex organic compounds is based on multicomponent reactions (MCRs), which involve the simple production of numbers of new covalent bonds in a single pot (1–2). A traditional multicomponent method for generated 3,4-dihydropyrimidine-2-(1H)-ones (DHPMs) orthicons' involves the Biginelli condensation of aldehydes, β-ketoester, and either urea or thiourea, which results in three components. Heterocyclic compounds play important roles in biological and pharmaceutical process. As several drug molecules contain heterocycles as a core structure, great efforts have been made to develop improved synthetic methods for this structure. Since they are the building blocks of numerous bioactive substances, including those with antibacterial, anticancer (3-4), anti-inflammatory (5), and antitubercular properties (6), toxoplasmosis (7) heterocyclic compounds with a pyrimidine nucleus are particularly interesting due to their applications in medicinal chemistry. Although Biginelli reaction is considered as a simple reaction for the synthesis of dihydropyrimidine, its authentic procedure suffers from low yield. Many improvements have been introduced and reported to overcome the low yield problem including the introduction of different catalysts like Lewis acids clay. In concordance with the essential importance of, there has been a growing demand for the development of eco-friendly and economic procedures for their preparation.

As previous literature a result, several catalysts, including graphite, zeolites, Lewis and Bronstd acids, ionic liquids, and heterogeneous acid catalysts, have been used to study the synthesis techniques for Tetrahydropyridine derivatives such as $NH_4H_2PO_4$/MCM-41 **(8),**ZrO_2/La_2O_3(9),$Ca(NO_3)_2.4H_2O$(10),Maleicacid(11),Cobaltperchloratehexahydrate(12), Trichloroacetic Acid (13), SiO_2 (NPs) Supported-BO_3H_3 (14), Chitosan Immobilized Ionic liquid (15), 2-thienylboronic acid, $Al(NO_3)_3 \cdot 9H_2O$ (16), t-BuOK (18), Holmium Chloride (19), MgO-ZrO_2 (20) , L-proline N-sulfonic acid (21), Pbmim]$(FeCl_4)_2$ (22),

Unfortunately, a number of the techniques that have been reported have one or more problems, including a tedious workup, an undesirable yield, lengthy reaction durations, and the need for organic solvents, toxicity, and the difficulty to reuse catalysts. However, in spite of their potential utility, many of these reported one-pot protocols suffer from drawbacks such as the use of expensive reagents, volatile strong acidic conditions and long reaction times. Therefore, to avoid these limitations, the introduction of a milder and more efficient method accompanied with higher yields is needed.

The aim of the present work is the introduction of a novel synthesis procedure for the synthesis of $ZrOCl_2$ and we reported the present work highly an efficient versatile and appropriate process. It is used for synthesis of tetrahydropyrimidine-2-thiones analogous with help of Transition metal catalyst. Our research perfectly and progressively the catalytic properties of $ZrOCl_2$ for numerous organic transformations has scaffold us to the identification that the effectiveness of this catalysts for the synthesis of titled analogous has not been previously reported. Hence, our aimed to focus been done to investigate the impact of catalyst in the $ZrOCl_2$ one-pot synthesis of titled via cyclocondensation of substituted aromatic carbaldehyde, ethyacetoacetae and thiourea.

2. METHODS AND MATERIALS:

2.1. EXPERIMENTAL:

All the analytical chemicals, synthetic grade reagents and solvents purchased from Fine chemicals and were used without further purification. The reaction progress was monitored by thin layer chromatography. The melting point of the all the newly synthesized compounds were determined open at one end and were uncorrected using an Electrochemical Mk3 apparatus. ^{1}HNMR &^{13}CNMR spectrum were recorded on 400MHz Bruckner spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilanes (Me_4Si) as an internal standard. Molecular mass of the synthesized compound were determined by LCMS spectrometer.

2.2. $ZrOCl_2$ catalyzed synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivatives.

