CHAPTER III

RESULTS AND DISCUSSION

The Biginelli dihydropyrimidine synthesis has attracted considerable attention in recent years. This multicomponent process involves the one-pot cyclocondensation of ethyl acetoacetate with aromatic aldehyde and urea (or thiourea) component under strongly acidic conditions. Dihydropyrimidinones have attracted increasing interest due to their diverse therapeutic and pharmacological properties such as antiviral, antibacterial, antihypertensive, antitumor, antibacterial, anticancer drugs, potent calcium channel blockers and anti human immunodeficiency virus (HIV).

Unfortunately, the original protocol (ethanol, catalytic HCl, reflux) provides only low to moderate yields of the desired dihydropyrimidine targets (DHPMs), in particular when a substituted aromatic aldehyde or thiourea are employed. 3,4-Dihydropyrimidin-2-(1*H*)-ones were reported by Pietro Biginelli who performed the three-component condensation reaction of ethyl acetoacetate, benzaldehyde and urea (or thiourea) using Brönsted acid catalysis. The reaction required strong acid, long reaction times and gave low yields. Several modified and improved procedures for the one-pot synthesis of dihydropyrimidinones have been reported. However many of the reported methods have drawbacks such as long reaction time, expensive catalyst, harsh reaction condition, the use of stoichiometric reagents or of toxic and inflammable solvents, difficult work-up or low yields of products, unsatisfactory yields and incompatibility with other functional groups. Consequently, the search for new catalyst and clean methods using less hazardous reagents and environmentally by

friendly condition such as solvent-free conditions, is therefore of considerable current interest. In this thesis, a facile method for the synthesis of 3,4-dihydropyrimidone-2-(1*H*)-ones by a one-pot condensation reaction between an aromatic aldehyde, ethyl acetoacetate and urea or thiourea under solvent-free conditions catalyzed by CsF-Celite is reported.

3.1 Study of the optimal condition for synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones using conventional heating

To establish the optimal conditions, an initial experiment on the reaction of benzaldehyde, ethyl acetoacetate and urea was carried out in different conditions.

3.1.1 Study of the concentration of catalyst

To find the best concentration of the catalyst, a set of experiment was carried out by mixing CsF-Celite in different concentration using benzaldehyde (0.10 ml, 1 mmol), ethyl acetoacetate (0.12 ml, 1 mmol), and urea (0.078 g, 1.3 mmol) and the mixture was stirred in a round bottom flask in a preheated sand bath at 80 °C for 1 h. The results were summarized in Table 3.1

Table 3.1 Study of the concentration of catalyst

Entry	Mole of CsF-Celite (mol%)	Reaction time (h)	Yield (%)
1	5 mol %	1	91
2	10 mol %	1	95
3	15 mol %	1	86

The results indicated that at 80 °C, the best concentration of catalyst to prepare the 3,4-dihydropyrimidine-2(1*H*)-ones was achieved with 10 mol% of CsF-Celite, an

equimolar of aldehyde and ethyl acetoacetate and 1.3 equivalent of urea (entry 2), which gave 95% yield.

3.1.2 Study of the concentration of urea

To find the appropriate concentration of the urea, a set of experiment was carried out by mixing urea in different concentrations using benzaldehyde (0.10 ml, 1 mmol), ethyl acetoacetate (0.12 ml, 1 mmol), CsF-Celite (10 mol%) and the mixture was stirred in a round bottom flask in a preheated sand bath at 80 °C for 1 h. The results were summarized in Table 3.2

Table 3.2 Study of the concentration of urea

Entry	Mole of urea (mmol)	Reaction time (h)	Yield (%)
1	1 mmol	1	93
2	1.2 mmol	1	94
3	1.3 mmol	1	95
4	1.5 mmol	1	95
5	2.0 mmol	1	94

The results indicated that at 80 °C, the best concentration of urea to prepare the 3,4-dihydropyrimidine-2(1*H*)-ones was achieved with 1.3 mmol of urea, equimolar of aldehyde and ethyl acetoacetate and CsF-Celite (10 mol%) (entry 3), which gave 95% yield.

3.1.3 Study of the temperature for heating

Benzaldehyde (0.10 ml, 1 mmol), ethyl acetoacetate (0.12 ml, 1 mmol), and urea (0.078 g, 1.3 mmol) were mixed with CsF-Celite (10 mol%) and the mixture was stirred in a preheated sand bath at 80 °C. The reaction was completed after 1h indicated by TLC monitoring and gave **4a** in 95% yields. The reaction was repeated in the same fashion at 110 °C. The result showed that after 1 h the starting materials, benzaldehyde, still remained in the reaction mixture. The reaction was stopped and worked up using the same protocol to afford pure product **4a** in 96% yield. This indicated that 3,4-dihydropyrimidine-2(1*H*)-ones can be prepared by heating either at 80 °C or 110 °C.

