Synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrimidinone derivatives using glutamic acid as an efficient catalyst

Khatereh Khandan-Barani[a]*, Mehrnoosh Kangani[a], Maryam Mirbaluchzehi[a], Zahra Siroos[a]

Department of Chemistry, Islamic Azad University, Zahedan Branch, PO Box 98135-978, Zahedan, Iran

*Corresponding author E-mail: kh_khandan_barani@yahoo.com

Abstract: The efforts to use green catalysts for the organic synthesis are undeniable. Natural Catalysts are biodegradable and easy access. Herein, glutamic acid was applied as a natural and green catalyst for the synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrimidinone derivatives under solvent-free and thermal conditions. The most advantages of this research are: use of natural, green and biodegradable catalyst, easy work-up and high yields.

Keywords: Glutamic acid, tetrahydrobenzo[*b*]pyran, 3,4-dihydropyrimidinone, solvent-free and thermal conditions

1. Introduction

Glutamic acid is one of the most common non-essential amino acids; German chemist Karl Ritthausen first isolated Glutamic acid from the wheat gluten in 1866, but its chemical structure was identified only in 1890; Glutamic acid is an excitatory neurotransmitter increasing the firing of neurons in the human central nervous system; This amino acid is also known for its ability to detoxify muscle cells [1,2].

Glutamic acid has one additional methylene group in its side chain than aspartic acid; the side chain carboxyl of aspartic acid is referred to as the β carboxyl group, while that of glutamic acid is referred to as the γ carboxyl group (Figure 1). The pKa of the γ carboxyl group for glutamic acid in a polypeptide is about 4.3, significantly higher than that of aspartic acid [3-5].

Because of the broad pharmacological activities of pyrimidinones and pyranes, different synthetic methods have been introduced by research groups [6-13]. Usually, these synthetic approaches are including a multi-step procedure [14]. Among the 12 principles of green chemistry, utilizing ‘‘safer solvents’’ (or solvents elimination) and to ‘‘design for energy efficiency’’ can be considered the most important ones for the synthetic chemists [15, 16], the catalysts which make the organic reactions environmentally benign and economically feasible are extremely demanded by chemical industries [17, 18].

According to mentioned reasons and in continue of our research on multi-component reactions [19-22] we herein report green synthesis of tetrahydrobenzo[*b*]pyran- and 3,4-dihydropyrimidinone derivatives under solvent-free and thermal conditions in the presence of glutamic acid as a natural and green catalyst via the condensation between aryl aldehydes,

dimedone and malononitrile and the reaction between aryl aldehydes, urea and ethyl acetoacetate (Scheme 1).

2. Experimental

2.1.General

Melting points and IR spectra of all compounds were measured on an Electro thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. The ^{1}H NMR spectra were obtained on Bruker DRX-400 Avance instruments with DMSO as a solvent. All reagents and solvents were obtained from Aldrich and Merck and used without further purification.

2.2.General procedure for synthesis of tetrahydrobenzo[b]pyrans

Glutamic acid (5 mol%) was added to a mixture of benzaldehyde (1 mmol), dimedone (1 mmol) and malononitrile (1 mmol), the reaction mixture was heated to 50°C and maintained for the appropriate time (Table 2). After completion of the reaction as monitored by thin-layer chromatography (TLC), the reaction mixture was washed with H_2O (3× 10 mL) to remove the catalyst. Then, the residue was recrystallized from EtOH. The structures of the synthesized compounds were characterized by their IR, melting points and ^{1}H NMR spectra (^{13}C NMR for **4c**) and were found to be identical with data described in the literature.

