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Chloromine-T :A Simple and Efficient Catalyst for One-Pot Synthesis of Biginelly 3,4- Di hydropyrimidin-2-(1H)-ones

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ABSTRACT
An efficient methodology was developed for the synthesis Biginelly 3,4- di hydropyrimdin-2-(1H)-ones derivatives. All the reactions were carried out via three component coupling of aldehyde, ethylacetoacetate and urea\thiourea in the presence of Chloromine-T. All the reactions were completed with 30 minutes of reaction time, with very good yields of the corresponding products.

Keywords: *3,4-di hydropyrimdin-2-(1H)-onesaldehydes, ethylacetoacetate, urea\thiourea, Chloromine-T.*

1. INTRODUCTION

The one pot multi component condensation represents a possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity. In 1893 Pietro Biginelly reported. The first synthesis of 3,4- di hydropyrimdin-2-(1H)-ones. By a very simple one-pot condensation reaction of an aromatic aldehyde, ethylacetoacetate, urea\thiourea, Chloromine-T. This efficient approach to partly reduced pyrimidinestermed the Biginelly Condensation [1-4].

The interest in synthesis of dihydropyrimidines Biginelly compounds stems from their close structural Relationship [5] to clinically important 1,4 -dihydropyridine calcium channel modulators of the type nifedipineetc and also because of interesting biological properties of several marine alkaloids found to be potent HIVgp-120CD_4 inhibitors [6-7].

In addition these compounds are known to exhibit a wide range of biological activities such as antiviral, antitumor, antibacterial, and anti-inflammatory [8]. In order to improve the efficiency of Biginelly reaction, many catalysts have been developed such as zirconium (IV) chloride [9], indium(III)bromide [10] ytterbium(III) resin [11], ionic liquids ($BMImPF_6$ and $BMImBF_4$) [12] ceric ammonium nitrate [13], $Mn(OAC)_3.12H_2O$ [14], lanthanide triflate [15], indium(III) chloride [16], lanthanum chloride [17], TFA [18], boric acid [19], vanadium(III) chloride [20], $Fecl_3.6H_2O$ [21], TMSl [22], zinctriflate [23]. As part my research program we have selected the Chloromine-T as a catalyst for one pot synthesis of 3,4dihydropyrimidine 2- (1H)-ones (Biginelli condensation).

2. EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^1H NMR spectra were recorded on Brucker-300 spectrometer in $CDCl_3$ using TMS as internal standard. MASS spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV.

2.1. General Procedure

A mixture of aldehyde (1 mmol), ethylacetoacetate (2 mmol), urea\thiourea (1.5 mmol) and chloromine-T (0.2 mmol) was grained in a mortar for a specified time (table-1). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the mixture was extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with brine and dried over $NaHSO_4$ and concentrated under reduced pressure to afford crude products, which were purified by recrystalization from ethanol. All the products were characterized by their ^1H NMR, IR and mass spectroscopy data.

2.2. Spectral Data

5-Ethoxycarbonyl-4-(4-phenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4a): IR (KBr): υ 3416, 3231, 3108, 2936, 2867, 1701, 1648, 1592, 1241, 1129, 1036, 951, 834, 764 $cm.^{-1}$; ^1H NMR ($CDCl_3$). δ 1.20 (t, 3H, *J* = 7.0 Hz), 2.32 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 5.20 (s, 1H), 7.25-7.35 (m, 5H) 7.35(brs, 1H).; EIMS: *m/z* (%). 260 (M^+18), 232 (42), 184 (100), 156 (32), 138 (51), 91 (60), 43(27).

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5-Ethoxycarbonyl-4-(4-methoxy phenyl) -6-methyl-3,4-dihydro pyrimidine-2(1H)-one (4b): IR (KBr): υ 3415, 3242, 3119, 2951, 2861, 1701, 1639, 1604, 1513, 1162, 1036, 947, 853, 742 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ 1.20 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 3.85 (s, 3H, OMe), 4.10 (q, 2H, *J* = 7.0 Hz), 5.20 (s, 1H), 6.80 (d, 2H, *J* = 7.5 Hz), 7.20 (d, 2H, *J* = 7.5 Hz).) 7.35(brs, 1H) 8.95(brs, 1H); EIMS: *m/z* (%). 290 (M^+ 28), 275 (56), 231 (68), 201 (15), 184 (100), 151 (50), 138 (20).91(35).

