*Available online www.jocpr.com*

**Journal of Chemical and Pharmaceutical Research, 2018, 10(5): 132-136**

**Research Article**

**ISSN : 0975-7384**
**CODEN(USA) : JCPRC5**

# Zinc (II) Acetate Catalyzed Synthesis Of 3,4-Dihydropyrimidin-2(1H)-Ones

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## ABSTRACT

*An efficient and new protocol for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPMs) 4(a-m) has been developed by using Zn(OAc)2 as a catalyst. This is one of the useful new catalyst that can be easily separated and are not contaminated by products. This method offers several advantages including high yields, short reaction times, simple work up procedure and easy isolation.*

**Keywords:** Aromatic aldehyde; Ethyl acetoacetate; Urea; Dihydropyrimidinones; Zinc acetate

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## INTRODUCTION

The Biginelli reaction is a well-known, simple and straightforward procedure for the synthesis of dihydropyrimidinones (DHPMs) by the three component condensation of aliphatic or aromatic aldehydes, β-ketoesters and urea. The original reaction was first reported by Pietro Biginelli in 1983 and was catalyzed by mineral acids[1,2]. These DHPMs are very interesting due to their wide spectra of biological activities and are used as a starting point to prepare complex heterocyclic scaffolds with pharmacological properties such as calcium channel blockers, mitotic kinesin inhibitors, antiviral, antibacterial, antifungal and anticancer activities [3-8] (Figure 1).

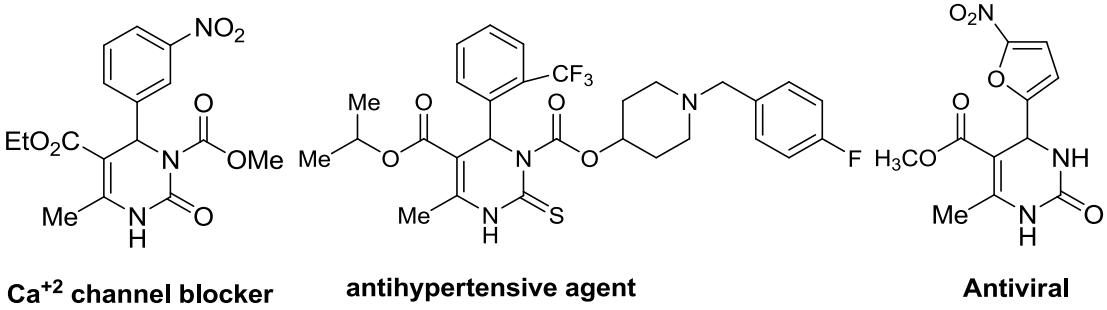



**Figure 1: Examples of biologically active DHPMs**

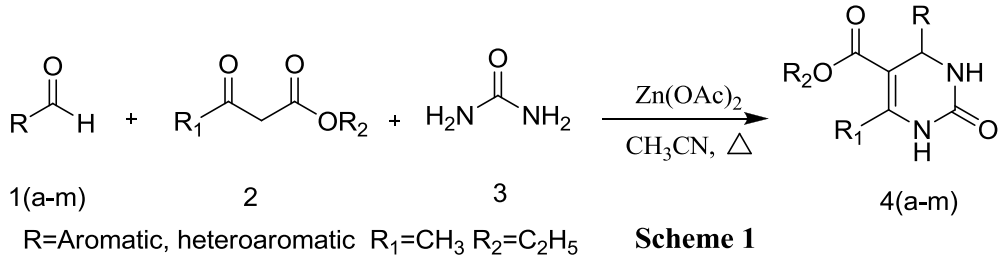
In order to improve the reaction yields or the scope of reaction numerous catalysts have been employed. Some of which could be mentioned here such as acid catalysts $InBr_3$, $InCl_3$, LiBr, $LiClO_4$, $CaCl_2$, $Ca(OTf)_3$, $LaCl_3$, $La(OTf)_3$, $BiCl_3$, $FeCl_3.6H_2O$, $BF_3.OEt_2$, $KHSO_4$, $ZnCl_2$ etc., [9-14] and by means of green chemistry processes like solvent free conditions microwave irradiation ultrasound irradiation and ionic liquids[15-18]. However, some methods suffered from drawbacks like low yield, longer reaction time, toxic reagents, expensive and involve difficult product

