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Original scientific paper

Glutamic acid as green and bio-based α-amino acid catalyst promoted one-pot access to polyfunctionalized dihydro-2-oxypyrroles

FARZANEH MOHAMADPOUR*

Young Researchers and Elite Club, Shiraz Branch, Islamic Azad University, Shiraz, Iran

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Abstract: A highly versatile and convenient synthetic route for biologically active α-amino acid, glutamic acid catalyzed facile and mild preparation of polyfunctionalized dihydro-2-oxypyrroles *via* one-pot, four condensation domino reaction between aromatic/aliphatic amines, dialkyl acetylenedicarboxylates and formaldehyde have been studied. The route includes green, biodegradable and inexpensive α-amino acid catalyst, high atom-economy, simplicity of operation and work-up procedures, without chromatographic purification steps. The solid catalyst, non-toxic or hazardous, easily handled with mild reaction conditions and excellent yields are the notable benefits of the highly efficient and expedient synthesis of these products.

Keywords: glutamic acid; green and biodegradable α-amino acid catalyst; polyfunctionalized dihydro-2-oxypyrroles; one-pot procedure; simple work-up.

INTRODUCTION

Polyfunctionalized heterocyclic compounds are playing important roles in drug discovery processes and in the analysis of drugs. In particular, pyrroles and their analogues have been receiving attention owing to their biological activities such as against human cytomegalovirus (HCMV) protease,[1] inhibition of human cytosolic carbonic anhydrase isozymes[2] and cardiac cAMP phosphordiestrase,[3] they have been used as PI-091[4] also. Many alkaloids have pyrrole rings.[5] In addition, these rings have been incorporated in oteromycin.[6] They exhibit various biological activities, for example 1,5-diydro-4-[4-(1*H*-imidazol-1-yl)phenol]-2*H*--pyrrol-2-ones[4] as VEGF-R (vascular endothelial growth factor receptor)[7] inhibitor. Some of them with biological properties are shown in Fig. 1.

To date, a number of methodologies have been reported for the preparation of these compounds that included various catalysts such as I_2,[8] $InCl_3$,[9] [*n*-Bu_4N][HSO_4],[10] $Al(H_2PO_4)_3$,[11] AcOH,[12] $Cu(OAc)_2{\cdot}H_2O$,[13] oxalic acid dihyd-

* E-mail: mohamadpour.f.7@gmail.com
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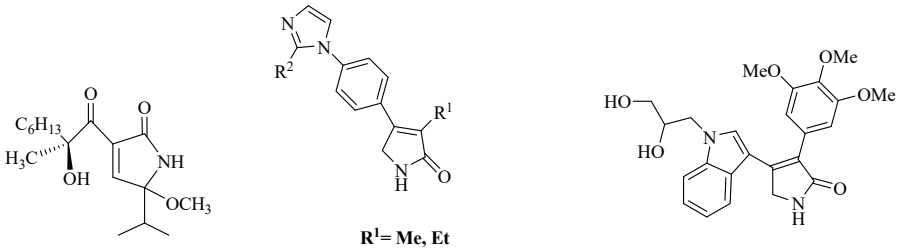
rate,[14] $ZrCl_4$,[15] 2,6-pyridinedicarboxylic acid,[16] Fe_3O_4@nano-cellulose–OPO_3H[17] and ethylenediammonium diformate (EDDF).[18] Some of these methods have limitations such as long reaction times, low yields and the use of strongly acidic conditions, high temperature, difficult work-up, toxic and expensive catalysts.



PI-091 **1,5-diydro-4-[4-(1H-imidazol-1-yl)phenol]-2H-pyrrol-2-ones** **VEGF-R inhibitor**

Fig. 1. Biologically active compounds with dihydro-2-oxypyrrole rings.

Due to our interest in the use of green catalysts[19] in multi-component reactions[20–23] and in continuation of our earlier efforts in employing green methodologies using L-glutamic acid (Fig. 2) as as catalyst,[24] herein, we report a convenient and green one-pot protocol for the facile and mild synthesis of polyfunctionalized dihydro-2-oxypyrroles. The synthesis *via* one-pot, four condensation domino reaction between aromatic/aliphatic amines, dialkyl acetylenedicarboxylates and formaldehyde, promoted by a biocatalyst *α*-amino acid, *i.e.*, glutamic acid, at room temperature proceeded with excellent yields and short reaction times.