To a mixture of aldehydes (1 mmol), ethyl acetoacetate (1 mmol), thiourea (2 mmol) and $ZrOCl_2 8H_2O$(10mol %) was stirred at 70 °C under solvent-free condition for 3.5 h. The completion of the reaction was monitored by TLC. After cooling, the reaction mixture was poured in to crushed ice and stirred for 30 min. The separated solid was filtered under suction, washed with cold water thoroughly and then recrystallized from methanol to afford the pure product. All products are known compounds, which were characterized by IR and 1H-NMR spectra.

2.2.1.Ethyl6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a):

Yield:83%;m.p-178–180°C;IR(KBr,cm-1):3354(NH),1688(C=O);1HNMR($CDCl_3$,400 MHz) δppm:9.815(NH,s,1H,),8.947(NH,s,1H,),7.651-7.296(Ar-H,5H,m),4.857(s,1H,pyrimidine) ,4.087-3.784(m,2H,-CH_2-),1.682(s,3H,CH_3), 1.124(t,J=8.8Hz,3H,CH_3,pyrimidine);^{13}CNMR (100MHz,$CDCl_3$)δppm; 173.28, 166.09, 161.11, 142.48, 129.57, 128.92, 127.04, 103.33, 60.45, 57.61, 17.88, 14.17; LCMS(m⁄z):246.45(M+);Molecular compound : $C_{13}H_{14}N_2O2S$.

2.2.2.5-Ethoxycarbonyl-4-(2-hydroxyphenyl)-6-phenyl-1,2,3,4-tetrahydropyrimidine-2-thione (4b) :

Yield: 87%; m.p-178–180°C; IR (KBr) νmax (cm-1): 3365 (NH), 3074 and 2965 (CH), 1698 (C=O), 1582 (C=S), 1495 (C=C), 1456 (C-O) and 1256 (C-C). 1H NMR ($CDCl_3$,400MHz) δ ppm: 10.625 (s, 1H, OH); 9.854 (s, 1H, NH); 8.784 (s, 1H, NH); 8.248-7.451 (m, 9H, Ar-H); 4.914 (s, 1H, H(4)); 3.454-3.331 (m, 2H, CH_2) and 0.878 (t, J=8.0 Hz, 3H, CH_3);^{13}CNMR (100MHz,$CDCl_3$)δppm;174.58,164.47,158.08,152.44,136.02,127.33,126.04,102.52,60.28,56.66,19.09,14.34 ;LCMS(m⁄z):293.21(M+H);Molecular compound : $C_{14}H_{16}N_2O_3S$

2.2.3.6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4c):

Yield: 90%; M.p : 197–199°C;IR (KBr,cm^{-1}):3384 (NH), 1689(C=O),1245(C=S);1H NMR (CDCl3,400 MHz)δppm: 9.701(s, 1H, NH); 8.614 (s, 1H, NH); 7.251-6.847 (m, 4H,Ar-H),4.804(s,1H,H(4));3.749(s,3H,-OCH_3),4.015-3.374(m,2H,CH_2),1.216(t,J=8.0Hz, 3H,CH_3);

^{13}CNMR(100MHz,CDCl3)δppm;174.58,164.47,158.08,152.44,136.02,127.33,126.04,102.52,60.28, 56.66, 19.09, 14.02; LCMS (m⁄z):307.65(M+H); Molecular compound: $C_{15}H_{18}N_2O_3S$

2.2.4.5-Ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-phenyl-1,2,3,4-tetrahydro pyrimidine-2-thione (4d) :

Yield: 91%; M.p : 197–199°C;IR (KBr,cm-1; IR (KBr) νmax (cm-1): 3405 (NH), 3077, 2925 (CH),1733 (C=O), 1566 (C=S), 1491 (C=C), 1452 (C-O) ,1288 (C-C). 1H NMR (400MHz,$CDCl_3$) δ ppm: 10.012(s, 1H, NH1), 9.074 (s, 1H, NH3),7.115(s,1H,Ar-H), 6.947-6.785 (m, 2H, Ar-H); 4.847 (s, 1H, H(4)),4.054-3.815 (m,2H,Ar-H), 3.714 (s,3H,OCH3), 3.057 (s, 3H, OCH_3), 1.127(t,J=9.2 Hz, 3H, CH3).^{13}C NMR (100MHz,$CDCl_3$)δ ppm:173.55, 164.77, 150.08, 145.33, 143.95, 135.47, 128.54, 125.84, 102.47, 58.99,55.17, 52.78,51.99, 19.05,14.11.LCMS (m⁄z):367.47(M+H); Molecular compound: $C_{16}H_{20}N_2O_4S$.