isolation procedures. Moreover, some of the methods are only practical for aromatic aldehydes. As part of our research program in developing various synthetic methodologies, herein we report, the Biginelli condensation using Zinc (II) Acetate $Zn(OAc)_2$ as an efficient catalyst. The catalyst $Zn(OAc)_2$ is known as an efficient catalyst in the literature for various organic transformations [19-22]. In this article we wish to report a simplified and rapid synthetic procedure with high atom economy for the Biginelli reaction.

## EXPERIMENTAL SECTION

### General Methods

All commercial reagents were used without purification and all solvents were reagent grade. All the reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel $60F_{254}$ percolated glass plates, which were visualized with UV light. Melting points were recorded on Buchi R-535 apparatus. IR spectra are recorded in KBr pellets on Nexus-670 spectrophotometer. $^1$H NMR spectra are recorded on Bruker 200 MHz spectrophotometer using TMS as an internal standard [13]. CNMR spectra are recorded on Bruker 75 MHz spectrophotometer and ESI-Mass spectra are obtained on shimadzu mass spectrophotometer.




**Scheme 1**

**Table 1: Zinc (II) acetate catalyzed synthesis of DHPMs 4(a-m)**

| Entry | R | $R^1$ | $R^2$ | Product[a] | Reaction Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| **a** | $C_6H_5$ | $CH_3$ | $C_2H_5$ | 4a | 1 | 90 |
| **b** | 2,4-$(F)_2$-$C_6H_3$- | $CH_3$ | $C_2H_5$ | 4b | 1.5 | 88 |
| **c** | 2,4,5-$(F)_3$-$C_6H_2$- | $CH_3$ | $C_2H_5$ | 4c | 1.5 | 87 |
| **d** | *O*-$(F)_3$-$C_6H_2$- | $CH_3$ | $C_2H_5$ | 4d | 2 | 86 |
| **e** | 2,4-$(Cl)_2$-$C_6H_3$- | $CH_3$ | $C_2H_5$ | 4e | 2 | 87 |
| **f** | 2-(Cl), 3-(OH)-$C_6H_3$- | $CH_3$ | $C_2H_5$ | 4f | 2.5 | 86 |
| **g** | 2-(B)r-$C_6H_4$- | $CH_3$ | $C_2H_5$ | 4g | 2.5 | 85 |
| **h** | 3-(CN)-$C_6H_4$- | $CH_3$ | $C_2H_5$ | 4h | 2.5 | 84 |
| **i** | 2-$(NO_2)$-$C_6H_4$- | $CH_3$ | $C_2H_5$ | 4i | 1.5 | 85 |
| **j** | 2-$(NO_2)$-(*E*)$C_6H_5$-CH=CH- | $CH_3$ | $C_2H_5$ | 4j | 3 | 87 |
| **k** | 4-(MeO)-$C_6H_4$- | $CH_3$ | $C_2H_5$ | 4k | 1 | 90 |
| **l** | 4-$(H_3C)_2$C-$C_6H_4$- | $CH_3$ | $C_2H_5$ | 4l | 1 | 89 |
| **m** | 2-Thienyl- | $CH_3$ | $C_2H_5$ | 4m | 1.5 | 86 |

[a]All the products were characterized by $^1$H NMR, IR and Mass spectra data
[b]Isolated and unoptimized yields

**General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones 4(a-m)**

To a stirred mixture of aromatic aldehyde (2 mmol) and ethyl acetoacetate (2.2 mmol) in acetonitrile (5 ml) was added Urea (3 mmol) and zinc acetate (0.3 mmol). The resulting reaction mixture was refluxed for a specified time as mentioned in the Table 1 After complete conversion of the starting material (aldehyde) as indicated by thin layer chromatography, the reaction mixture was cooled to room temperature, poured into water and extracted with EtOAc three times (3 × 20 ml). The combined organic layers were washed with brine dried over anhydrous $Na_2SO_4$ and the organic layer was concentrated to obtain the crude product. The crude product was purified by recrystallization (Ethyl acetate) to give pure products 4(a-m). Formation of 4(a-m) was confirmed by their elemental and spectral data analysis (**Scheme 1**).