2.3.General procedure for synthesis of 3,4- dihydropyrimidin-2(1H)-ones

A mixture of ethyl acetoacetate (2 mmol), aldehyde (2 mmol), urea (2 mmol) and catalytic amount of glutamic acid (5 mol%) was heated to 100°C under solvent-free conditions and maintained for the appropriate time (Table 4). After completion of the reaction as monitored by thin-layer chromatography (TLC), the residue was washed with water (3× 10 mL) and

recrystallized from ethanol to afford 3,4-dihydropyrimidinone in excellent yields. The structures of the synthesized compounds were characterized by their IR, melting points and ^{1}H NMR spectra and were found to be identical with data described in the literature.

Selected spectroscopic data of some products is given below:

2-Amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4a**): FT-IR: (KBr, ν_{max}/cm^{-1}): 3395, 3324 (NH_2), 3209 (CH_{sp}^2), 2963, 2882 (CH_{sp}^3), 2198 (CN), 1664 (C=O).^{1}H NMR (400.1MHz, DMSO-d_6): δ=0.94 (s, 3H), 1.02 (s, 3H), 2.09 (d. *J*= 15.9 Hz, 1H), 2.24 (d, *J* = 16.0 Hz, 1H), 2.65 (s,2H), 4.15 (s,1H), 6.99 (br, 2H), 7.11-7.29 (m, 5H) ppm.

2-Amino-3-cyano-4-(2'-hydroxy-5'-nitrobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4c**): Yellow Solid, FT-IR (KBr, ν_{max}/cm^{-1}): 3433, 3333 (NH_2), 3059 (CH_{sp}^2), 2960 (CH_{sp}^3), 2190 (CN), 1669 (C=O). ^{1}H NMR (400.1MHz, DMSO-d_6): δ=1.04 (s, 3H), 1.09 (s, 3H), 2.08 (d, *J* = 16.1 Hz, 1H), 2.21 (d, *J* = 16.1 Hz, 1H), 2.55 (s, 2H), 4.28 (s, 1H), 7.14 (s, 2H), 7.18-7.31 (m, 3H), 10.43 (s, 1H) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ= 26.5, 27.9, 31.2, 35.7, 40.1, 49.3, 61.4, 112.8, 119.0 (CN), 119.7, 120.04, 130.8, 132.7, 139.4, 158.4, 161.8, 165.5, 194.8 (C=O) ppm.

2-Amino-3-cyano-4-(4'-methylbenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (**4e**): FT-IR (KBr, ν_{max}/cm^{-1}): 3425, 3327 (NH_2), 3042 (CH_{sp}^2), 2958 (CH_{sp}^3), 2191 (CN), 1676 (C=O). ^{1}H NMR (400.1 MHz, DMSO-d_6): 1.02 (s, 3H), 1.06 (s, 3H), 2.12 (d, *J* = 16.0 Hz, 1H), 2.25 (d, *J* = 16.0 Hz, 1H), 2.29(s, 3H), 2.56 (s, 2H), 4.33 (s, 1H), 4.52 (s, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.11-7.14 (m, 2H) ppm.

2-Amino-3-cyano-4-(4'-chlorobenzyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (**4h**): FT-IR (KBr, ν_{max}/cm^{-1}): 3394, 3312 (NH_2), 3060 (CH_{sp}^2), 2962 (CH_{sp}^3), 2190 (CN), 1666

(C=O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 0.95 (s, 3H), 1.04 (s, 3H), 2.10 (d, *J* = 16.1 Hz, 1H), 2.19 (d, *J* = 16.1 Hz, 1H), 2.51 (s, 2H), 4.19 (s, 1H), 7.08 (s, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H) ppm.

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**8a**): FT–IR (KBr, ν_{max}/cm^{-1}): 3332 (NH), 3320 (NH), 1697 (2C=O). ^{1}HNMR (400.1 MHz, DMSO-d_6):δ=1.08 (t, *J* = 7.1 Hz, 3H), 2.24 (s,3H), 3.97 (q, *J* = 7.1 Hz, 2H), 5.13 (s,1H), 7.21-7.33 (m, 5H), 7.77(s, 1H), 9.23 (s, 1H).

