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Synthesis and Characterization of 3,4-Dihydropyrimidin-2-(1*H*)-ones: Development of Efficient Protocol for Biginelli Reaction using GeI_4

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ABSTRACT

A simple and efficient methodology for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives has been developed by the condensation of aldehydes, ethyl acetoacetate and urea using Germanium (IV) iodide as catalyst. All the reactions were carried out at acetonitrile reflux and completed within 2 to 5 hours of reaction with good yields. All the products were very clear and confirmed by spectroscopy analysis.

Keywords: Aldehydes, diketones, urea, GeI_4, 3,4-dihydropyrimidinones..

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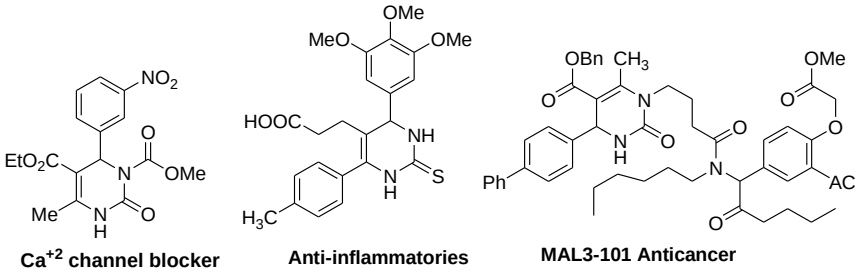
INTRODUCTION

Multicomponent condensation strategies offer significant advantages over conventional synthesis. In 1893, Pietro Biginelli, Italian chemist reported a cyclocondensation between aldehydes, ethyl acetoacetate and urea under strongly acidic conditions to obtain a heterocyclic system of dihydropyrimidinone (DHPM), since then it become familiar as Biginelli reaction.[1] The DHPM derivatives exhibits wide range of biological activities such as antibacterial, antiviral, antitumor, anti-epileptic, anti-malarial, anti-tubercular and anti-inflammatory activities. Some of them have been successfully used as calcium channel blockers, antihypertensive agents,[2] α-1a-antagonists and neuropeptide antagonists. Moreover several alkaloids containing the DHPM core unit have been isolated from marine source, which also shows interesting biological properties. Among the most notable are the Batzelladine and Crambine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors.[3]



Ca^{+2} channel blocker **Anti-inflammatories** **MAL3-101 Anticancer**

Figure-1.Biologically active 3,4-dihydropyrimidinones

The biological importance of DHPMs attracted many researchers and academicians. Hence, several attempts have been made to synthesize DHPM derivatives using various protocols of non-conventional,[4] conventional methods by using various catalysts such as metal halides,[5,6] metal oxyhalides,[7] metal triflates,[8] polymer catalysts,[9] acid catalysts,[10] base catalysts,[11] Borates,[12] and Proline.[13] But many of the methods suffer some drawbacks such as long reaction time, low yields, tedious workup, procedures use of expensive catalysts. Therefore, the development of efficient, inexpensive protocol is still in demand. As part of our research program, we have demonstrated a simple and efficient methodology for the preparation of 3,4-dihydropyrimidi none derivatives by the condensation of aldehydes, ethyl acetoacetate and urea in presence of Germanium (IV) iodide at acetonitrile reflux.

MATERIALS AND METHOD:

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on Perkin-Elmar (FT-IR 240-c) spectrophotometer using KBr disk. ^{1}H NMR-Spectra were recorded on Gemini spectrometer in $CDCl_3$ using TMS as internal standard and teta-values are expressed in

ppm. Mass- spectra were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the preparation of 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-di hydro pyrimidin-2-(1*H*)-one:

To a stirred mixture of aldehyde (1mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol) in acetonitrile (5 mL) was added GeI_4 (0.1mmol) and refluxed for a specified period (2-5 h) mentioned in the table-1. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the solvent was removed under reduced pressure and crushed ice was added to the residue and stirred for some time. The solid was filtered and recrystallized from methanol to get pure product of corresponding derivative. All the products were confirmed by their spectral data.

Spectral data for compounds:

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

Solid; Mp. 201-203 °C. IR (KBr): υ 3416, 3231, 3108, 2936, 2867, 1701, 1646, 1552, 1241, 1129, 1036, 951, 834, 764 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.15 (t, 3H, *J* = 7.0 Hz), 2.26 (s, 3H), 4.10 (q, 2H, *J* = 7.0 Hz), 5.20 (s, 1H), 7.36-7.24 (m, 5H), 7.43 (s, 1H), 9.00 (s, 1H).; EIMS *m/z* (%): 260 (m^+ 20), 232 (42), 184 (100), 156 (32), 138 (51), 91 (60), 43 (27).

