FORMIC ACID AS A NATURAL GREEN AND BIO-BASED CATALYST PROMOTED FOR THE FACILE SYNTHESIS OF FUNCTIONALIZED DIHYDRO-2-OXYPYRROLES UNDER AMBIENT TEMPERATURE

Farzaneh MOHAMADPOUR[1*]

Formic acid as a natural green and bio-based catalyst employed for the eco-friendly synthesis of functionalized dihydro-2-oxypyrroles under ambient temperature with no necessity of chromatographic purification steps. Use of natural green and bio-based catalyst, good yields, mild and one-pot procedure and operational simplicity are among the other added advantages that make this approach an attractive alternative for the synthesis of these biologically active compounds.

Keywords: Functionalized dihydro-2-oxypyrroles, Formic acid, Natural green and bio-based catalyst, Environment-friendly procedure, Simple work-up

1. Introduction

Synthesis of heterocyclic compounds has attracted great interests due to their wide applicability in life and nature. The compounds with pyrrole ring systems have been known to exhibit a wide range of pharmacological and biological properties. For example these heterocyclic compounds have been used as biological and pharmaceutical properties such as human cytomegalovirus (HCMV) protease [1], CD45 protein tyrosinphosphatase [2], anti- cancer [3], they has been used as Thiomarinol A4 as antibiotic has pyrrole rings [4], many of number alkaloids with biological activities have pyrrole rings [5], and these rings have been used as UCS1025A [6], Oteromycin [7]. In addition, these rings have been used HIV integrase [8], and they have also herbicidal [9] activities.
In recent decades, a number of synthesis routes of these compounds have been reported that is including various catalysts such as $Cu(OAc)_2.H_2O$ [10], $InCl_3$ [11], I_2 [12], AcOH [13], $[n\text{-}Bu_4N][HSO_4]$ [14], $Al(H_2PO_4)_3$ [15], oxalic acid [16] and $ZrCl_4$ [17]. Some of the limitations of these methodologies are low yields, toxic organic solvents and catalyst, harsh reaction conditions and expensive materials. In recent years, the design and development of bioactive heterocyclic compounds synthesis performed through multi-component reactions (MCRs) [18] involving three or more reactants in one-pot, have attracted considerable interest since such processes improve atom economy, efficiency and convergence. Based on the

[1] Young Researchers and Elite Club, Shiraz Branch, Islamic Azad University, Shiraz, Iran, corresponding author. mohamadpour.f.7@gmail.com

above considerations and in continuation of our efforts to develop green methodologies [19-23], finally, we have reported formic acid as a natural green and bio-based [24] catalyst for the mild synthesis of functionalized dihydro-2-oxypyrroles via one-pot four-component condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature with good yields and short reaction times.

2. Experimental

General

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

General procedure for preparation of functionalized dihydro-2-oxypyrroles (5a-q)

A mixture of amine (**1**, 1.0 mmol) and dialkyl acetylenedicarboxylate (**2**, 1.0 mmol) was stirred in MeOH (3 mL) for 15 min. next, amine (**3**, 1.0 mmol) and formaldehyde **(4**, 1.5 mmol) and formic acid (15 mol %) were added and the reaction was stirred for appropriate time. After completion of the reaction (by thin layer chromatography TLC), the mixture was separated with filtration and the solid washed with ethanol (3×2 mL) with no column chromatographic separation to give pure compounds (**5a-q**). The catalyst is solvable in ethanol and was removed from the reaction mixture. Products were characterized by comparison of spectroscopic data (^{1}HNMR). Spectra data some of known products are represented below:

Methyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5a):

Yield: 88%; M.p. 175-177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (6H, s, $2CH_3$), 3.77 (3H, s, OCH_3), 4.52(2H, s, $C\underline{H}_2$-N), 7.06 (2H, d, *J*=8.4 Hz, ArH), 7.14 (2H, d, *J*=8.4 Hz, ArH), 7.21(2H, d, *J*=8.4 Hz, ArH), 7.68 (2H, d, *J*=8.8 Hz, ArH), 8.03 (1H, s, NH).

Ethyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5i):

Yield: 87%; M.p. 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J*=7.2 Hz, $CH_2\underline{CH_3}$), 2.37 (6H, s, $2CH_3$), 4.23 (2H, q, *J*=7.2 Hz, $2\underline{CH_2}CH_3$), 4.53 (2H, s, $C\underline{H}_2$-N),7.06 (2H, d, *J*=8.4 Hz, ArH), 7.14 (2H, d, *J*=8.4 Hz, ArH), 7.21 (2H, d, *J*=8.4 Hz, ArH), 7.69 (2H, d, *J*=8.4 Hz, ArH), 8.01 (1H, s, NH).

Methyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5m):
Yield: 88%; M.p. 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (3H, s, CH_3), 3.83 (6H, s, $2OCH_3$), 4.50 (2H, s, $C\underline{H}_2$-N), 6.89 (4H, d, *J*=17.6 Hz, ArH), 7.13 (1H, s, ArH) ,7.68 (1H, s, ArH), 8.03 (1H, s, NH).

Ethyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5p):
Yield: 85%; M.p. 151-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (3H, t, *J*=7.2Hz, $CH_2\underline{CH_3}$), 3.83 (6H, s, $2OCH_3$), 4.23 (2H, q, *J*=7.2 Hz, $\underline{CH_2}CH_3$), 4.50 (2H, s, $C\underline{H}_2$-N), 6.87 (2H, d, *J*=8.8 Hz, ArH), 6.93 (2H, d, *J*=8.8 Hz, ArH), 7.12 (2H, d, *J*=8.8 Hz, ArH), 7.69 (2H, d, *J*=8.8 Hz, ArH), 8.02 (1H, s, NH).

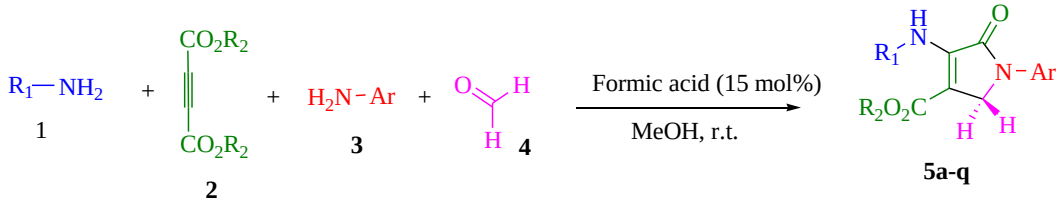
Methyl4-(4-fluoroyphenylamino)-1-(4-fluorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5q):

Yield: 89%; M.p. 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.79 (3H, s, OCH_3), 4.52 (2H, s, $C\underline{H}_2$-N), 7.04 (2H, t, *J*=8.4 Hz, ArH), 7.08-7.16 (4H, m, ArH), 7.73-7.76 (2H, m, ArH), 8.05 (1H, s, NH).

3. Result and discussions

Initially, for optimizing the reaction conditions, the one-pot four-component reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was tested as a model reaction at ambient temperature (Table 1). A control experiment revealed that in the absence of the catalyst, a trace amount of product was detected after 10 h which indicated that the catalyst's presence is necessary for this reaction (Table 1, entry 1). To further optimize reaction conditions, we investigated the effect of the loading amount of formic acid on the model reaction in methanol (Table 1). The optimum yield of product **5e** (82%) was obtained in the presence of 15 mol% of formic acid (Table 1, entry 4). By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower yield (Table 1, entry 2). While increasing the catalyst loading to 20 mol% has no significant effect on the product yield (Table 1, entry 12). Subsequently, a survey of solvents showed methanol to be the best choice (Table 1, entry 4). Low yields were obtained when the model reaction was performed in DMF, EtOH, H_2O, CH_3CN, CH_2Cl_2 and $CHCl_3$ (Table 1). Also, when the reaction was performed under solvent-free conditions, the product was generated in a low yield (Table 1, entry 10). Finally, we have reported synthesis of functionalized dihydro-2-oxypyrroles *via* one-pot, four condensation domino reaction between aromatic/aliphatic amines **(1** and **3)**, dialkyl acetylenedicarboxylate **2** and formaldehyde **4** in the presence of formic acid as a green and readily available

catalyst under mild reaction conditions (Scheme 1) in good yields, and the results are summarized in Table 2.