**Spectral Data for all the Compounds**

**5-Ethoxycarbonyl-4-(4-phenyl)-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one** (**4a**)

Solid, mp, 201-203°C. IR (KBr): $\upsilon_{max}$ $cm^{-1}$: 3416, 3231, 3108, 2936, 2867, 1701, 1648, 1592, 1241, 1129, 1036, 951, 834. $^1$H NMR (DMSO-$d_6$): δ 1.15 (t, 3H, *J*=7.0 Hz, $OCH_2\underline{CH_3}$), 2.32 (s, 3H, $\underline{CH_3}$), 4.05 (q, 2H, *J*=7.0 Hz, $O\underline{CH_2}CH_3$), 5.25 (s, 1H-<u>CH</u>), 7.25-7.40 (m, 5H, Ar-H), 7.75 (br, 1H, NH), 8.98 (br, 1H, NH).; $^{13}$C NMR (DMSO-$d_6$): δ 165.3, 152.5, 148.6, 144.7, 128.5, 127.2, 126.4, 99.2, 59.1, 53.8, 17.6, 14.3. EIMS *m/z* (%): 260 ($m^+$18), 232 (42), 184 (100. Anal. Calcd. (%) For $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.64; H, 6.25; N, 109.2.

**5-(Ethoxycarbonyl)-4-(2,4-difluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4b)**

Solid, mp 182-184°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3255, 1740, 1650. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.18 (t, 3H, $OCH_2\underline{CH_3}$), 2.39 (s, 3H, $\underline{CH_3}$), 4.10 (q, 2H, $O\underline{CH_2}CH_3$), 5.7 (s, 1H,-<u>CH</u>), 6.1 (s, 1H, NH), 6.75-6.90 (m, 2H, Ar-H), 7.4 (m, 1H, Ar-H), 8.6 (s, 1H, NH). $^{13}$C NMR (200 MHz, $CDCl_3$) δ: 14.63, 18.98, 56.44, 61.35, 101.89, 122.78, 135.66, 148.08, 155.37, 158.67, 159.65, 165.90. ESI-MS, m/z 297 $[M+H]^{+1}$, 255. Anal. Calcd for $C_{14}H_{14}F_2N_2O_3$; C, 56.76; H, 4.76; N, 9.46. Found C, 56.72; H, 4.78; N, 9.43.

**5-(Ethoxycarbonyl)-4-(2,4,5-trifluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4c)**

Solid, mp. 217-220°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3253, 1741, 1652. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.19 (t, 3H, $OCH_2\underline{CH_3}$), 2.40 (s, 3H, $\underline{CH_3}$), 4.10 (q, 2H, $O\underline{CH_2}CH_3$), 5.6 (s, 1H,-<u>CH</u>), 6.7 (s, 1H, NH), 6.8-6.9 (m, 1H, Ar-H), 7.08-7.10 (m, 1H, Ar-H), 8.9 (s, 1H, NH). $^{13}$C NMR (200 MHz, $CDCl_3$) δ: 13.22, 17.45, 28.72, 47.95, 58.90, 96.77, 104.35, 104.73, 105.01, 115.51, 115.84, 148.59, 151.54, 164.48. ESI-MS, m/z 315 $[M+H]^{+1}$. Anal. Calcd for $C_{14}H_{13}F_3N_2O_3$; C, 53.51; H, 4.71; N, 8.91. Found C, 53.48; H, 4.69; N, 8.94.