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

Solid; Mp. 214-215 °C. IR (KBr): υ 3418, 3241, 3129, 3072, 2943, 1714, 1678, 1608, 1513, 1452, 1305, 1213, 1011, 947, 862, 740 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.20 (t, 3H, *J* = 7.1 Hz), 2.30 (s, 3H), 3.80 (s, 9H), 4.10 (q, 2H, *J* = 7.1 Hz), 5.20 (s, 1H), 5.68 (s, 1H), 6.55 (s, 2H), 9.12 (s, 1H).; EIMS *m/z* (%): 350 (m^+100), 321 (25), 277 (38), 234 (12), 183 (50), 176 (22), 161 (18), 148 (20), 130 (15), 99 (42), 61 (15).

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

Solid; Mp. 206-207 °C. IR (KBr): υ 3415, 3237, 3110, 3084, 2941, 2876, 1706, 1641, 1604, 1522, 1420, 1363, 1229, 1123, 961, 734 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 6.0 Hz), 2.30 (s, 3H), 3.99 (q, 2H, *J* = 6.0 Hz), 5.20 (s, 1H), 7.48-7.66 (m, 4H), 7.86 (s, 1H), 9.32 (s, 1H).; ^{13}C NMR (50 MHz, DMSO-d_6): δ 163.4, 152.7, 152.0, 149.1, 146.7, 127.3, 124.2, 98.2, 59.7, 53.2, 18.3, 14.1.; EIMS *m/z* (%): 306 (m^+ 20), 276 (38), 232 (50), 201 (15), 183 (100), 155 (42), 137 (22).

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

Solid; Mp. 209-210 °C. IR (KBr): υ 3230, 3107, 3068, 2907, 1707, 1646, 1292, 1215, 1092, 784 cm^{-1}.; ^1H NMR (200 MHz, DMSO-d_6): δ 1.12 (t, 3H, *J* = 7.1 Hz), 2.22 (s, 3H), 3.98 (q, 2H, *J* = 7.1 Hz), 5.18 (d, 1H, *J* = 5.0 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.44 (d, 1H), 7.86 (d, 2H, *J* = 8.4 Hz).; EIMS *m/z* (%): 295 (m^+100), 277 (25), 183 (26), 148 (37), 130 (31).

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

Solid; Mp. 227-230 °C. IR (KBr): υ 3354, 3262, 2983, 2854, 1698, 16056, 1493, 1371, 1223, 1167, 785 cm^{-1}.; ^1H NMR (200 MHz, DMSO- d_6): δ 1.25 (t, 3H, *J* = 7.0 Hz), 2.25 (s, 3H), 4.18 (q, 2H, *J* = 7.0 Hz), 4.80 (d, 1H, *J* = 4.0 Hz), 6.10 (d, 1H, *J* = 14.0, 5.0 Hz), 6.35 (d, 1H, *J* = 14.5 Hz), 7.15-7.40 (m, 5H), 7.45 (s, 1H), 8.96 (s, 1H).; EIMS m/z (%): 286 (m^+ 17), 259 (100), 224 (28), 196 (80), 149 (34), 84 (72).

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

Solid; Mp. 220-222 °C. IR (KBr): u_{max} 3377, 3241, 2926, 2855, 1728, 1568, 1461, 1376, 1282, 1233, 1104, 1041, 862, 722 cm^{-1}.; ^1H NMR (200 MHz, DMSO-d_6): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.20-1.36 (m, 16H), 1.40 (m, 2H), 2.15 (s, 3H), 3.95-4.10 (brs, 2H), 5.15 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(2-naphthyl)-3,4-dihydropyrimidin-2(1*H*)-one (3g):

Solid; Mp. 245-247 °C. IR (KBr): υ 3241, 3229, 3118, 2973, 1704, 1658, 1549, 1452, 1432, 1234, 1082, 967, 872, 750 cm^{-1}.; ^1H NMR (200 MHz, DMSO-d_6): δ 1.18 (t, 3H, *J* = 7.0 Hz), 2.38 (s, 3H), 4.05 (q, 2H, *J* = 7.0 Hz), 5.80 (d, 1H, *J* = 3.1 Hz), 7.30-7.45 (m, 5H), 7.75 (t, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 8.0 Hz), 8.28 (d, 1H, *J* = 8.0 Hz), 9.14 (s, 1H).; EIMS; m/z (%): 310 (m^+ 20), 217 (38), 176 (100), 133 (18), 119 (40), 91 (32), 84 (15), 69 (50).