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4c): IR (KBr): υ 3415, 3237, 3110, 3084, 2941, 2876, 1706, 1641, 1522, 1412, 1363, 1229, 961, 734 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ 1.13 (t, 3H, *J* = 6.0 Hz), 2.28 (s, 3H), 4.01 (q, 2H, *J* = 6.0 Hz), 5.18 (s, 1H J=3.0 Hz), 7.12 (d,1H, J=7.0 Hz), 7.48(d,2H, J=7.0 Hz), 7.70(d, 2H, J=7.0 Hz),9.12(brs,1H, NH).; EIMS: *m/z* (%). 306 (M^+20), 276 (38), 232 (50), 201 (15), 183 (100), 155 (42), 137(22).

5-Ethoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4d): IR (KBr): υ 3418, 3241, 3129, 3072, 2943, 1714, 1678, 1608, 1513, 1452, 1305, 1213, 1011, 947, 862, 741 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ8.95 (s, 1H, NH), 7.30 (s, 1H), 6.55 (s, 2H), 5.20 (s, 1H), 4.20 (q, 2H J=7.0Hz), 3.80 (s, 6H), 3.70 (s, 3H), 2.30 (s, 3H) 1.20 (t, 3H, J=7.0 Hz).; EIMS: *m/z* (%). 350 (M^+100), 321 (25), 277 (38), 234 (12), 183 (50), 176 (22), 161(18), 148(20), 130(15), 99942), 61(15).

5-Ethoxycarbonyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4e): IR (KBr): υ3325, 3234, 3126, 3047, 2985, 2939, 1698, 1653, 1456, 1082, 874, 785 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ8.98 (s,1H,NH), 7.25 (s,1H,NH), 7.18 (s, 1H), 6.21 (d, 1H, *J* = 3.0 Hz), 6.02 (d, 1H, *J* = 3.0 Hz), 5.22 (s, 1H), 4.05 (q, 2H, J=6.5 Hz), 1.80 (t, 3H, *J* = 6.5 Hz),2.21 (s, 3H).; EIMS: *m/z* (%). 250 (M^+80), 221 (97), 177 (100),110 (34).

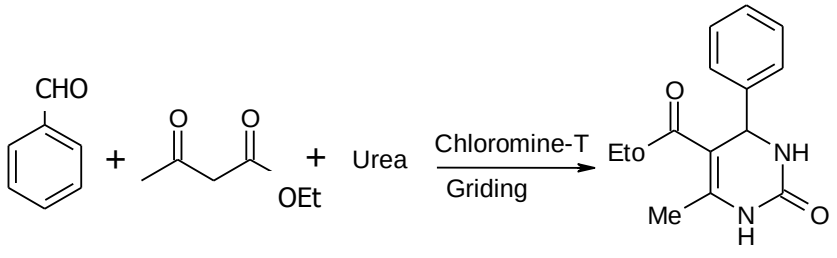
5-Ethoxycarbonyl-4-((E)2-Phenylethyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4f): IR (KBr): υ 3354, 3262, 2983, 2854, 1695, 1656, 1495, 1372, 1224, 1163, 785, 743 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ8.96 (s, 1H, NH), 7.45(s, 1H, NH), 7.15-740(m, 5H), 6.35(d, 1H J=14.5 Hz), 6.10(dd, 1H, j=14.5, 5.0 Hz), 4.80(d, 1H, J=4.0 Hz), 4.18 (q, 2H, J=7.0 Hz), 2.25(s, 3H), 1.25(t, 3H, J=7.0 Hz); EIMS: *m/z* (%): 286 (M^+ 17), 259 (100), 224 (28), 196 (80), 149 (34), 84 (72).

5-Ethoxycarbonyl-4-(2-thienyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4g): IR (KBr): υ 3245, 3234, 3164, 3120, 3043, 2979, 2946, 1718, 1689, 1632, 1535, 1462, 1251, 1065, 851, 745 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ9.10(s, 1H, NH), 7.58 (s, 1H, NH), 7.10(d, 1H, J=5.0 Hz), 6.80-6.90(m, 2H), 5.40(s, 1H), 4.05(q, 2H, J=8.0 Hz), 2.03(s, 3H), 1.22(t, 3H, J=8.0 Hz). EIMS: *m/z* (%). 266 (M^+80), 237 (100), 221 (22), 193 (65),145 (30), 117 (15), 110 (24), 83 (42).