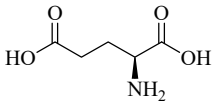


Fig. 2. Structure of L-glutamic acid.

EXPERIMENTAL

Chemicals and apparatus

Melting points of all compounds were determined using an Electro-thermal 9100 apparatus, whereas ^{1}H-NMR spectra were recorded on a Bruker DRX-300 and DRX-400 Avance instrument with $CDCl_3$ as the solvent. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies and used without further purification.

*General procedure for preparation of polyfunctionalized dihydro-2-oxypyrroles (**5a**–**s**)*

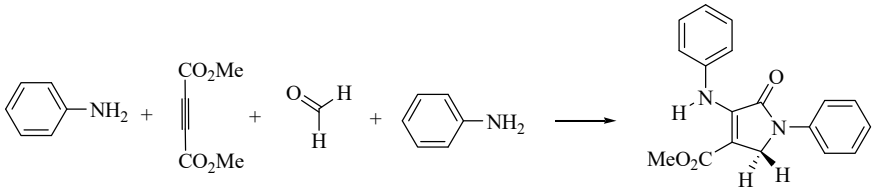
A mixture of amine (aromatic/aliphatic) **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol) was stirred in MeOH (3 mL) for 15 min. Then, amine **3** (1.0 mmol), formaldehyde (**4**, 1.5 mmol) and L-glutamic acid (0.03 g) were added, and, the reaction was stirred for an appropriate time. After completion of the reaction, monitored by thin-layer chromatography (TLC:*n*-hexane/ethyl acetate (3:1)), the mixture was filtrated and the solid was washed by ethanol (3×2 mL). The catalyst was dissolved in ethanol and removed from the reaction

mixture (**5a**–**s**). The products were characterized by comparison of the spectroscopic data (^{1}H--NMR). Corresponding data of the synthesized compounds are given as Supplementary material to this paper.

RESULTS AND DISCUSSION

In pursuit of our continued interest in the development of eco-safe, mild and facile synthetic procedures, we have decided to explore the use of glutamic acid as a green and bio-based catalyst for synthesis of polyfunctionalized dihydro-2--oxypyrroles. The glutamic acid catalyzed four-component reaction between aniline (1.0 mmol), dimethyl acetylenedicarboxylate (DMAD, 1 mmol), aniline (1.0 mmol) and formaldehyde (1.5 mmol) as a model reaction under mild conditions for the synthesis of polyfunctionalized dihydro-2-oxypyrroles was investigated. The amount of catalyst was studied with this method and in the absence of glutamic acid: a trace amount of this product was generated after 10 h (Table I, entry 1). Good yields were obtained in the presence of the catalyst. The best amount of catalyst was 20 mol % (0.03 g) (Table I, entry 5). A higher amount of the catalyst did not increase the yields products (Table I, entry 13), the results are summarized in Table I. The effect of various solvents was investigated for this protocol: H_2O, EtOH, DMF, CH_2Cl_2, CH_3CN and $CHCl_3$. Also, when the reaction was

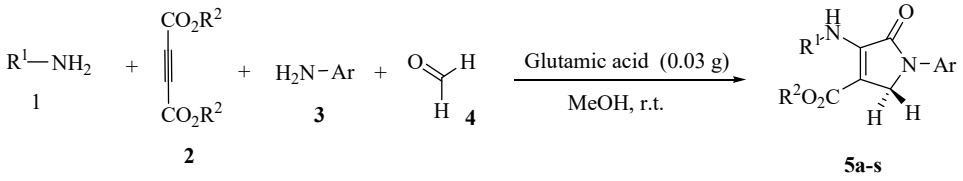
TABLE I. Optimization of the reaction condition in the presence of different amounts of glutamic acid; the reaction conditions: aniline (2 mmol), dimethyl acetylenedicarboxylate (1 mmol) and formaldehyde (1.5 mmol) and glutamic acid in various solvents at room temperature



Entry	Catalyst amount, g	Solvent	τ / h	Yield[a], %
1	Catalyst free	MeOH	10	Trace
2	0.007	MeOH	8	37
3	0.01	MeOH	6	59
4	0.02	MeOH	3.5	76
5	0.03	MeOH	2	91
6	0.03	Solvent free	5	34
7	0.03	H_2O	6	22
8	0.03	EtOH	3	61
9	0.03	DMF	5	43
10	0.03	CH_2Cl_2	8	28
11	0.03	CH_3CN	5	48
12	0.03	$CHCl_3$	8	24
13	0.04	MeOH	2	92