3.1.4 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-ones under conventional heating method

With optimal condition for condensation in hand, we then examined the generality of these conditions to other substrates. The results are summarized in Table 3.3

Table 3.3 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-ones through the Biginelli cyclocondensation (conventional heating method, 80 ºC and 110 °C)

Entry	R'	R"	R	X	DHPM	Temp (°C)	Time (h)	Yield %	m.p.(°C)	Reported m.p. (°C)
1	Me	OEt	C_6H_5	O	**4a**	80	1	95	201-203	202-203[113]
2	Me	OEt	C_6H_5	O	**4a**	110	2	96	201-203	202-203[113]
3	Me	OEt	4-OMe-C_6H_4	O	**4b**	80	3	97	202-203	202-204[114]
4	Me	OEt	4-OMe-C_6H_4	O	**4b**	110	3	96	202-203	202-204[114]
5	Me	OEt	4-Cl-C_6H_4	O	**4c**	80	3	91	213-215	214-215[113]
6	Me	OEt	4-Cl-C_6H_4	O	**4c**	110	3	93	213-215	214-215[113]
7	Me	OEt	2-Cl-C_6H_4	O	**4d**	80	3	94	215-216	215-217[113]
8	Me	OEt	2-Cl-C_6H_4	O	**4d**	110	3	95	215-216	215-217[113]
9	Me	OEt	4-NO_2-C_6H_4	O	**4e**	80	3	95	207-208	207-208[113]
10	Me	OEt	4-NO_2-C_6H_4	O	**4e**	110	3	93	207-208	207-208[113]
11	Me	OEt	4-NMe_2-C_6H_4	O	**4f**	80	2	97	255-258	257-258[113]
12	Me	OEt	4-NMe_2-C_6H_4	O	**4f**	110	3	96	255-258	257-258[113]

In this study, synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-ones were carried out under solvent-free condition using aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.3 mmol) and CsF-Celite (10 mol%). The mixture was heated using conventional heating method at 80 °C or 110 ºC. It was found that most of reactions were completed and gave the corresponding products in high yields. In some cases,

increasing temperature to 110 °C resulted in slightly higher yields (entry 2, 6 and 8). Substitution of electron-withdrawing group and electron-donating group gave different results. Under this reaction conditions, benzaldehyde reacted fastest. The reaction was completed in 1 h at 80 °C to afford 95% of the product. An electron-donating group at 4-position, such as 4-OMe, 4-$N(CH_3)_2$, reacted to give an excellent yield of 96-97% at 80 °C and 110 °C (entry 3, 4, 11 and 12). Reactants with an electron-withdrawing group, such as 4-Cl and 2-Cl reacted to give lower yields than those with an electron-donating group. The 4-NO_2 substituent also gave lower yield at 110 °C. The reaction gave a better result when performed the reaction at 80 °C.

When comparing the m.p. and ^{1}H NMR of the resulting products with the previous literature, it was found that most of the reactions gave the products with the same purities.

3.1.5 Study on reusing the catalyst

To establish the generality of the procedure, the study of reusing catalyst was carried out. CsF-Celite catalyst from the reaction of benzaldehyde, ethyl acetoacetate and urea was recovered and reused in the same reaction for three cycles and gave results shown in Table 3.4

Table 3.4 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-ones by conventional method using reused catalyst.

Entry	Substrate	X	T(ºC)	Reaction time (h)	Yield %
1	C_6H_5	O	80	1	95[a]
2	C_6H_5	O	80	1	94
3	C_6H_5	O	80	1	95
4	C_6H_5	O	80	1	95

[a] the reaction was carried out using a freshly prepare catalyst.

The result shows that the recycled catalyst can be reused in the reaction with consistent catalyst efficiency giving similar yields.

3.2 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-thiones by conventional heating

Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-thiones by conventional heating method were carried out under solvent-free condition using mole ratio of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), thiourea (1.3 mmol) and CsF-Celite (10 mol%) and gave the result shown in Table 3.5.

Table 3.5 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*)-thiones through the Biginelli cyclocondensation (conventional heating method, 80 ºC and 110 °C)

Entry	R'	R"	R	X	DHPM	Temp (ºC)	Time (h)	Yield %	m.p. (ºC)	Reported m.p. (ºC)
1	Me	OEt	C_6H_4	S	**5a**	80	1	96	208-210	209-211[115]
2	Me	OEt	C_6H_4	S	**5a**	110	3	97	208-210	209-211[115]
3	Me	OEt	4-OMe-C_6H_4	S	**5b**	80	2	97	148-150	150-152[116]
4	Me	OEt	4-OMe-C_6H_4	S	**5b**	110	3	98	148-150	150-152[116]
5	Me	OEt	4-Cl-C_6H_4	S	**5c**	80	3	95	194-196	192-194[116]
6	Me	OEt	4-Cl-C_6H_4	S	**5c**	110	3	96	194-196	192-194[116]
7	Me	OEt	2-Cl-C_6H_4	S	**5d**	80	2	90	210-212	209-210[116]
8	Me	OEt	2-Cl-C_6H_4	S	**5d**	110	3	92	210-212	209-210[116]
9	Me	OEt	4-NO_2-C_6H_4	S	**5e**	80	3	94	107-108	109-111[116]
10	Me	OEt	4-NO_2-C_6H_4	S	**5e**	110	3	93	107-108	109-111[116]
11	Me	OEt	4-NMe_2-C_6H_4	S	**5f**	80	3	96	256-258	-
12	Me	OEt	4-NMe_2-C_6H_4	S	**5f**	110	3	96	254-258	-
13	Me	OEt	3-OH-C_6H_4	S	**5g**	80	3	94	182-184	182-184[115]
14	Me	OEt	3-OH-C_6H_4	S	**5f**	110	3	92	182-184	182-184[115]