5-Ethoxycarbonyl-4-(2-thienyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4h): IR (KBr): υ 3247, 2932, 1726, 1651, 1608, 1584, 1435, 1408, 1332, 1289, 1089, 1009, 946, 769, 742.cm.$^{-1}$; ^{1}H NMR ($CDCl_3$). δ10.20(brs, 1H, NH), 6.40(brs, 1H NH), 5.28(brs, 2H),4.60(s, 1H), 4.12(q,2H, J=6.0 Hz), 2.25(s, 3H), 1.20-1.35(m, 9H), 0.94(t, 3H J=6.0 Hz); EIMS: *m/z* (%). 253 (M^+20), 230 (15), 209 (28), 186 (10), 183 (100), 155(78), 137(65), 91(22), 84(10), 69(18), 40(35).

3. RESULT AND DISCUSSIONS

In a typical experiment, benzaldehyde, ethylacetoacetate, urea/thiourea and the Chloromine-T were mixed in a mortar and grinned well for 20 minutes to afford the corresponding product, 5-ethoxy carbonyl-4-(4-phenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (**4a**) in very good yields as shown in the Scheme-1. The product **4a** was confirmed by its ^{1}H NMR, IR and mass spectroscopy data.



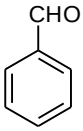
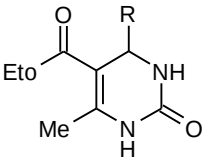
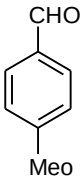
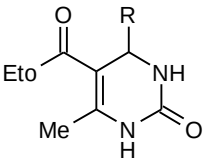
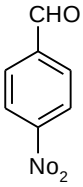
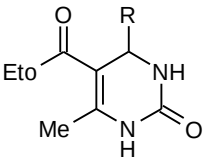
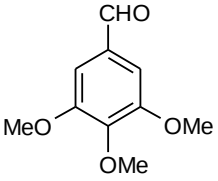
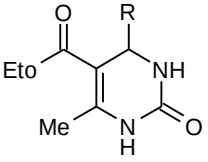
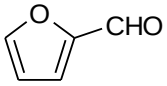
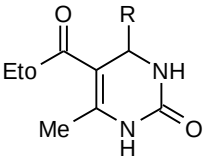
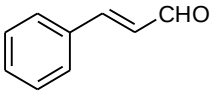
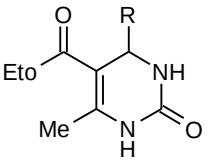
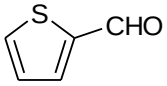
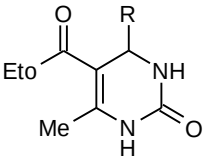
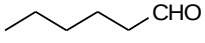
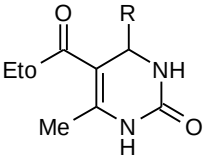
1 **2** **3** **4**

Scheme-1

Encouraged by the result obtained with benzaldehyde, we have applied this methodology to a variety of aldehydes containing electron withdrawing and electron donating groups in ring system and the results were mentioned in the table-1. In general, all the reactions were completed with 30 minutes of reaction time. Electron withdrawing group containing aldehydes reacted comparatively

slowly than other aldehydes. Acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde were reacted very smoothly to afford the corresponding products under these conditions without forming any side products. In a similar manner, the aliphatic aldehyde also reacted smoothly to obtain the Biginelly pyrimidine deriva-tive in very good yield. Several of 3,4-dihydropyrimidines have been synthesized in 76-88% yield and the results are summarized in Table 1.

Table 1: Synthesis of 3,4-Dihydropyrimidines by using Chloromine-T as catalyst

S.No	Aldehyde(R)	Product (4a-4h)	Time (min)	Yield (%)	Melting Points (^{0}C)
A			20	84	201-203
B			20	88	198-201
C			30	76	207-209
D			20	88	214-216
E			20	88	210-212
F			30	75	227-230
G			30	80	206-208
H			40	76	150-152

We have examined the role of catalyst chloromine-T, while using in different quantities. In the first experiment, benzaldehyde (1mmol), ethyl acetoacetate (2mmol), urea\thiourea (1.5mmol) and the catalyst chloromine-T (1mmol) were grinned well in a mortar for 20 minutes and the TLC observation shows that the reaction was completed. In second experiment, the same quantity of reactants was treated with 0.5 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction was completed. In third experiment, the same quantity of reactants was treated with 0.2 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction was completed. In fourth experiment, the same quantity of reactants was treated with 0.1 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction 50% was completed. From these experiments, we concluded that the use of catalyst 20% is enough for the completion of reaction and all the reactions were carried out using the catalyst in 20%.

4. CONCLUSION

In summary, we have demonstrated, a simple and efficient methodology for the synthesis of 3,4-dihydropirimidines derivatives using Chloromine-T as catalyst. In this protocol, the catalyst Chloromine-T was used in 20%. All the reactions were completed with 30 minutes of reaction time and the yields were very good.

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