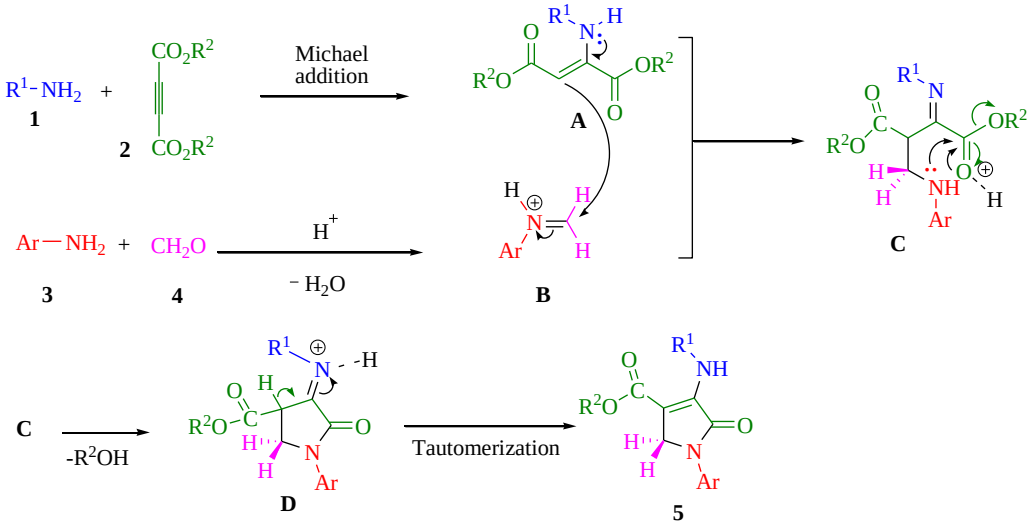
Scheme 1. Synthesis of functionalized dihydro-2-oxypyrroles.

Table 1

Optimization of the reaction condition in the presence of different amounts of formic acid and different solvents on the synthesis of 5e [a]

Entry	Formic acid (mol %)	Solvent	Time (h)	Isolated Yields (%)
1	Catalyst free	MeOH	10	trace
2	5	MeOH	7	44
3	10	MeOH	5	63
4	**15**	**MeOH**	**4**	**82**
5	15	DMF	6	48
6	15	EtOH	4	61
7	15	H_2O	6	22
8	15	CH_3CN	6	51
9	15	CH_2Cl_2	8	11
10	15	Solvent free	6	47
11	15	$CHCl_3$	8	16
12	20	MeOH	4	83

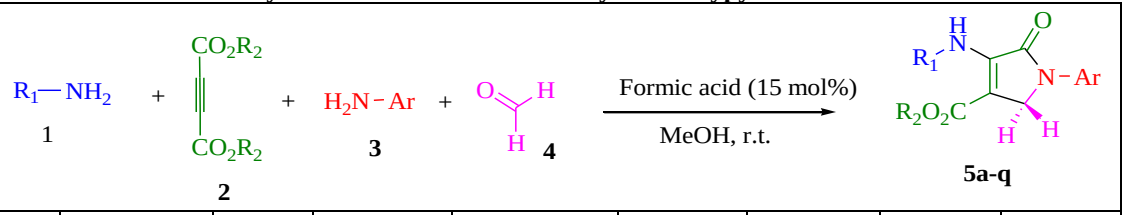
[a] Reaction conditions: aniline (2.0 mmol), dimethyl acetylenedicarboxylate (1.0 mmol) and formaldehyde (1.5 mmol) and catalyst in various solvents at room temperature.



