A SIMPLE AND EFFICIENT CATALYST FOR ONE-POT SYNTHESIS OF BIGINELLY 3,4- DI HYDROPYRIMIDIN-2-(1H)-ONES

INTRODUCTION

Multi component reaction (MCR) is a versatile tool for synthetic organic chemistry; one can generate and construct more than two reaction output bonds in a single reaction. It improves efficacy and minimizes energy losses and yield losses. Researchers of organic chemistry successfully utilized these MCRs for the construction of diversely substituted molecules.

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc. Hence, they have attracted considerable attention in the design of
biologically active molecules. Pyrimidine derivatives which occurs in natural products like nucleic acid, vitamin-B and having remarkable pharmaceutical importance because of their broad spectrum of biological activities. Several analogs of nucleic acids like fluorouracil which has been used in cancer treatment.

Pyrimidines are among those molecules that make life possible as being some of the building blocks of DNA and RNA. Pyrimidine is considered to be a resonance hybrid of the charged and uncharged cannonical structures, its resonance energy has been found to be less than benzene or pyridine.

The naturally occuring pyrimidine derivatives was first isolated by Gabrial and Colman in 1870, and its structure was confirmed in 1953 as 5-β-D-gluco-pyranoside of divicine.

Different methods for the synthesis of pyrimidinones have been cited in the literature\(^1\). A series of new bis-1,8-naphthyridines, 1,8-naphthyridiny1-2-pyrazolines (1) and 2-thioxopyrimidines (2) were synthesized by Mogilaiah et al.\(^2\)

![Figure 1](image-url)
Oliver Kappe et al.\textsuperscript{3} have synthesized dihydropyrimidine-5-carboxylic acid (4) in two steps by multicomponent condensation of benzyl or allyl β-ketoesters (3) with aldehyde and urea, followed by suitable benzyl or allyl deprotection strategies.

![Figure - 2](image)

The condensation of the azaenolates derived from readily available ketimines with fluorinated nitriles offers an efficient and straightforward entry to new fluorinated 1,3-vinylogous amides. These versatile compounds in turn react with triphosgene to yield new fluorinated pyrimidin-2(1H)-ones (6) in high yields\textsuperscript{4}.

![Scheme - 1](image)

Fikret Karci et al.\textsuperscript{5} have synthesized 4-amino-1H-benzo [4,5] imidazo[1,2-a] pyrimidin-2-one (7) by the reaction of 2-amino-benzimidazole with ethylcyanoacetate.

There are many other methods of pyrimidine ring synthesis which are of more
limited scope. The reaction of 1,3-dicarbonyl compound or an equivalent reagent with formamide provides a route of several pyrimidine which are unsubstituted at the 2-position.

![Figure 3](image.png)

**Figure 3**

Biginelly\textsuperscript{6} investigated that condensation of aromatic aldehyde with β-ketoester and urea yield the pyrimidine derivatives.

It is revealed from the literature survey that pyrimidine derivatives have been found to possessing biological activities as Anti HIV\textsuperscript{7,8}, Antiviral\textsuperscript{9}, Antimicrobial\textsuperscript{10}, Herbicidal\textsuperscript{11-17}, Antagonists\textsuperscript{18-22}, Antitumor\textsuperscript{23}, Antiinflammatory and anticonvulsant\textsuperscript{24,25}, Carcinostatic\textsuperscript{26}, Antimalarial\textsuperscript{27} and Antithyroid\textsuperscript{28}.

Sanjay Batra et al\textsuperscript{29} have synthesized several 1-(2-cyano-3-aryl-allyl)-3-urea by the reaction between allylamines generated from Baylis-Hilman acetates and substituted isocyanates and isothiocyanate.
Anjani et al reported the reaction of 2-phenylamino-4-(3'-fluorophenylamino)-o-(4'‐acetylphenylamino)-s-triazene with different aromatic aldehydes to form chalcones (9). Chalcones were cyclised with hydrazine hydrate, and thiourea to form pyrazolines (10) and aminopyrimidinethione (11) respectively.\textsuperscript{30}
2,4,6-Tri(hetero)aryl-substituted pyrimidines (12) were synthesized in a three-component one-pot process based upon a coupling–isomerization sequence of an electron-poor (hetero)aryl halide and a terminal propargyl alcohol subsequently followed by a cyclocondensation with amidinium salts by Thomas and coworkers.\textsuperscript{31}