**5-(Ethoxycarbonyl)-4-(*α*, *α*, *α*-trifluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4d)**

Solid, mp. 182-184°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3255, 1740, 1650. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.18 (t, 3H, $OCH_2\underline{CH_3}$), 2.25 (s, 3H, $\underline{CH_3}$), 4.0 (q, 2H, $O\underline{CH_2}CH_3$), 5.25 (s, 1H,-<u>CH</u>), 5.4 (s, 1H, NH), 7.60 (s, 4H, Ar-H), 9.2(s, 1H, NH). $^{13}$C NMR (200 MHz, $CDCl_3$) δ: 12.25, 16.22, 52.28, 57.54, 97.10, 120.82, 121.42, 121.47, 121.90, 122.11, 122.15, 124.16, 127.08, 127.53, 128.43, 131.17, 144.47, 147.18, 150.44, 156.28, 163.46. ESI-MS, m/z 327 $[M+H]^{+1}$. Anal. Calcd for $C_{15}H_{15}F_3N_2O_3$; C, 54.88; H, 4.61; N, 8.53. Found C, 54.90; H, 4.64; N, 8.49.

**5-(Ethoxycarbonyl)-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4e)**

Solid, mp. 218-220°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3430, 3340, 1710, 1668, 1358, 1276. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.03 (t, 3H, $OCH_2\underline{CH_3}$), 2.25 (s, 3H, $\underline{CH_3}$), 3.90 (q, 2H, $O\underline{CH_2}CH_3$), 5.60 (s, 1H, <u>CH</u>), 7.22-7.40 (m, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.65 (s, 1H, NH), 9.30 (s, 1H, NH). $^{13}$C NMR (200 MHz, $CDCl_3$) δ: 14.52, 57.66, 61.05, 103.27, 125.55, 127.34, 128.62, 131.44, 132.53, 144.22, 160.11, 163.26, 177.43. ESI-MS, m/z 329 $[M+H]^{+1}$. Anal. Calcd for $C_{14}H_{14}Cl_2N_2O_3$; C, 51.08; H, 4.29; N, 8.51. Found C, 51.11; H, 4.31; N, 8.60.

**5-(Ethoxycarbonyl)-4-(2-chloro-3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*) one (4f)**

Solid, mp. 248-250°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3429, 3341, 1711, 1667, $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.05 (t, 3H, $OCH_2\underline{CH_3}$), 2.41 (s, 3H, $\underline{CH_3}$), 4.0 (q, 2H, $O\underline{CH_2}CH_3$), 5.81 (s, 1H, <u>CH</u>), 6.25 (s, 1H, NH), 6.8 (d, 1H, Ar-H), 6.85 (d, 1H, Ar-H), 7.15 (t, 1H, Ar-H), 8.85 (s, 1H, NH), 9.4 (s, 1H, OH). ESI-MS, m/z 311 $[M+H]^{+1}$. Anal. Calcd for $C_{14}H_{15}ClN_2O_4$; C, 54.11; H, 4.87; N, 9.02. Found C, 54.04; H, 4.90; N, 9.09.

**5-Ethoxycarbonyl-6-methyl-4-(2-bromophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4g)**
Solid, mp 240-242°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3430, 3340, 3220, 1690, 1636,$^1$H NMR (200 MHz, DMSO-$d_6$) δ: 1.05 (t, 3H, $OCH_2\underline{CH_3}$), 2.40 (s, 3H, $CH_3$), 4.0 (q, 2H, $O\underline{CH_2}CH_3$), 5.80 (s, 1H, CH), 6.20 (s, 1H, NH), 7.15 (m, 1H, Ar-H), 7.3.(d, 2H), 7.55 (d,1H) , 8.9 (s, 1H, NH). $^{13}$C NMR (200 MHz, DMSO-$d_6$) 17.7, 50.6, 53.9, 98.1, 122.1, 128.4, 128.6, 129.3, 132.6, 143.2, 149.3, 151.2, 165.4. ESI-MS m/z 339 $[M+H]^+$. Anal. Calcd for $C_{14}H_{15}BrN_2O_3$; C, 49.57; H, 4.46; N, 8.26. Found C, 49.61; H, 4.42; N, 8.30.