Scheme 2. Proposed mechanistic route for the synthesis of functionalized dihydro-2-oxypyrroles

Table 2

Synthesis of functionalized dihydro-2-oxypyrroles



Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	M.p. ˚C	Lit. M.p. ˚C
1	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5a**	3.5	88	175-177	177-178[16]
2	n-C_4H_9	Me	Ph	**5b**	3	82	60-62	60[16]
3	$PhCH_2$	Me	4-Cl-C_6H_4	**5c**	4.5	79	145-147	147-148[16]
4	$PhCH_2$	Me	4-Br-C_6H_4	**5d**	5	76	119-121	120-121[16]
5	Ph	Me	Ph	**5e**	4	82	155-157	155-156[16]
6	$PhCH_2$	Et	Ph	**5f**	5	81	131-133	130-132[17]
7	$PhCH_2$	Me	Ph	**5g**	4.5	82	139-141	140-141[17]
8	Ph	Et	Ph	**5h**	4	83	138-140	138-140[17]
9	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5i**	3.5	87	130-132	131-132[17]
10	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5j**	4	74	171-173	171-173[18]
11	4-F-C_6H_4	Et	4-F-C_6H_4	**5k**	3	86	173-175	172-174[18]
12	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5l**	4	72	166-168	168-170[18]
13	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5m**	4	88	171-173	172-175[18]
14	$PhCH_2$	Me	4-F-C_6H_4	**5n**	4.5	84	168-170	166-168[19]
15	n-C_4H_9	Et	4-Br-C_6H_4	**5o**	4	85	92-94	94-96[19]
16	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5p**	4.5	85	151-153	152-154[19]
17	4-F-C_6H_4	Me	4-F-C_6H_4	**5q**	3	89	165-167	163-165[20]

[a] Isolated yield.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of functionalized dihydro-2-oxypyrroles are shown in Table 3.

Table 3

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of functionalized dihydro-2-oxypyrroles.

Entry	Compound	Catalyst	Conditions	Time/Yield (%)	References
1	**5e**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6h/91	[10]
2	**5e**	$InCl_3$	MeOH, r.t.	3h/85	[11]
3	**5e**	I_2	MeOH, r.t.	1 h/82	[12]
4	**5e**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/88	[14]
5	**5e**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[15]
6	**5e**	$ZrCl_4$	MeOH, r.t.	4 h/84	[17]
7	**5e**	Formic acid	MeOH, r.t.	4 h/82	This work
8	**5h**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5h/85	[10]
9	**5h**	$InCl_3$	MeOH, r.t.	3h/85	[11]
10	**5h**	I_2	MeOH, r.t.	1 h/81	[12]
11	**5h**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/86	[14]
12	**5h**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[15]
13	**5h**	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[17]
14	**5h**	Formic acid	MeOH, r.t.	4 h/83	This work

This study reveals that formic acid has shown its extraordinary potential to be an alternative natural green, bio-based, low-cost and available readily catalyst for the one-pot simple synthesis of these biologically active heterocyclic compounds, in addition good yields and short reaction times are the notable advantages this present methodology.

4. Conclusions

In summary, highly efficient, facile and mild synthetic route for preparation of functionalized dihydro-2-oxypyrroles catalyzed by formic acid as a natural green, bio-based and easily available catalyst under ambient temperature was studied. This method has presented one-pot approach for the synthesis of these biologically active compounds with many merits in comparison with other reported results including natural green and low-cost catalyst, one-pot procedure, short reaction times, good yields, facile reaction profile and simple work-up.

Acknowledgments

We gratefully acknowledge financial support from the Research Council of the Young Researchers and Elite Club of Islamic Azad University of Shiraz.

R E F E R E N C E S

[1]. *A.D. Borthwick, A.J. Crame, P.F. Ertl, A.M. Exall, T.M. Haley, G.J. Hart, A.M. Mason, M.K. Pennell, O.M.P. Singh, G.G. Weingarten, J.M. Woolven*, "Design and synthesis of pyrrolidine-5,5-trans-lactams (5-oxohexahydropyrrolo[3,2-b]pyrroles) as novel mechanism-based inhibitors of human cytomegalovirus protease. 2. Potency and chirality", Journal of Medicinal Chemistry, **vol. 45**, no. 1, 2002, pp. 1-18.