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**8c**):

FT–IR (KBr, ν_{max}/cm^{-1}): 3241 (NH), 3110 (NH), 1705 and 1648 (2C=O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ=1.10 (t, *J* =7.0 Hz, 3H), 2.30 (s, 3H), 4.05 (q, *J* = 7.1 Hz,2H), 5.69 (d, *J* = 2.3 Hz, 1H,), 7.48 (d, *J* = 9.2 Hz, 2H), 7.56 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 2H), 9.10 (s, 1H).

5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**8d**):

FT–IR (KBr, ν_{max}/cm^{-1}): 3332 (NH), 3218 (NH), 1666 (2C=O).^{1}H NMR (400.1 MHz, DMSO-d_6): δ=1.12 (t, *J* =7.1 Hz, 3H), 2.28 (s, 3H), 3.98 (q, *J* = 7.1 Hz, 2H), 5.36 (d, *J* = 2.2, 1H), 7.18 (d, *J* = 9.1, 2H),7.60 (s, 1H), 7.75 (d, *J* = 9.1, 2H), 9.15 (s, 1H).

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**8f**):

FT–IR (KBr, ν_{max}/cm^{-1}): 3245 (NH), 3110 (NH), 1710 and 1648 (2C=O). ^{1}HNMR (400.1 MHz, DMSO-d_6):δ=1.15 (t, *J* = 6.8 Hz, 3H), 2.29 (s, 3H), 3.66 (s, 3H), 3.71 (q, *J* = 6.7 Hz, 2H), 5.05 (s, 1H), 6.79-7.12 (m, 4H), 7.59 (s, 1H), 9.24 (s, 1H).

3. Result and discussion

The reaction between benzaldehyde, dimedone and malononitrile was chosen as a model. The reaction was performed in different temperature and amount of catalyst.

As can be seen in Table 1 the best results was obtained in the presence of 5 mol% of catalyst at 50 ^{o}C.

Encouraged by the remarkable results obtained from above conditions, and in order to show the generality and scope of this protocol, we used various aldehydes. Thus, a variety of aromatic aldehydes, including those with electron withdrawing and electron-donating groups, were tested using this method. The desired products were obtained in good yields using catalytic amount of glutamic acid and the results are shown in Table 2.

We proposed mechanism for the synthesis of tetrahydrobenzo[*b*]pyrans in the presence of glutamic acid as catalyst. First, Knoevenagel condensation between **1** and **2** produced 2-benzylidene malononitrile **3**, Michael addition of **3** with **5** (1,3-dicarbonyl compound), and followed cyclization and tautomerization afforded the corresponding product. Glutamic acid can hold molecules and further catalyze reactions possible activated by hydrogen bonds (Scheme 2).

Next, the reaction conditions were optimized for the synthesis of 3,4-dihydropyrimidinone derivatives. The reaction between benzaldehyde, urea and ethylacetoacetate was chosen as a model reaction (Scheme 3). The reaction was performed in different temperature and amount of catalyst (Table 3). The best results were obtained with 5 mol % of catalyst at 100 ^{o}C.

Using the optimized reaction condition in the hand (Table 3, Entry 2), a variety of

3,4-dihydropyrimidinones were synthesized and the results are summarized in Table 4. A variety of 3,4-dihydropyrimidinones with *ortho*, *meta* and *para* substitutions on the benzene ring were examined. Nitro and halogen substitutions were tolerated very well and gave excellent yields in shorter reaction times than those of methyl and methoxy, groups (Table 4).

The accessibility of the present work in comparison with the reported results in the literature, some of the results has been accumulated in Table 5. The results show that glutamic acid is a more efficient catalyst with respect to the reaction time exhibits broad applicability in similar yield.

Conclusion

We have developed a simple, efficient, and green protocol for the synthesis of tetrahydrobenzo[*b*]pyran- and 3,4-dihydropyrimidinone derivatives using glutamic acid catalyst under solvent-free conditions. The short reaction times, simple work-up in the isolation of the products in high yields with high purity, solvent-free conditions, and using a green and natural catalyst are noteworthy features of this new procedure.