\[ \text{Figure - 5} \]

\[ \text{2-(3-aryl-2-phenyl-3,4-dihydropyrazol-5-yl)-1-N-alkoxyphthalimido-benzimidazole (13) and 4-(1-N-alkoxyphthalimido-benzimidazol-2-yl)- 6-arylpyrimidin-2-amine (14) were described, which were synthesized.}^{32} \]

\[ \text{Figure - 6} \]
Herve Ganeste and co-workers\textsuperscript{33} synthesized substituted 1H-pyrimidin-2-one (15) with selective dopamine D3-receptor antagonists activity.

\begin{center}
\includegraphics[width=0.2\textwidth]{figure7.png}
\end{center}

\textbf{Figure - 7}

2-Alkylamino-6-[1-(2,6-difluorophenyl)alkyl]-3,4-dihydro-5-alkyl pyrimidin-(3H)-ones (16) (F (2)-NH-DABOs) 4,5 belonging to dihydro-alkoxy-benzyl-oxopyrimidine (DABO)\textsuperscript{34} and bearing different alkyl and arylamino side chains at the C (2)-position of the pyrimidine ring were designed as active against wild type (wt) Human Immunodeficiency virus type 1 (HIV-1) and some relevant HIV-1 mutants.

\begin{center}
\includegraphics[width=0.2\textwidth]{figure8.png}
\end{center}

\textbf{Figure - 8}

Thirty six allyl substituted oxopyrimidine analogues\textsuperscript{35} such as barbituric acid (BA), barbiturates, uracil, thymine, and related derivatives including 13 new compounds were synthesized and their pharmacologic effects ([hypnotic activity, anticonvulsant
activity against pentylentetrazol (PTZ)-induced seizures, and LD(50)]) and interactions with the barbiturates were evaluated in mice and rats.

Bruce M. A. and co-workers\textsuperscript{36} have prepared the dihydro-pyrimidinones (IX) as NPY antagonists. Sidler and Larsen\textsuperscript{37} have reported pyrimidinone derivatives (X), useful as an $\alpha$-adrenergic receptor antagonists.

Pyrimidinone derivatives\textsuperscript{38} (XI) have been found to be calcium channel blocker.

A series of 4(6)- and 5-phenyl substituted 2-amino- and 2-[(alkoxycarbonyl) amino]-1,4,5,6-tetrahydropyrimidines (17) were prepared and evaluated for central nervous system effects in animal models by Klaus et al.\textsuperscript{39}

![Figure - 9](image)

A series of 2,4,6 trisubstituted pyrimidines (18) and triazines (19) have been synthesized and screened for its in vitro antileishmanial activity profile in promastigote model. Nine compounds have shown >94% inhibition against promastigotes at a concentration of 10 $\mu$g/mL.\textsuperscript{40}
Figure - 10

Thiamin (vitamin B1) combines with benzaldehyde in alkaline solutions to form 2-(1-hydroxybenzyl)thiamin (HBzT), a reactive intermediate in the thiamin-catalyzed benzoin condensation. In neutral solutions, HBzT fragments into pyrimidine and thiazole constituents by cleavage of the bridging methylene–thiazole bond. The fragmentation was promoted by protonation of the pyrimidine moiety of HBzT. \(^{41}\)

2,4-Dichloro-6-phenylpyrimidine was prepared by arylation of halogenated pyrimidines via a Suzuki coupling reaction.\(^{42}\) It was also prepared by substitution reactions of chloropyrimidines with lithium reagents.\(^{43}\)

Chloramines:

The disinfectant potential of chlorine-ammonia compounds or chloramines was identified in the early 1900s. The potential use of chloramines was considered after observing that disinfection by chlorine occurred in two distinct phases. During the initial phase, chlorine reducing compounds (i.e., demand) cause the rapid disappearance of free available chlorine. However, when ammonia was present bactericidal action was observed to continue [even though free chlorine residual was dissipated]. The subsequent disinfection phase occurs by the action of the inorganic chloramines.
Chloramines are formed by the reaction of ammonia with aqueous chlorine (i.e., HOCl). Initially, chloramines were used for taste and odor control. However, it was soon recognized that chloramines were more stable than free chlorine in the distribution system and consequently were found to be effective for controlling bacterial regrowth. As a result, chloramines were used regularly during the 1930s and 1940s for disinfection. Due to an ammonia shortage during World War II, however, the popularity of chloramination declined. Concern during the past two decades over chlorinated organics (e.g., THM and HAA formation) in water treatment and distribution systems, increased interest in chloramines because they form very few disinfection byproducts (DBPs).
PRESENT WORK

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

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 derivative in very good yield.

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

<table>
<thead>
<tr>
<th>S.No</th>
<th>Aldehyde(R)</th>
<th>Product(4a-4h)</th>
<th>Time (min)</th>
<th>Yield(%)</th>
<th>Melting Points (°C)</th>
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<tbody>
<tr>
<td>a</td>
<td>CHO</td>
<td></td>
<td>20</td>
<td>84</td>
<td>201-203°C</td>
</tr>
<tr>
<td>b</td>
<td>CHO MeO</td>
<td></td>
<td>20</td>
<td>88</td>
<td>198-201°C</td>
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<tr>
<td>c</td>
<td>CHO NO₂</td>
<td></td>
<td>30</td>
<td>76</td>
<td>207-209°C</td>
</tr>
<tr>
<td>d</td>
<td>CHO MeO MeO</td>
<td></td>
<td>20</td>
<td>88</td>
<td>214-216°C</td>
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<tr>
<td>e</td>
<td>CHO</td>
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<td>88</td>
<td>210-212°C</td>
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<tr>
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<td>30</td>
<td>75</td>
<td>227-230°C</td>
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<tr>
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<td>CHO</td>
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<td>80</td>
<td>206-208°C</td>
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<tr>
<td>h</td>
<td>CHO</td>
<td></td>
<td>40</td>
<td>76</td>
<td>150-152°C</td>
</tr>
</tbody>
</table>
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.

EXPERIMENTAL SECTION:

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 CDCl3 using TMS as internal standard. MASS spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV.

GENERAL PROCEDURE
A mixture of aldehyde (1 mmol), ethylacetocacetate (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 recrystallization from ethanol. All the products were characterized by their $^1$H NMR, IR and mass spectroscopy data.

**SPECTRAL DATA**

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

IR (KBr): $\nu$ 3416, 3231, 3108, 2936, 2867, 1701, 1648, 1592, 1241, 1129, 1036, 951, 834, 764 cm.$^{-1}$; $^1$H NMR (CDCl$_3$). $\delta$ 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).

**5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (4b):**

IR (KBr): $\nu$ 3415, 3242, 3119, 2951, 2861, 1701, 1639, 1604, 1513, 1162, 1036, 947, 853, 742 cm.$^{-1}$; $^1$H NMR (CDCl$_3$). $\delta$ 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): $\nu$ 3415, 3237, 3110, 3084, 2941, 2876, 1706, 1641, 1522, 1363, 1229, 961, 734 cm.$^{-1}$; $^1$H NMR (CDCl$_3$). $\delta$ 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): $\nu$ 3418, 3241, 3129, 3072, 2943, 1714, 1678, 1608, 1513, 1452, 1305, 1213, 1011, 947, 862, 741 cm.$^{-1}$; $^1$H NMR (CDCl$_3$). $\delta$ 8.95 (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): $\nu$ 3325, 3234, 3126, 3047, 2985, 2939, 1698, 1653, 1456, 1082, 874, 785 cm.$^{-1}$; $^1$H NMR (CDCl$_3$). $\delta$ 8.98 (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; ¹H NMR (CDCl₃). δ 8.96 (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; ¹H NMR (CDCl₃). δ 9.10(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; ¹H NMR (CDCl₃). 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).
Chapter - V, References:


35. Yamamoto, I.; Yakugakuzasshi, 2005, 125, 73-120.


