Environmentally Benign Syntheses and Characterization of 4-Aryldihydropyrimidin-2(1H)-ones

Syed Salman Shafqat¹, Amir Azam Khan¹, Misbahul Ain Khan², Nicholas Kuan Hoo Tien¹, Mohd Syahmi Jamaludin¹, Pang Suh Cem³

¹Department of Mechanical and Manufacturing Engineering, Faculty of Engineering, Universiti Malaysia Sarawak (UNIMAS), 94300 Kota Samarahan, Sarawak, Malaysia.

²Department of Chemistry, The Islamia University of Bahawalpur, Pakistan.

³Department of chemistry, Faculty of Resource Science & Technology Universiti Malaysia Sarawak (UNIMAS), 94300 Kota Samarahan, Sarawak, Malaysia.

Abstract. A general, simple, efficient, cost-effective and environmental benign procedure for the syntheses of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones (DHPMs) has been developed. The reaction is efficiently catalysed by using various amino acids viz., glycine, L-proline, L-cysteine, leucine and tryptophan. Reactions give excellent yields under reflux conditions. The chemical structures of these compounds were identified by Fourier Transform-Infra Red Spectroscopy (FT-IR), Gas Chromatography-Mass Spectroscopy (GC-MS) and Nuclear Magnetic Resonance Spectroscopy (¹H NMR). Physical parameters such as m.p., mixed m.p. as well as TLC also helped to characterize the expected products. The progress of the reaction time and purity was checked by TLC and the products were purified by recrystallization using ethyl acetate as a solvent. The synthesized molecule has numerous biological applications as it is anti-microbial, anti-inflammatory and anti-hypertensive in character.

Key Words: Green Approach, Amino Acids, 4-Aryldihydropyrimidinone.

1 Introduction

The synthesis of dihydropyrimidinones (DHPMs) has gained importance in recent years due to structural similarities between dihydropyrimidinones and pyrimidine [1]. Pyrimidines are one of biologically important families. Pyrimidine bases such as cytosine (C), thymine (T), are basic constituents in nucleic acids [2]. This class of heterocyclic compounds has also very important pharmaceutical activities such as antimicrobial [3], anti-inflammatory [4], antitumor [3] antihypertensive agents [5], chemical modulators, calcium channel modulators as well as melanin

concentrating hormone receptor, antagonists[6], antifungal[7], as inhibitors to replicate hepatitis B, and inhibitors of specific organic acid transporters [8], [9].

In 1893, Pietro Biginelli reported synthesis of 4-dihydropyrimidin-2(1H)-one by cyclocondensation of ethyl acetoacetate, benzaldehyde, and urea by simply heating a mixture of these three components in the presence of acid as a catalysts under reflux conditions [10].

Scheme I: General Scheme of Biginelli condensation

Now Biginelli reaction is an important multicomponent reaction for the preparation of biologically active dihydropyrimidinone derivatives. Usually the synthesis of 4-aryldihydropyrimidin-2(1H)-ones (DHPMs) is carried out by the condensation of an aromatic aldehyde, ethyl acetoacetate, urea/thiourea in the presence of metal salts [11], [12], Bronsted and Lewis acids [13], ionic liquids [14] microwave irradiations [15] or refluxing acetic acid for few hours [16].

Many of these classical methods, however, suffer from drastic reaction conditions, lower yields, difficult workup process, excessive use of chemicals as well as catalyst and environmental impact such as carcinogenic solvents and non-biodegradable catalysts [17]. Although a variety of methods are reported for the synthesis of DHPMs, only few examples were developed with the aim of replacing conventional toxic and polluting Bronsted and Lewis acid catalysts with efficient and green catalysts such as recyclable catalyst under solvent-free conditions [18], amino acid catalyzed [19], [20], [21], Mesoporous SBA-15 nanoparticles [22] and Quaternary Ammonium-treated clay in water catalyzed [23] synthesis of DHPMs. Drawbacks of these classical methods and catalytic efficacy of environmental benign catalyst gave us a direction to introduce new efficient catalysts for preparation of 4-aryl-3,4-dihydropyrimidin-2(1H)-ones with cost effectiveness and mild conditions with high yields.

We had earlier communicated our preliminary finding that amino acids can be efficiently used for these reactions [19]. Dihydropyrimidinone (DHPM) synthesis was carried out by using benzaldehyde and urea/thiourea.

Amino acids are also being reported as efficient catalysts in the Knoevenagel condensations, reduction, oxidation, electrophilic α -fluorination and amination, transamidation, as well as promoter of some of the reactions [24], [25].

We are extending this Biginelli, amino acid catalyzed reaction, using some other aryl aldehydes which are now being communicated.

2 Experimental Work

Most of the chemicals used during the development of this environmentally benign synthesis were of laboratory grade and were used as it is. Progress of the reactions were monitored by using Silica TLC plates and UV light was used as a spot locating agent. IR were recorded on Perkins Elmer FTIR (spectrum RXI) spectrometer. Mass spectra were recorded GC-

MS Shimadzu QP2010. ^1H NMR spectra were recorded on (NMR; Jeol JNM-ECA500).