[2]. *W.R. Li, S.T. Lin, N.M. Hsu, M.S. Chern*, "Efficient total synthesis of pulchellalactam, a CD45 protein tyrosine phosphatase inhibitor", Journal of Organic Chemistry, **vol. 67**, no. 14, 2002, pp. 4702-4706.

[3]. *Y.L. Lampe, R.G. Chou, R.G. Hanna, S.V. DiMeo, P.W. Erhardt, A.A. Hagedorn, W.R. Ingebretsen, E. Cantor*, "(Imidazolylphenyl) pyrrol- 2- one inhibitors of cardiac cAMPphosphodiesterase", Journal of Medicinal Chemistry, **vol. 36**, no. 8, 1993, pp. 1041-1047.

[4]. *H. Shiozawa, S. Takahashi*, "Configurational studies on thiomarinol", Journal of Antibiotics, **vol. 47**, no.7, 1994, pp. 851-853.

[5]. *Y. Chen, D.X. Zeng, N. Xie, Y.Z. Dang*, "Study on photochromism of diarylethenes with a 2, 5-dihydropyrrole bridging unit: a convenient preparation of 3, 4-diarylpyrroles from 3,4-diaryl-2,5-dihydropyrroles", Journal of Organic Chemistry, **vol. 70**, no. 13, 2005, pp. 5001-5005.

[6]. *C. Grunwald, C. Rundfeldt, H.J. Lankau, T. Arnold, N. Hofgen, R. Dost, U. Egerland, H.J. Hofmann, K. Unverferth*, "Synthesis, pharmacology, and structure− activity relationships of novel Imidazolones and Pyrrolones as modulators of GABAA receptors", Journal of Medicinal Chemistry, **vol. 49**, no. 6, 2006, pp. 1855-1866.

[7]. *S.B. Singh, M.A. Goetz, E.T. Jones, G.F. Billes, R.A. Giacobbe, L. Herranz, S. Stevens Miles, D.L. Williams, S. Stevens-Miles, D.L. Williams*, "a novel antagonist of endothelin receptor", Journal of Organic Chemistry, **vol. 60**, no. 21, 1995, pp. 7040-7042.

[8]. *T. Kawasuji, M. Fuji, T. Yoshinaga, A. Sato, T. Fujiwara, R. Kiyama*, "3-Hydroxy-1, 5-dihydro-pyrrol-2-one derivatives as advanced inhibitors of HIV integrase", Bioorganic & Medicinal Chemistry, **vol. 15**, no. 16, 2007, pp. 5487-5492.

[9]. *L. Zhang, Y. Tan, N.X. Wang, Q.Y. Wu, Z. Xi, G.F. Yang*, "Design, syntheses and 3D-QSAR studies of novel N-phenyl pyrrolidin-2-ones and N-phenyl-1H-pyrrol-2-ones as protoporphyrinogen oxidase inhibitors", Bioorganic & Medicinal Chemistry, **vol. 18**, no. 22, 2010, pp. 7948-7956.

[10]. *L. Lv, S. Zheng, X. Cai, Z. Chen, Q. Zhu, S. Liu*, "Development of Four-Component Synthesis of Tetra- and Pentasubstituted Polyfunctional Dihydropyrroles: Free Permutation and Combination of Aromatic and Aliphatic Amines", ACS Combinatorial Science, **vol. 15**, no. 4, 2013, pp. 183-192.

[11]. *S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri*, "A simple and efficient approach to one-pot synthesis of mono- and bis-N-aryl-3-aminodihidropyrrol-2-one-4-carboxylate catalyzed by $InCl_3$", Chinese Chemical Letters, **vol. 25**, no. 1, 2014, pp. 58-60.

[12]. *A.T. Khan, A. Ghosh, M. Musawwer Khan*, "One-pot four-component domino reaction for the synthesis of substituted dihydro-2-oxypyrrole catalyzed by molecular iodine", Tetrahedron Letters, **vol. 53**, no. 21, 2012, pp. 2622-2626.