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Table 1. Optimization of the reaction conditions and amount of catalyst for the synthesis of tetrahydrobenzo[*b*]pyrans

Entry	Catalyst (mol %)	T(˚C)	Time (min)	Yield (%)
1	5	25	50	65
2	5	35	40	70
3	**5**	**50**	**15**	95
4	5	60	15	90
5	5	70	15	80
6	10	50	25	75
7	15	50	45	65
8	20	50	45	55
9	-	50	24	Trace

Table 2. synthesis of tetrahydrobenzo[*b*]pyran derivatives

Entry	R	Product	Time (min)	Isolated Yield (%)	M.p (°C)	M.p reported (°C)
1	C_6H_5	4a	15	90	227-229	226-228 [23]
2	4-OCH_3-C_6H_4	4b	20	82	191-193	194-196 [23]
3	2-OH-4-NO_2-C_6H_3	4c	15	85	208-210	-
4	4-Br-C_6H_4	4d	10	92	198-200	201-203 [24]
5	4-CH_3-C_6H_4	4e	20	80	206-208	208-210 [23]
6	4-NO_2-C_6H_4	4f	10	95	183-185	181-183 [25]
7	4-$(Me)_2N$-C_6H_4	4g	25	75	202-204	198-200 [26]
8	4-Cl-C_6H_4	4h	15	90	214-217	215-217 [27]
9	2-Cl-C_6H_4	4i	10	93	217-219	214-215 [23]
10	2-NO_2-C_6H_4	4j	15	90	228-230	224-226 [28]

Table 3. Optimization of the reaction conditions and the amount of catalyst for the synthesis of 3,4-dihydropyrimidinone derivatives

Entry	Catalyst (mol %)	T(°C)	Time (h)	Yield (%)
1	5	80	5	80
2	**5**	**100**	**3**	96
3	5	115	3	96
4	5	120	3	90
5	5	130	3	85
6	10	100	5	75
7	15	100	5	70
8	20	100	5	65
9	-	100	24	Trace

Table 4. Synthesis of 3,4-dihydropyrimidinonederivatives

Entry	R	Product	Time (h)	Isolated Yield (%)	M.p (°C)	M.p reported (°C)
1	H	8a	3	95	203-206	201-203 [29]
2	4-CH_3	8b	3	85	213-215	214-215 [30]
3	4-NO_2	8c	2	95	208-210	209-210 [31]
4	4-Cl	8d	2	90	214-215	212-213 [32]
5	4-Br	8e	1.5	92	195-197	197-200 [33]
6	4-OMe	8f	4	80	201-203	202-204 [34]
7	4-F	8g	2	93	182-184	183-185 [35]
8	4-NMe_2	8h	4	80	252-254	255-256 [36]
9	3-NO_2	8i	2	92	229-231	227-229 [37]
10	3-Cl	8j	2	90	188-190	191-193 [38]

Table 5 . Comparison the result of glutamic acid with other catalysts reported in the literature for preparation of tetrahydrobenzo[*b*]pyran and 3,4-dihydropyrimidinone derivatives

Entry	Product	Catalysts	conditions	Time	Yield (%)	Ref
1	4	HDBMB	12 mol%; water; 80 ^{o}C	6 h	94	[39]
2	4	TBAB	10 mol%; ethanol; reflux	30 min	95	[28]
3	4	TBAF	10 mol %; water; reflux	30 min	94	[40]
4	4	[TEBSA] HSO_4	10 mol%; H_20; 90 ^{o}C	1 h	91	[41]
5	4	Na_2SeO_4	0.1 g; H_2O-C_2H_5OH; reflux	3 h	90	[42]
6	4	Glutamic Acid	5mol %; Solvent-free; 50^{o}C	10 min	95	This work
7	8	$InBr_3$	Ethanol, reflux	420 min	98	[43]
8	8	P_2O_5	Ethanol, reflux	240 min	91	[44]
9	8	Bioglycerol-based sulfonic acid	Acetonitrile, reflux, N_2atm	240 min	89	[45]
10	8	sulfonic acidsilica	Ethanol, reflux	360 min	94	[46]
11	8	p-Toluene sulfonic acid	Ethanol, reflux	150 min	91	[47]
12	8	Dowex-50W	Solvent-free, 130^{0}C	180 min	93	[48]
13	8	$Cu(NH_2SO_3)_2$	Acetone, reflux	300 min	79	[8]