**5-Ethoxycarbonyl-6-methyl-4-(3-cyanophenyl)-3,4-dihydropyrimidin-2-(1*H*)-one (4h)**
Solid**.** mp 228-230°C; IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3219, 2975, 2227, 1697, 1634, 1454, 1385, 1363, 1251, 1200, 1075, 1019, 935, 825, 756. $^1$H NMR (200 MHz, DMSO-$d_6$) δ: 1.07 (t,3H, $OCH_2\underline{CH_3}$), 2.25 (s, 3H, $CH_3$), 3.97 (q, 2H, $O\underline{CH_2}CH_3$), 5.21 (s,1H, CH), 7.42 (d, 2H), 7.80 (d, 2H), 7.88 (s, 1H, NH), 9.33 (s, 1H, NH). $^{13}$C NMR (200 MHz, DMSO-$d_6$) δ: 14.5, 18.3, 54.3, 59.8, 98.7, 110.5, 119.2, 127.8, 133.0, 149.8, 150.5, 152.3, 165.6. ESI-MS m/z 286 $[M+H]^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3$; C, 63.15; H, 5.30; N, 14.73. Found C, 63.09; H, 5.35; N, 14.68.

**5-(Ethoxycarbonyl)-4-(2–nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (4i)**
Solid, mp. 238-240°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3338, 3289, 2996, 1685, 1572, 1355, 1310. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.14 (t, 3H, $CH_3$), 1.98 (s, 3H, $CH_3$), 4.15 (q, 2H, $CH_3\underline{CH_2}O$), 5.15 (s, 1H, CH), 6.8–7.38 (m, 4H, Ar–H), 7.22 (s, 1H, NH), 9.35 (s, 1H, NH). $^{13}$C NMR (200 MHz, $CDCl_3$) δ: 18.37, 56.36, 60.44, 101.48, 123.21, 125.72, 126.52, 130.26, 130.83, 142.77, 159.61, 161.12, 175.87. ESI-MS m/z 306 $[M+H]^+$. Anal. Calcd for $C_{14}H_{15}N_3O_5$; C, 55.08; H, 4.95; N, 13.76. Found C, 55.11; H, 4.89; N, 13.80.

**5-Ethoxycarbonyl-4-(($E$)$_2$-Phenylethyl-4-nitro)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-one (4j)**
Solid, mp. 216-218°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3354, 3262, 2983, 2854, 1695, 1656, 1495, 1372, 1224, 1163, 785, 743. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.30 (t, 3H, $CH_3$), 2.30 (s, 3H), 4.25 (q, 2H), 5.0 (s, 1H), 6.40 (d, 1H), 6.6 (s, 1H), 7.10(s, 1H, NH), 7.50 (s, 1H), 7.65 (t, 3H), 8.15 (s, 2H), 8.9 (s, NH), 18.96 (s, 1H, NH). ESI-MS, m/z 332 $[M+H]^{+1}$. 286 (M+17). Anal. Calcd for $C_{16}H_{17}N_3O_5$; C, 58.00; H, 5.17; N, 12.68. Found C, 57.98; H, 5.20; N, 12.70.

**5-(Ethoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4k)**
Solid, mp.198-200°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3246, 3115, 2955, 1704, 1647, 1513, 1461, 1422, 1386, 1328, 1287, 1222, 1172, 1087, 952, 865, 779, 699, 67 $cm^{-1}$.; $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.20 (t, 3H $CH_3$), 2.32 (s, 6H $CH_3$), 4.08 (q, 2H $CH_2$), 5.30 (s, 1H CH), 6.95 (s, 1H, NH) 7.10-7.24 (m, 4H ArH), 8.85 (s, 1H NH), ESI-MS, m/z 275 $[M+H]^{+1}$. 274.37 (M+). Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.61; H, 6.65; N, 10.17.