2.2.5.5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-phenyl-1,2,3, 4-tetrahydropyrimidine-2-thione (4e)

Yield: 89%; M.p: 214–216°C; IR (KBr) νmax (cm-1): 3324 (NH), 3057, 2988 (CH), 1728 (C=O), 1593 (C=S), 1482 (C=C), 1433 (C-O) and 726 (C-Cl). 1H NMR (CDCl3, 400MHz) δ ppm: 10.214 (s, 1H, NH1); 9.562(s, 1H, NH3), 7.758-7.298 (m, 4H, Ar-H); 5.024 (s, 1H, H(4)); 3.847-3.667 (m,2H, CH2),1.087 (t, J=8.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 400MHz) δ ppm: 175.36, 165.77, 145.87, 143.88, 134.65, 130.44, 128.77, 128.14, 127.26, 123.08, 121.71, 101.47, 60.47, 54.49, 13.87; LCMS (m⁄z):312.58(M+2); Molecular compound: $C_{14}H_{15}ClN_2O_2S$.

2.2.6. Ethyl 4-(2-bromo-6-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyr imidine-5-carboxylate (4f):

Yield: 88%; M.p: 212–214°C; IR (KBr) νmax (cm^{-1}): 3514 (OH), 3346 (NH), 3074, 2967 (CH), 1718 (C=O), 1577 (C=S), 1488 (C=C), 1382 (C-O), 1266 (C-C) and 821 (C-Br). 1H NMR ($CDCl_3$) δ ppm: 10.147 (s, 1H, OH); 9.748 (s, 1H, NH1); 8.884 (s, 1H, NH3); 7.218-6.817 (m, 3H, Ar-H); 5.012 (s, 1H, H(4)); 3.984-3.714 (m, 2H,- CH_2-) ;1.119 (t, J=7.6 Hz, 3H, CH_3);^{13}C NMR (100MHz,$CDCl_3$) δ ppm:176.04, 163.17, 158.33, 152.84, 142.09, 136.11,129.24,126.32,103.04,59.15,57.28,52.78,50.99,17.05,13.85:LCMS(m⁄z):372.01(M+2); Molecular compound: $C_{14}H_{15}BrN_2O_3S$.

2.2.7.Ethyl6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4g):