14	8	Zeolite	toluene, reflux	720 min	80	[49]
15	8	$Cu(OTF)_3$	Acetonitrile, 25^0C	360 min	94	[50]
16	8	Glutamic Acid	Solvent-free, 100^0C	90 min	92	This work

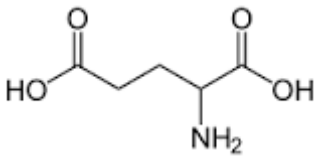
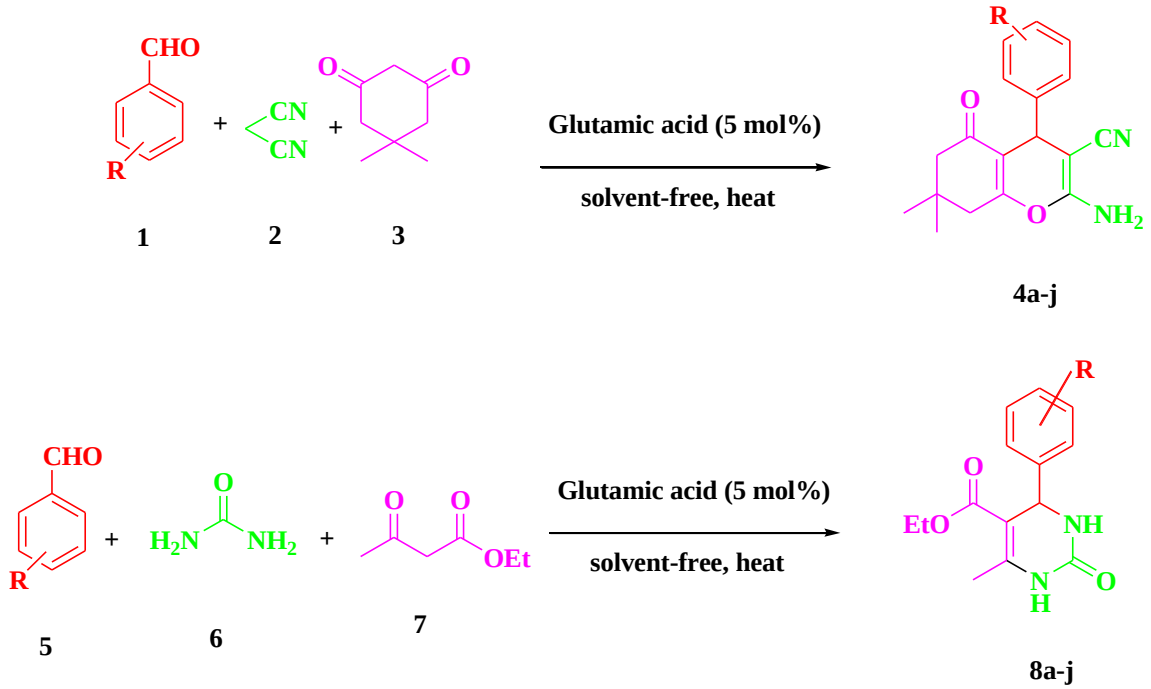
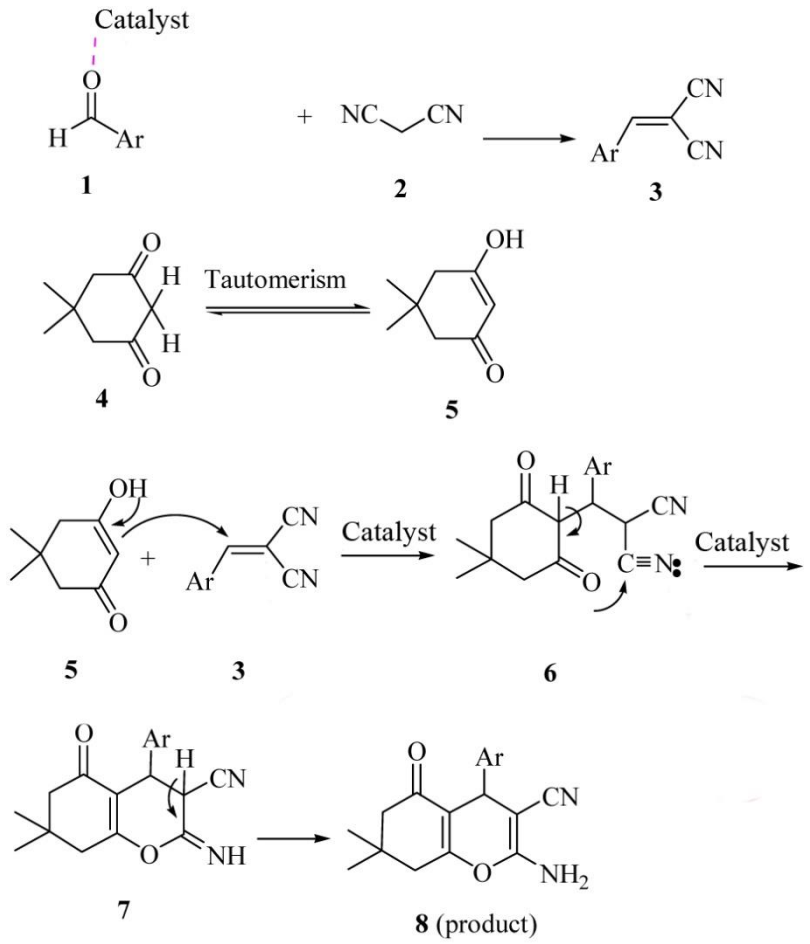