2.1 Synthesis of 4-Aryldihydropyrimidin-2(1H)-ones:

General Method: A reactions mixture containing 40 mmol of aromatic aldehyde, 40 mmol of ethyl acetoacetate, 45 mmol of urea, 0.01 mmol of an amino acid were dissolved in 10 ml of ethanol. The reaction mixture was heated under reflux for two hours. The reaction mixture was work up by allowing to cool down to room temperature and was diluted with ice cold water and the precipitated product was isolated. The product was recrystallized from ethyl acetate o purify.

Four aromatic aldehydes were used by using this general procedure to syntheses four different 4-Aryldihydropyrimidin-2(1H)-ones by employing five different amino acids as catalysts.

2.1.1 By using *p*-chlorobenzaldehyde (4): 4.5g of *p*-chlorobenzaldehyde (4) was mixed with 5.2 g of ethyl acetoacetate (1), 4g of urea (2) and .01mmol of glycine in 10 ml of ethanol. The reaction mixture was heated in reflux conditions for 2 hours. The reaction was allowed to stand to room temperature and then crushed ice was added to it, pale yellow crystals of 5-Ethoxycarbonyl-6-methyl-4-*p*-chlorophenyldihydropyrimidin-2-one (4) were collected and recrystallized to purify the product. The product was characterized through its m.p., IR, Mass spectrum and ^1H -NMR. After this the reaction was carried out by employing few other amino acids. These products were identical in their physical and chemical characteristics to the product obtained by using glycine. The proposed reaction is presented in scheme (scheme II) and results are described in (Table 1).

Scheme II: Synthesis of 5-ethoxycarbonyl-6-methyl-4-*p*-chlorophenyldihydropyrimidin-2-one

2.1.2: By using *p*-nitrobenzaldehyde (5): Condensation of *p*-nitrobenzaldehyde (5) with ethyl acetoacetate (1) and urea (2) was conducted by using Glycine as a catalyst as a test reaction. This reaction gave good yield of 5-Ethoxycarbonyl-6-methyl-4-*p*-nitrophenyldihydropyrimidin-2-one (6). So this reaction was carried out by employing other available amino acids. The products were characterized through m.p., IR, Mass spectrum and ^1H -NMR. The proposed reaction is presented in scheme (scheme III) and results are summarized in (Table 2).

Scheme III: Synthesis of 5-ethoxycarbonyl-6-methyl-4-*p*-nitrophenyldihydropyrimidin-2-one (6)

2.1.3 By using 2-hydroxybenzaldehyde (7):

Condensation of 2-hydroxybenzaldehyde (7) with ethyl acetoacetate (1) and urea (2) was carried out in the presence of Glycine as catalyst using ethanol as a solvent. This reaction gave a very good yield of 5-Ethoxycarbonyl-6-methyl-4-*o*-hydroxyphenyldihydropyrimidin-2-one (8). The same reaction was also carried out in the presence of other available amino acids. The product (8) was characterized through its m.p., IR, Mass spectrum and ¹H-NMR and verified its structure. The proposed reaction is presented in scheme (scheme IV) and results are summarized in (Table3).

Scheme IV: Synthesis of 5-ethoxycarbonyl-6-methyl-4-*o*-hydroxyphenyldihydropyrimidin-2-one (8)

2.1.4 By using 4-hydroxybenzaldehyde (9):

Condensation of 4-hydroxybenzaldehyde (9) with ethyl acetoacetate (1) and urea (2) in the presence of Glycine gave 5-Ethoxycarbonyl-6-methyl-4-*p*-hydroxyphenyldihydropyrimidin-2-one (10). Some other amino acids were also used to prepare product (10). The product (10) was characterized through its TLC, m.p., IR, Mass spectrum and ¹H-NMR. All the products were identical in the characteristics. The proposed reaction is presented in scheme (scheme V) and results are presented in (Table 4).

Scheme V: Synthesis of 5-ethoxycarbonyl-6-methyl-4-*p*-hydroxyphenyldihydropyrimidin-2-one (10)

Table 1: Characterization of 5-Ethoxycarbonyl-6-methyl-*p*-chlorophenyldihydropyrimidin-2-one (4)

Entry	Catalyst	Yield %	m.p. °C	IR cm ⁻¹	MS(m/z)
			Lit [26] m.p210		
1	glycine	92	207	3236 (N-H)	
2	L-cysteine	94	206	3113 (aro C-H)	294(M+)
3	L-proline	95	208	2985(ali C-H)	265(30%)
4	<i>B</i> -alanine	93	206	1710 (C=O)	221(25%)
5	tryptophan	90	205	1646 (C=C)	183(100%)
				1461 (C-H)	
				1281(C-O)	
				776 (Cl)	

Table 2: Synthesis and characterization of 5-Ethoxycarbonyl-6-methyl-4-nitrophenyldihydropyrimidin-2-one (6)