5-Ethoxycarbonyl-6-methyl-4-(pyridine-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3h):

Solid; Mp. 223-224 °C. IR (KBr): υ 3295, 1714, 1705, 1680, 15185, 1072 cm^{-1}.; ^1H NMR (200 MHz, DMSO-d_6): δ 2.22 (s, 3H), 2.14 (s, 3H), 5.30 (d, 1H, *J* = 2.9 Hz), 7.23-7.40 (m, 2H), 7.80 (s, 1H), 8.44-8.54 (m, 2H), 9.14 (s, 1H).; ^{13}C NMR (50 MHz, DMSO-d_6): δ 194.6, 162.7, 152.8, 149.5, 148.4, 137.3, 122.9, 121.0, 109.4, 30.8, 19.3.; EIMS *m/z* (%): 261 (m^+ 47), 216 (18), 188 (19), 183 (100), 173 (17), 155 (64), 110 (12), 78 (71), 67 (36), 52 (37).

5-Ethoxycarbonyl-6-methyl-4-(furan-2-yl)-3,4-dihydropyrimidin-2(1*H*)-one (3i):

Solid; Mp. 209-210 °C. IR (KBr): υ 3327, 3226, 3143, 3083, 2978, 2841, 1704, 1611, 1546, 1322, 1261, 1203, 1019, 871, 761cm^{-1}.; ^1H NMR (200 MHz, DMSO- d_6): δ 1.10 (t, 3H, *J* = 6.0 Hz), 2.10 (s, 3H), 4.00 (q, 2H, *J* = 6.0 Hz), 5.15 (d, 1H, *J* = 3.0 Hz), 6.10 (d,1H, *J* = 3.5 Hz), 7.10 (d, 1H, *J* = 3.5 Hz), 7.15 (s, 1H), 7.83 (s, 1H), 9.00 (s, 1H).; EIMS *m/z* (%): 250 (m^+ 42), 221 (63), 177 (100), 110 (31), 71 (28), 57 (49), 42 (12).

5-Ethoxycarbonyl-6-methyl-4-(4-methyl-phenyl)-3,4-dihydropyrimidin-2(1*H*)-one(3j): Solid; Mp. 214-215 °C. IR (KBr): υ 3325, 3151, 3058, 2973, 2847, 1691, 1654, 1563, 1232, 1132, 1051, 947, 880, 754 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.20 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 3.85 (s, 3H), 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 (s, 1H), 8.95 (s, 1H).; ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.3, 158.2, 158.5, 148.3, 137.6, 127.4, 113.9, 99.7, 59.8, 54.9, 53.1, 17.5, 14.1.; EIMS; m/z (%): 274 (m^+ 28), 245 (31), 229 (42), 201 (49), 183 (100), 155 (40), 138 (28), 91 (35).

5-Ethoxycarbonyl-6-methyl-4-(2,4-dichlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (3k): Solid; Mp. 238-240 ^{o}C. IR (KBr): υ 3413, 3356, 3218, 3105, 2963, 2847, 1704, 1634, 1581, 1462, 1403, 1320, 1227, 1098, 1031, 931, 852, 735 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.18 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 4.05 (q, 2H, *J* = 7.0 Hz), 5.45 (q, 1H, *J* = 2.8 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.40 (d, 1H, *J* = 8.0 Hz), 7.54 (s, 1H), 7.76 (s, 1H).; EIMS *m/z* (%): 329 (m^+ 35), 299 (45), 293 (60), 183 (100), 155 (30), 137 (45), 91 (10), 84 (12), 69 (28).

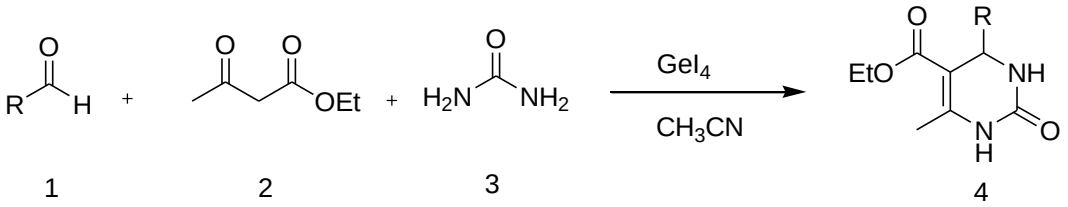
5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one(3l): Solid; Mp. 230-231 °C. IR (KBr): υ 3476, 3323, 3215, 3107, 2963, 1704, 1638, 1461, 1215, 1092, 830, 784 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.08 (t, 3H, *J* = 7.0 Hz), 2.21 (s, 3H), 3.96 (q, 2H, *J* = 7.0 Hz), 5.02 (s, 1H), 6.85-7.03 (m, 4H), 7.64 (s, 1H), 9.14 (s, 1H), 9.34 (s, 1H).; ^{13}C NMR (50 MHz, DMSO-d_6): δ 165.3, 155.4, 152.1, 147.6, 135.3, 127.3, 114.9, 99.7, 59.0, 53.3, 17.6, 14.0.; EIMS *m/z* (%): 276 (m^+ 100), 248 (100), 231 (28), 204 (80), 168 (87), 136 (48).