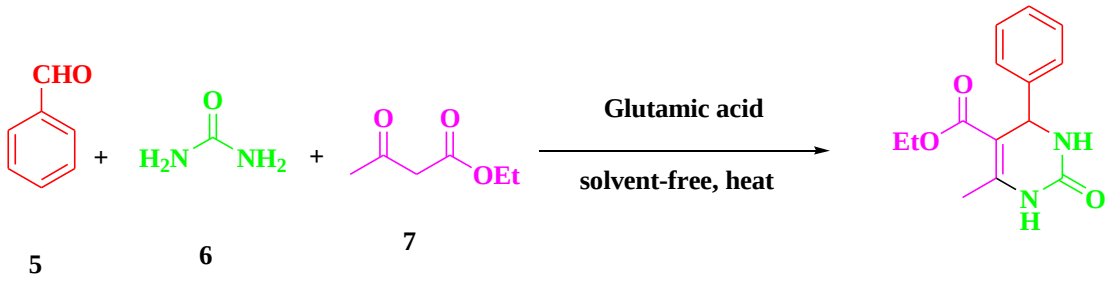
Figure 1. The structure of glutamic acid



Scheme 1. Synthesis of tetrahydrobenzo[b]pyran and 3,4-dihydropyrimidinone derivatives in the presence of glutamic acid as catalyst under solvent-free and thermal conditions



Scheme 2. Proposed mechanism for the synthesis tetrahydrobenzo[b]pyran in the presence of glutamic acid as catalyst



5 6 7

Scheme 3. Model reaction for the synthesis of 3,4-dihydropyrimidinone derivatives