[a]Isolated yield

performed under solvent-free conditions the product was generated in a low yield (Table I, entry 6). Herein, the reaction occurred efficiently to afford the corresponding polyfunctionalized dihydro-2-oxypyrroles in 91 % yield when 20 mol % (0.03 g) glutamic acid was used in MeOH at room temperature (Table I, entry 5). With the optimized conditions defined, the scope of the glutamic acid catalyzed synthesis of polyfunctionalized dihydro-2-oxypyrroles was further expanded by using of amine (aromatic/aliphatic) **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol), amine **3** (1.0 mmol) and formaldehyde (**4**, 1.5 mmol) at ambient temperature (Scheme 1).



Scheme 1. Synthesis of polyfunctionalized dihydro-2-oxypyrroles.

It was found that the reaction proceeded efficiently, afforded the targeted products (**5a**–**s**) without by-products, in high yields and the results are offered in Table II.

TABLE II. Glutamic acid catalyzed synthesis of polyfunctionalized dihydro-2-oxypyrroles

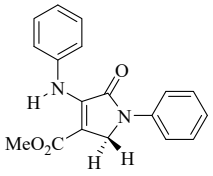
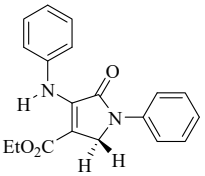
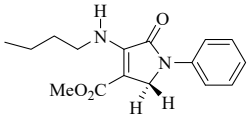
Entry	R^1	R^2	Ar	Product	τ / h	Yield[a] %	M. p., °C	
							Found	Ref.
1	Ph	Me	Ph	**5a** 	2	91	156–158	155–156[8]
2	Ph	Et	Ph	**5b** 	2	88	138–140	138–140[12]
3	n-C_4H_9	Me	Ph	**5c** 	2	89	59–61	60[8]

TABLE II. Continued

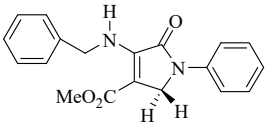
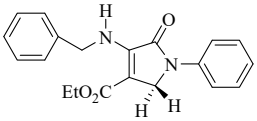
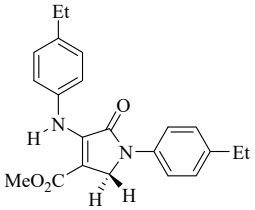
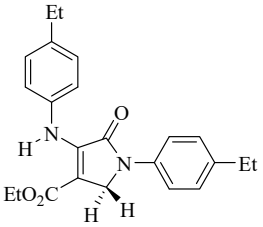
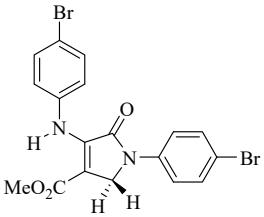
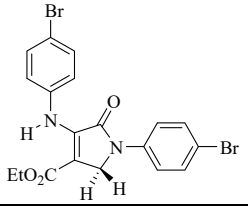
Entry	R^1	R^2	Ar	Product	τ / h	Yield[a] %	M. p., °C Found	M. p., °C Ref.
4	$PhCH_2$	Me	Ph	**5d** 	3	87	141–143	140–141[12]
5	$PhCH_2$	Et	Ph	**5e** 	3	84	131–133	130–132[12]
6	4-Et-C_6H_4	Me	4-Et-C_6H_4	**5f** 	2.5	86	125–127	124–125[17]
7	4-Et-C_6H_4	Et	4-Et-C_6H_4	**5g** 	3.5	87	102–104	102–104[17]
8	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5h** 	3	84	176–178	175–177[10]
9	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5i** 	3.5	81	171–173	169–171[12]