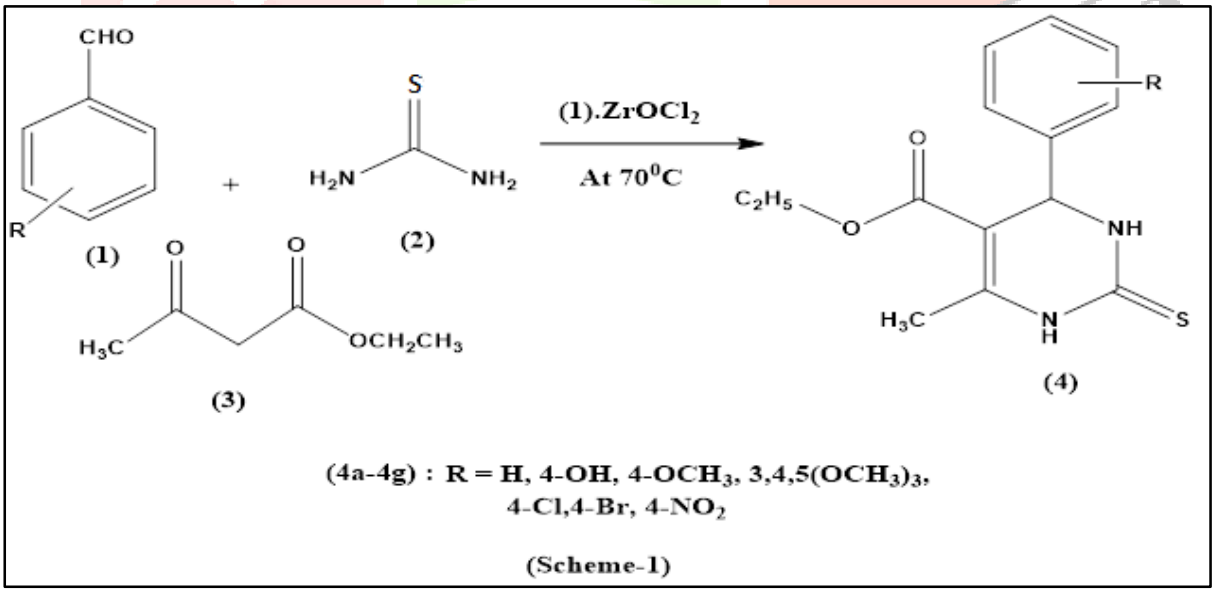
Yield: 86%; M.p: 207–209°C; IR (KBr) νmax (cm-1): 3358 (NH), 3066, 2984 (CH), 1726 (C=O), 1579 (C=S), 1489 (C=C), 1385 (C-O), 1265 (C-C) ; 1H NMR (400MHz,CDCl3) δ ppm: 10.247 (s, 1H, NH1); 9.774 (s, 1H, NH3); 7.910-7.365 (m,4H, Ar-H); 5.147 (s, 1H, H(4)); 4.012-3.847 (m, 2H, CH_2) ,0.988 (t, J=7.2 Hz, 3H, CH_3).^{13}C NMR (100MHz,CDCl3)δppm:177.21,163.04,161.37,150.84,143.35,137.55,129.24,127.02,103.85,6179.54,58.28,18.25,13.90:LCMS(m⁄z):322.74(M+H);Molecularcompound: $C_{14}H_{15}N_3O_4S$

2.2.8.Ethyl4-(4-methylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(4h):

Yield: 89%; M.p: 219–221°C M.p: IR (KBr) νmax (cm-1): 3324 (NH), 3081, 2974 (CH), 1722 (C=O), 1577 (C=S), 1485 (C=C), 1384 (C-O), 1261 (C-C),^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H, NH), 8.718 (s,1H,NH), 7.547-7.296(m,4H,Ar-H), 4.874 (s, 1H, 4(H)), 4.092-3.897(m,2H,-CH_2-), 2.258 (s, 3H,CH_3), 1.876 (s, CH_3, 3H), 1.182 (t, J= 8.0 Hz, 3H,CH_3). ^{13}H NMR (100 MHz, $CDCl_3$) δ ppm: 173.99, 160.08, 156.73, 143.88,136.05,129.77, 127.36,121.56,115.81,103.29,60.22,56.41,19.25,17.36,13.03.LCMS(m⁄z):322.74(M+H); Molecular compound: $C_{14}H_{15}N_3O_4S$

3. RESULTS AND DISCUSSION:

In this investigation, the catalytic activity of $ZrOCl_2$ was first investigated using three-component reaction of substituted benzaldehyde, ethyl acetoacetate, and thiourea as a model reaction. After carrying out the reaction at different conditions, the best results have been obtained with 10 mmol% Lew's acid catalyst at70^{o}C after 3.5hrswith 92% yield under solvent-free conditions. One important aspect of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. Our initial work started with screening of solvent and catalyst loading so as to identify optimal reaction conditions for the synthesis of tertahydropyrimidin-2(1H)-thiones derivative.The solvents acetone, acetonitrile, ethanol, toluene and methanol were examined and reaction with no solvent at 70^{o}C was found to be the most successful. We also evaluated the amount of $ZrOCl_2$ required for the reaction, and it is concluded that 10m mol% of catalyst is sufficient to promote the reaction.



(Scheme-1)

In order to fine-tune the reaction conditions, the effect of catalyst amount (Table-1) and reaction temperature (Table-2) were optimized carefully. The efficiency of the reaction is mainly affected by the amount of the catalyst. Simple heating of a neat mixture of substituted aromatic aldehydes, β – diketones (ethyl acetoacetate), and thiourea at 70 °C under solvent free condition in the absence of catalyst led to fair yields and only a highly impure product obtained after 9 h, while good results were afforded in the presence of $ZrOCl_2$.The amount of catalyst increases catalyst produced 92% of the product after 3.5 h (entry 2). The

optimum amount of the catalyst was 20% mmole and higher amount of catalyst did not improve the yield% considerably. This was due to the fact that beyond a certain concentration, more catalyst sites exist than that required by the reactant molecules and, hence, the additional amount of catalyst does not increase the rate of the reaction.