Replacing urea with thiourea also gave similar results. Under this reaction conditions, benzaldehyde reacted fastest. The reaction was completed in 1 h at 80 °C to afford 96% of the product. Increasing the reaction temperature to 110 °C for 3 h only gave a little higher yield (97%). It was found that most of reactions were

completed and gave the corresponding products in high yield at 80 °C and 110 °C. The reaction yields range from 90-98%. An electron-donating group at 4-position, such as 4-OMe, 4-$N(CH_3)_2$, reacted to give excellent yield of 96-98% at 80 °C and 110 °C (entry 3, 4, 11 and 12).

Reactants with an electron-withdrawing group, such as 4-Cl and 4-NO_2, reacted to give lower yields than those with an electron-donating group. The *o*-chlorobenzaldehyde also gave lower yield (90%) at 80 °C for 2h. The reaction gave slightly higher yield (92%) when increasing temperature to 110 °C and using longer reaction time (3h).

In case of substituted 3-OH, 3-OH-DHPM **5f** (Monastrol) was obtained with a high yield of 94% at 80 °C, 3 h. On the other hand, increasing reaction time and temperature gave lower yield (92%). This might be the results of decomposition of the product at high temperature.

3.3 Synthesis of substituted 3,4-dihydropyrimidine-2(1*H*) under microwave heating method

Synthesis of 3,4-dihydropyrimidinones was preformed in the same manner using a household microwave heating. The result is shown in Table 3.6

We have also explored the use of microwave to increase the reaction rate an efficiency of this new procedure. Synthesis of 3,4-dihydropyrimidinones was preformed in the same manner using a household microwave heating. The result is shown in Table 3.6

Table 3.6 Synthesis of substituted 3,4-dihydropyrimidinones through the Biginelli cyclocondensation (microwave method)

Entry	R'	R"	R	X	DHPM	Time (sec)	W	Yield %	M.p. (°C)	Reported M.p. (°C)
1	Me	OEt	C_6H_5	O	**4a**	180	850	95	201-203	202-203[102]
2	Me	OEt	4-OMe-C_6H_4	O	**4b**	150	450	96	202-203	202-204[103]
3	Me	OEt	4-Cl-C_6H_4	O	**4c**	370	450	97	213-215	214-215[101]
4	Me	OEt	2-Cl-C_6H_4	O	**4d**	140	600	90	215-216	215-217[101]
5	Me	OEt	4-NO_2-C_6H_4	O	**4e**	150	450	94	207-208	207-208[101]
6	Me	OEt	4-NMe_2-C_6H_4	O	**4f**	180	600	90	255-258	257-258[101]
7	Me	OEt	C_6H_4	S	**5a**	140	850	93	208-210	209-211[103]
8	Me	OEt	4-OMe-C_6H_4	S	**5b**	180	600	96	148-150	150-152[104]
9	Me	OEt	4-Cl-C_6H_4	S	**5c**	370	450	97	210-212	192-194[104]
10	Me	OEt	2-Cl-C_6H_4	S	**5d**	150	600	96	194-196	210-212[104]
11	Me	OEt	4-NO_2-C_6H_4	S	**5e**	180	450	94	107-108	109-111[104]
12	Me	OEt	4-NMe_2-C_6H_4	S	**5g**	180	600	95	256-258	-
13	Me	OEt	3-OH-C_6H_4	S	**5f**	180	850	95	182-184	182-184[103]

Most of the reactions were completed in 2.30-3 min and gave high yields (90-97%). The reaction time was shorter than the conventional heating method. Substituted 4-Cl gave the highest yield at 97% for both urea and thiourea, which were completed in 6.10 min at 450 W. For 4-NMe_2 substituent, replacing urea with thiourea

gave different results. Thiourea resulted 4-NMe_2-DHPM in higher yield than that of urea at 600W.

2-Chlorobenzaldehyde reacted with urea at 600 W, 2.20 min gave the corresponding product in low yield (90%). On the other hand this compound reacted with thiourea at 600 W, 2.30 min to give product 96% yield.

In case of substituted 3-OH, 3-OH-DHPM (Monastrol) was obtained with a high yield at 95% at 850 W, 3 min. Most of DHPM products were received with the same purity as the products obtained by conventional heating method by comparison of m.p. and ^{1}H NMR.