TABLE II. Continued

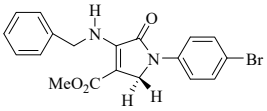
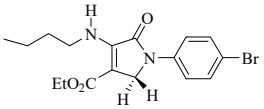
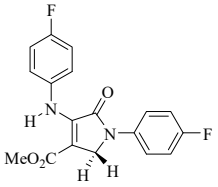
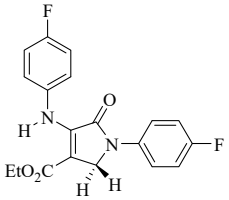
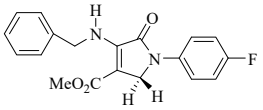
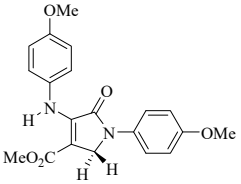
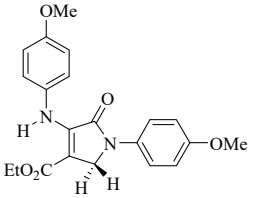
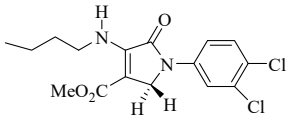
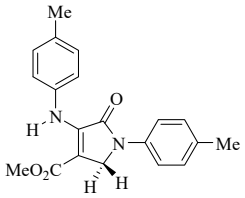
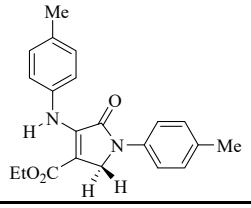
Entry	R^1	R^2	Ar	Product	τ / h	Yield[a] %	M. p., °C Found	M. p., °C Ref.
10	$PhCH_2$	Me	4-Br-C_6H_4	**5j** 	3.5	82	118–120	120–121[8]
11	n-C_4H_9	Et	4-Br-C_6H_4	**5k** 	3	85	96–98	94–96[11]
12	4-F-C_6H_4	Me	4-F-C_6H_4	**5l** 	1.5	94	161–163	163–165[9]
13	4-F-C_6H_4	Et	4-F-C_6H_4	**5m** 	1.5	91	171–172	172–174[10]
14	$PhCH_2$	Me	4-F-C_6H_4	**5n** 	2	88	168–170	166–168[11]
15	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5o** 	2.5	87	171–173	172–175[10]
16	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5p** 	3	86	153–155	152–154[11]

TABLE II. Continued

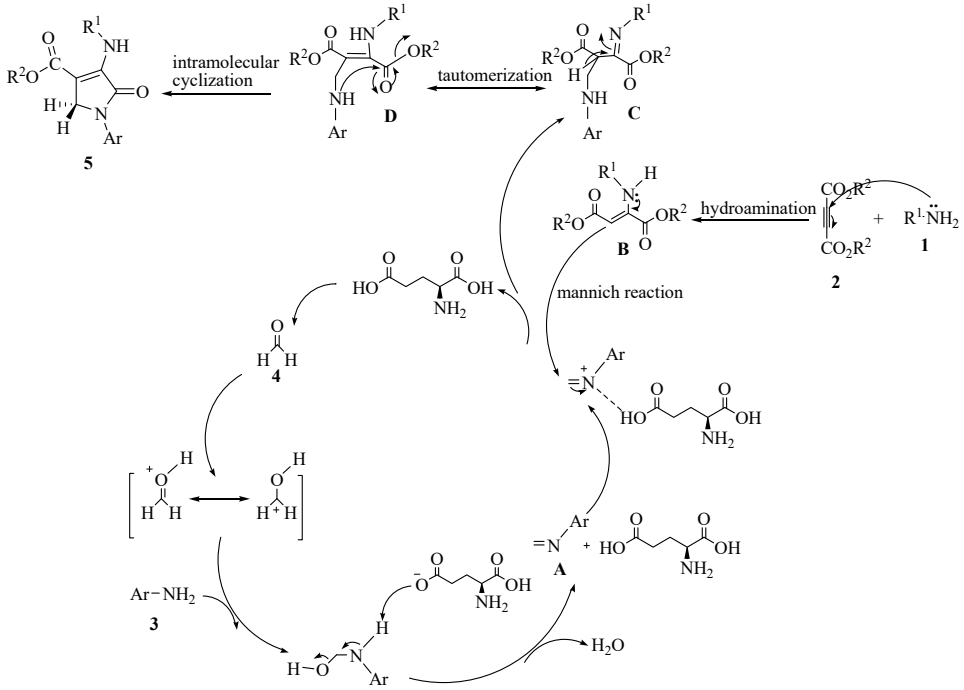
Entry	R^1	R^2	Ar	Product	τ / h	Yield[a] %	M. p., °C Found	M. p., °C Ref.
17	n-C_4H_9	Me	3,4-Cl_2-C_6H_3	**5q** 	3	83	95–97	97–99[11]
18	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5r** 	1.5	90	175–176	177–178[11]
19	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5s** 	2	88	131–133	131–132[12]