Table-1 . Effect of $ZrOCl_2$amount on the Biginelli reaction under solvent free condition

Entry	Loaded Catalyst (%mmol)	Time (hrs.)	Yield (%)
1	0	10	10
2	2.5	7.5	37
3	5.0	5.0	61
4	10	3.5	92
5	20	3.5	92

The effect of temperature on the reaction progress was also studied (Table -2). Obtained results showed that the reaction time was obviously reduced with increasing temperature. Higher temperatures, above 70 °C, had no important effecton the yield% and only decreased the reaction time. Therefore, considering technical points of view, the temperature70 °Cwas selected for all reactions. Enhancing temperature above70 °C had no much influence on the yield% and reaction time.

Table -2 . Effect of reaction temperature on the three components condensation of 3,4,5-Trimethoxybenzaldehyde with ethyl acetoacetate and thiourea

Entry	Temperature (°C)	Time (h)	Yield (%)
1	RT	12	36
2	40	8	52
3	65	5	75
4	70	3.5	92

In order to evaluate the generality of this methodology, a range of desired product were synthesized under the optimized reaction conditions. The starting materials such as substituted aryl aldehydes and thiourea underwent a smooth transformation into the corresponding tetrahydropyrimidine-2-thiones in good to excellent yields. In all cases, aromatic aldehydes with substituents having electron-withdrawing groups reacted faster than electron-donating substituents and successfully produced the expected products in good yields and excellent selectivity. Strong electron withdrawing substituent–NO 2 , distinctly increased the reactivity of aldehydes toward the condensation reaction and led to 85% of product after 2.5 h (entry 2); whereas, benzaldehyde produced 72% of conversion after 3.5 h (entry 2). Noteworthy, the Br group on the meta-position slightly affected the reactivity of aldehyde toward the condensation reaction. Chlorinated benzaldehyde showed the reactivity pattern of 4-Cl. This reactivity pattern confirmed the role of electronic effects on the reaction progress. Electron donating methyl substituent on the ortho-position decreased the efficacy of the reaction and only 47% was obtained.

Table-3: Comparison of the catalytic activity of $ZrOCl_2$with some other catalysts.

Entry	Catalyst	Catalyst amount(mmol)	Time(h)	Yield (%)
1	TiO_2	10	3.5	54
2	$FeCl_3$	10	3.5	72
3	$ZnCl_2$	10	3.5	48
4	$ZrOCl_2$	10	3.5	92

The spectral evidence of the titled derivatives that exhibited the different values of IR such as the vibrations frequencies at 3584-3324 (NH), 1753-1688 (C=O), 2988-2925 (C-H), 3057-3081(Ar-C-H), 1593 (C=S), 1482-1495 (C=C), 1288-1256 (C-C) are respectively.1HNMR values appears at 10.625 -10.147δppm of hydroxyl group, the methoxy protons appears at 3.749-3.570δppm and 10.247 δppm of NH protons.

4. CONCLUSION:

An efficient, mild, and excellent methodology has been developed for the synthesis of tertahydrhydropyrimidin-2(1H)-thiones followed by one-pot three-component reaction of ethyl acetoacetate, substituted aromatic aldehydes, and thiourea under solvent ethanol condition promoted $ZrOCl_2 8H_2O$ catalyst. This catalyst could be reused after a simple work-up and used several times without noticeable reduction in the catalytic activity. Good to excellent yields, relatively short reaction times, simple operation and easy work-up are some advantages of this protocol. This improved reaction condition allows the preparation of a wide variety of substituted tertahydrhydropyrimidin-2(1H)-thiones in high yields and excellent purity under mild reaction conditions. We believe the applicability of $ZrOCl_2 8H_2O$ with the mentioned advantages makes our method superior among other reported methods to synthesize titled derivatives.

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