Entry	Catalyst	Yield %	$\frac{m.p^{\circ}C}{\text{Lit } 208^{[26]}}$	IR cm^{-1}	MS (m/z)	1H NMR
1	glycine	95	207			NMR (500MHz, $CDCl_3$) 1H 8.18(2H) J=9.17 (d)
2	L-cysteine	96	208	3283 (N-H) 3102(aro C-H)		2H 7.50 (2H) J=9.17 (d) 3H 5.552(1H) J=3.06 (d)
3	L-proline	92	208	2985(ali C-H) 1717(C=O)	305(M+) 288(20%) 276(15%)	4H 5.74(1H) (s) 5H 2.37(3H) (s)
4	B-alanine	93	207	1682(C=O) 1642(C=C) 1502 and 1323(NO2)	183(100%)	6H 4.10(2H) (q) 7H 1.17(3H) 6.88 8H 7.4159 (1H) incomplete splitting
5	tryptophan	94	206	1232 (C-O)		

Table 3: Synthesis and characterization of 5-Ethoxycarbonyl-6-methyl-2-hydroxyphenyldihydropyrimidin-2-one (8)

Entry	Catalyst	Yield %	$\frac{m.p^{\circ}C}{\text{Lit } 265^{[26]}}$	IR cm^{-1}	MS (m/z)	1H NMR
1	glycine	92	260	3232 (O-H) 3220 (N-H)		(NMR500 MHz,DMSO-d6, 9.35 (1H) (s) 9.12 (1H) (s)
2	L-cysteine	90	261	3101 (aro C-H) 2978 (ali C-H)	276 (M+) 247(20%) 229(30%)	7.63(1H)(s) incomplete splitting 7.02(2H)(d) J=8.41 6.68(2H)(d) J=8.41
3	L-proline	93	259	1727 (C=O) 1682 (C=O)	183(50%) 57(100%)	5.03 (1H) (d) 3.97 (2H) (qss)
4	B-alanine	90	261	1653 (C=C), 1513 (C-H)		2.22 (3H) (s) 1.09 (3H) (t)
5	tryptophan	94	259	1212 (C-O).		

Table 4: Synthesis and characterization of 5-Ethoxycarbonyl-6-methyl-4-hydroxyphenyldihydropyrimidin-2-one (10)

Entry	Catalyst	Yield %	$\frac{m.p^{\circ}C}{\text{Lit } 227^{[27]}}$	IR cm^{-1}	MS (m/z)	1H NMR
1	glycine	92	220	3232 (O-H) 3220 (N-H)		(NMR500 MHz,DMSO-d6, 9.35 (1H) (s) 9.12 (1H) (s)
2	L-cysteine	90	220	3101 (aro C-H) 2978 (ali C-H)	276 (M+) 247(20%) 229(30%)	7.63(1H)(s) 7.02(2H)(d) J=8.41 6.68(2H)(d) J=8.41
3	L-proline	93	219	1727 (C=O) 1682 (C=O)	183(50%) 57(100%)	5.03 (1H) (d) 3.97 (2H) (qss)
4	B-alanine	95	220	1653 (C=C), 1513 (C-H)		2.22 (3H) (s) 1.09 (3H) (t)
5	tryptophan	91	222	1212 (C-O).		

3 Results and Discussion

In this study as part of our continued effort to develop environmental benign and new catalysis systems with a reduced environmental impact, the utility of five amino acids *viz.* glycine, L-proline, L-cysteine, lucien and tryptophan is explored as catalysts for the multi component synthesis of 4-aryldihydropyrimidin-2(1H)-ones. All the amino acids gave promising results with high yields under reflux conditions. Initially, a model reaction was conducted by heating a mixture of *p*-chlorobenzaldehyde, ethyl acetoacetate and urea using glycine as a catalyst and excellent results were obtained. The product 5-ethoxycarbonyl-6-methyl-4-*p*-chlorophenyldihydropyrimidin-2-one (**4**) was obtained in almost quantitative yield (92%). Keeping in view of this successful result various other amino acids were employed for the reaction with equal success. All the product were characterized through its m.p., IR, mass spectrum and ¹H NMR (**Table-1**). The efficacy of amino acid catalysts was further tested in the synthesis of diverse 4-aryldihydropyrimidin-2(1H)-ones with comparable results (**Table1-4**). Plausible mechanism for the glycine -catalyzed synthesis of 4-aryldihydropyrimidin-2(1H)-ones has been proposed (**Scheme VI**). The reaction may proceed through the protonation of aromatic aldehyde (A) by the amino acid which provides this proton to catalyze the reaction. Further reaction proceeds via intermediates B and C as depicted in the scheme.

Scheme VI: Amino Acid catalyzed mechanism of Biginelli Condensation

4 Conclusion

In summary, amino acids were successfully employed as catalyst for the synthesis of various 4-aryldihydropyrimidin-2(1H)-ones. Simple and mild reaction conditions, low cost, readily available and biodegradable catalyst are the important features of this protocol. For the present work, only a few representative aromatic aldehydes and urea were used to check the feasibility of amino acids as a catalyst in these reactions. The yields in all these reactions were comparable and the use of these catalysts can be

extended to study the utilization of other aldehydes in Biginelli reactions.

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