3.1.13.5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1*H*)-one(3m): Solid; Mp. 206-208 °C. IR (KBr): υ 3245, 3231, 3164, 3120, 3043, 2979, 2946, 1718, 1688, 1632, 1535, 1462, 1251, 1065, 851, 740 cm^{-1}.; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.22 (t, *J* = 7.0 Hz, 3H), 2.03 (s, 3H), 4.05 (q, 2H, *J* = 7.0 Hz), 5.40 (s, 1H), 6.80-6.90 (m, 2H), 7.10 (d, 1H, *J* = 5.0 Hz), 7.58 (s, 1H), 9.10 (s, 1H).; EIMS *m/z* (%): 266 (m^+ 80), 237 (100), 221 (22), 193 (65), 145 (30), 117 (15), 110 (24), 83 (42).

RESULTS AND DISCUSSION:

In a typical experiment, benzaldehyde (**1**), ethyl acetoacetate (**2**) and urea (**3**) were reacted in presence of the catalyst GeI_4 at acetonitrile reflux. The condensation was completed within 3 hours to afford the corresponding product, 5-ethoxycarbonyl-4-(4-phenyl)-6-methyl-3,4-dihydro pyrimidin-2-(1*H*)-one (**3a**) in very good yields, as shown in the scheme-1. To optimize the reaction conditions, we have studied the role of the catalyst Germanium (IV) iodide using in different mole ratios at room temperature as well as reflux. The observation shows that 10% mole catalyst and

reflux temperature were found to be as suitable reaction condition.

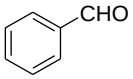
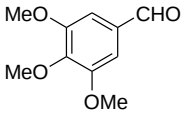
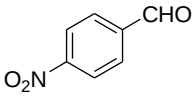
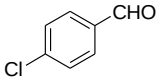
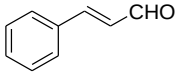
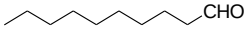


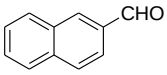
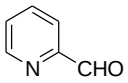
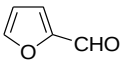
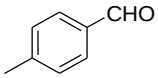
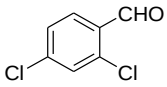
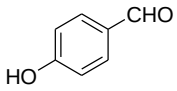
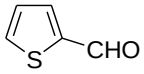
1 2 3 4

Scheme-1.

Encouraged by the result obtained with benzaldehyde, ethyl acetoacetate and urea, we have extended this methodology to various aldehydes such as aromatic aldehydes containing electron withdrawing and electron donating groups, hetero aromatic and aliphatic systems, which were reacted smoothly with ethylacetoacetate and urea to give corresponding 3,4-dihydropyrimidi none derivatives in very good to excellent yields. All the reactions were carried out using the catalyst Germanium (IV) iodide in catalytic amount (10 mol %) only. In general, aromatic aldehydes exhibit modest increase in reaction rate relative to aliphatic aldehydes. Electron withdrawing containing aldehydes react at a relatively slower rate than electron donating groups containing aldehydes. All the reactions were completed within 2 to 5 hours of reaction time at acetonitrile reflux. The product, 3,4-dihydropyrimidinone derivatives were obtained in 75-90% yields **(**table-1**)**. All the products were confirmed by their ^{1}H NMR, ^{13}C NMR, IR and Mass spectral analysis.

Table-1: GeI_4-Catalyzed rapid synthesis of 3,4-dihydropyrimidinones (3a-m).

Entry	Aldehyde	Product	Reaction Time (h)	Yield (%)
1		**3a**	3.0	82
2		**3b**	2.5	85
3		**3c**	5.0	80
4		**3d**	4.0	81
5		**3e**	4.0	75
6		**3f**	5.0	77

7		**3g**	5.0	80
8		**3h**	3.0	76
9		**3i**	2.0	90
10		**3j**	3.0	85
11		**3k**	4.0	82
12		**3l**	5.0	80
13		**3m**	3.0	79

CONCLUSION:

In summary, we have demonstrated a simple and efficient methodology for the synthesis of 3,4-dihydropyrimidinones using GeI_4 as catalyst at acetonitrile reflux, *via* smooth cyclo condensation of aldehydes, ethyl acetoacetate and urea successfully. All the reactions were completed within 2-5 hours of reaction time and yields were 75-90%. This method is applicable to aliphatic, heteroaromatic and aromatic aldehydes containing electron donating as well as electron with-drawing groups successfully.

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