**5-(Ethoxycarbonyl)-4-(iso-propyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one(4l)**
Solid, mp. 160-162°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3240, 3117, 2961, 2608, 2522, 1771, 1740, 1703, 1644, 927, 759, 663. $^1$H NMR (200 MHz, $CDCl_3$): δ 0.76-0.81 (m, 6H, $CH_3$), 1.07 (t, 3H, $CH_3$), 1.69 (m, 1H), 2.19 (s, 3H, $CH_3$), 4.02 (q, 2H, $CH_2CH_3$), 4.89 (s, 1H, NH), 7.54 (s ,1H), 9.00 (s, 1H, NH). ESI-MS, m/z 303 226.21 $[M+H]^{+1}$. Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found C, 67.49; H, 7.30; N, 9.31.

**5-Ethoxycarbonyl-4-(2-thienyl)-6-methyl-3,4-dihydropyrimidine-2(1*H*)-one (4m)**
Solid, mp. 225-227°C. IR (KBr) $\upsilon_{max}$ $cm^{-1}$: 3245, 3234, 3164, 3120, 3043, 2979, 2946, 1718, 1689, 1632, 1535, 1462, 1251, 1065, 851, 745. $^1$H NMR (200 MHz, $CDCl_3$) δ: 1.25 (t, 3H-$OCH_2CH_3$), 2.30 (s, 3H, $CH_3$), 4.15 (q, 2H, $CH_2CH_3$), 5.6 (s, 1H, NH), 6.9-7.3 (m, 4H-Ar-H), 8.9 (s, 1H, NH), ESI-MS, m/z 287 $[M+H]^{+1}$. 266 (M+ 80). Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.18; H, 5.28; N, 10.54.

## RESULTS AND DISCUSSION

In this article we have used a new protocol to Biginelli reaction and synthesized 3,4-di hydropyrimidin-2(1*H*)-ones 4(a-m) in good yields by using new catalyst $Zn(OAc)_2$. All the reactions were carried out in acetonitrile. Synthesis of DHPMs 4(a-m) involves one-pot three component condensation reaction between aromatic aldehydes 1(a-m), ethyl acetoacetate 2 and urea 3. To confirm the catalyst role, a blank experiment was carried out with ethyl acetoacetate, benzaldehyde and urea in acetonitrile at reflux temperature, without using the catalyst. There was no product formation even after 20 hours. In another experiment, the catalyst was used in equivalent and stirred at room

temperature, but product was not found and the same reaction was carried out at 80°C-85°C, the reaction was completed within 2.0 hour. In another set of experiments, the (0.3 mmol) catalyst was used and The experiments were completed (product was found) within 1.0 hour. So the catalyst was finalized with (0.3 mmol). In all the cases, the catalyst was used with respect to aldehyde. Encouraged by the result obtained with the above experiments, we have applied this procedure to various aldehydes such as substituted aromatic and heterocyclic aldehydes have been subjected to this condensation successfully. In all the cases the catalyst zinc acetate was used in catalytic amount (0.3 mmol) only. All the reactions were completed within 1.0-3.0 hours of time at 75°C-80°C C of reaction temperature. Furthermore, the aromatic aldehydes carrying either electron donating or electron withdrawing substituents afforded high yields of corresponding dihydropyrimidinone derivatives in high yields.

## CONCLUSION

The objective of the present research work is to develop various new synthetic methodologies, Here we have developed a simple and efficient methodology for the synthesis of 3,4 dihydro pyrimidinones derivatives. We reported $Zn(OAc)_2$ as a new catalyst for the above 3,4 dihydro pyrimidinones (DHPMs) derivatives, The new catalyst reduced the reaction time and the yields were very good. In conclusion, this method is very easy to handle and environmentally benign and the recovery of the products in this case is easy. The products thus obtained were characterized by $^{1}H$ NMR, $^{13C}$ NMR, IR and Mass Spectra.

## ACKNOWLEDGEMENTS

We are thankful to the Director IICT Hyderabad and the Department of Chemistry Kakatiya University, Warangal for providing necessary facilities and encouragement for the execution of present research work.

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