[a]Isolated yield

The proposed mechanism for the synthesis of polyfunctionalized dihydro-2--oxypyrroles is illustrated in Scheme 2. Initially, the amine **3** reacts with formaldehyde **4** in the presence of glutamic acid to form imine **A**. Also, the Michael reaction between amine **1** and dialkyl acetylenedicarboxylate **2** gives enamine **B**. Activated imine **A** undergoes a Mannich type reaction with enamine **B** to generate intermediate **C**, which converts to more stable tautomeric form **D**. The intramolecular cyclization in intermediate **D** to the corresponding polyfunctionalized dihydro-2-oxypyrroles **5** take place in the final step.

Comparison of the catalytic ability of some of the catalysts, reported in the literature, for the synthesis of polyfunctionalized dihydro-2-oxypyrroles are shown in Table III.

This study reveals that α-amino acid, glutamic acid, has shown its extraordinary potential to be an alternative green, inexpensive, biodegradable, and highly efficient biocatalyst for the synthesis of these polyfunctionalized heterocyclic compounds with excellent yields and short reaction times under ambient temperature.



Scheme 2. The proposed mechanistic route for the synthesis of polyfunctionalized dihydro-2-oxypyrroles.

TABLE III. Comparison of catalytic ability of some of the catalysts, reported in the literature, for the synthesis of polyfunctionalized dihydro-2-oxypyrroles; based on the four-component reaction of aniline, dimethyl/diethyl acetylenedicarboxylate and formaldehyde

Entry	Product	Catalyst	Conditions	τ/Yield, %
1	**5a**	I_2	MeOH, r.t.	1 h/82[8]
2	**5a**	$InCl_3$	MeOH, r.t.	3h/85[9]
3	**5a**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/88[10]
4	**5a**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81[11]
5	**5a**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6 h/91[13]
6	**5a**	$ZrCl_4$	MeOH, r.t.	4 h/84[15]
7	**5a**	EDDF	EtOH, Reflux	3 h/89[18]
8	**5a**	Glutamic acid	MeOH, r.t.	2 h/91[a]
9	**5b**	I_2	MeOH, r.t.	1 h/81[8]
10	**5b**	$InCl_3$	MeOH, r.t.	3 h/85[9]
11	**5b**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/86[10]
12	**5b**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80[11]
13	**5b**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5 h/85[13]
14	**5b**	$ZrCl_4$	MeOH, r.t.	3.5 h/83[15]
15	**5b**	EDDF	EtOH, Reflux	3.5 h/84[18]
16	**5b**	Glutamic acid	MeOH, r.t.	2 h/88[a]

[a]This work

CONCLUSIONS

In conclusion, a catalytic methodology is reported that enables the green, operationally simple and convenient synthesis of the corresponding polyfunctionalized dihydro-2-oxypyrroles, including some relevant drugs and pharmacologicaly active derivatives in the presence of biologically active α-amino acid, glutamic acid as a green and biodegradable catalyst at room temperature. Remarkable E factors, green, readily available and inexpensive biocatalyst, one-pot procedure, short reaction times, excellent yields, facile reaction profile, mild reaction conditions, economic availability of the catalyst and easy isolation procedures, without chromatographic purification steps, are the features of this methodology.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

ГЛУТАМИНСКА КИСЕЛИНА КАО ЕКОЛОШКИ БИОКАТАЛИЗАТОР У СИНТЕЗИ ПОЛИФУНКЦИОНАЛИЗОВАНИХ ДИХИДРО-2-ОКСИПИРОЛА У ЈЕДНОМ РЕАКЦИОНОМ КОРАКУ

FARZANEH MOHAMADPOUR

Young Researchers and Elite Club, Shiraz Branch, Islamic Azad University, Shiraz, Iran

Проучавана је високо прилагодљива синтеза полифункционализованих дихидро-2-оксипирола, у једном реакционом кораку, преко четири домино реакције полазећи од ароматичних/алифатичних амина,диалкил-ацетилендикарбоксилата и формалдехида. Еколошки, биодеградабилан и приступачан катализатор α-амино киселина, омогућава високу атом-економичност, једноставно руковање и обраду реакционе смеше. При синтези жељених производа реакција се одвија без хроматографских пречишћавања, опасних и токсичних катализатора уз благе реакционе услове и одличан принос.

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