[13]. *Q. Zhu, H. Jiang, J. Li, S. Liu, C. Xia, M. Zhang*, "Concise and versatile multicomponent synthesis of multisubstituted polyfunctional dihydropyrroles", Journal of Combinatorial Chemistry, **vol. 11**, no. 4, 2009, pp. 685-696.

[14]. *S.S. Sajadikhah, N. Hazeri*, "Coupling of amines, dialkyl acetylenedicarboxylaes and formaldehyde promoted by $[n\text{-}Bu_4N][HSO_4]$: an efficient synthesis of highly functionalized dihydro-2-oxopyrrols and bis-dihydro-2-oxopyrroles", Research on Chemical Intermediates, **vol. 40**, no. 2, 2014, pp. 737-748.

[15]. *S.S. Sajadikhah, N. Hazeri, M.T, Maghsoodlou, S.M. Habibi Khorasani, A. Beigbabaei, A.C. Willis*, "$Al(H_2PO_4)_3$ as an efficient and reusable catalyst for the multi-component synthesis of highly functionalized piperidines and dihydro-2-oxypyrroles", Journal of the Iranian Chemical Society, **vol. 10**, no. 5, 2013, pp. 863-871.

[16]. *S.S. Sajadikhah, N. Hazeri, M.T. Maghsoodlou*, "A one-pot multi-component synthesis of N-aryl-3-aminodihydropyrrl-2-one-4-carboxylate catalyzed by oxalic acid dehydrate", Journal of Chemical Research, **vol. 37**, no. 1, 2013, pp. 40-42.

[17]. *S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, S. Mohamadian-Souri*, "$ZrCl_4$ as an efficient catalyst for one-pot four-component synthesis of polysubstituted dihydropyrrol-2-ones", Research on Chemical Intermediates, **vol. 42**, no. 4, 2016, pp. 2805-2814.

[18]. *A. Strecker*, "Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper", Liebigs Annalen der Chemie, **vol. 75**, no. 1, 1850, pp. 27-45.

[19]. *F. Mohamadpour*, "ASCORBIC ACID AS A NATURAL GREEN, HIGHLY EFFICIENT AND ECONOMICAL CATALYST PROMOTED ONE-POT FACILE SYNTHESIS OF 12-ARYL-TETRAHYDROBENZO[α]XANTHENE-11-ONES, 1,8-DIOXO-OCTAHYDROXANTHENES AND 14-ARYL-14*H*-DIBENZO[α,j]XANTHENES UNDER SOLVENT-FREE CONDITIONS", Scientific Bulletin, Series B: Chemistry and Materials, **vol. 80**, no. 2, 2018, pp. 101-116.

[20]. *F. Mohamadpour*, "Green and Convenient One-Pot Access to Polyfunctionalized Piperidine Scaffolds *via* Glutamic Acid Catalyzed Knoevenagel-Intramolecular [4+2] aza-Diels-Alder Imin-Based Multi-Component Reaction Under Ambient Temperature", POLYCYCLIC AROMATIC COMPOUNDS, 2018, doi: 10.1080/10406638.2018.1472111.

[21]. *F. Mohamadpour, M. Lashkari*, "Three-component reaction of *β*-keto esters, aromatic aldehydes and urea/thiourea promoted by caffeine: A green and natural, biodegradable catalyst for eco-safe Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/tiones derivatives under solvent-free conditions", Journal of the Serbian Chemical Society, **vol. 83**, no. 6, 2018, pp. 673-684.

[22]. *F. Mohamadpour, M.T. Maghsoodlou, R. Heydari, M. Lashkari*, "Saccharin: a green, economical and efficient catalyst for the one-pot, multi-component synthesis of 3,4‐dihydropyrimidin-2-(1H)-one derivatives and 1H-pyrazolo [1,2‐b] phthalazine-5,10-dione derivatives and substituted dihydro-2-oxypyrrole", Journal of the Iranian Chemical Society, **vol. 13**, no. 8, 2016, pp. 1549-1560.

[23]. *F. Mohamadpour, M.T. Maghsoodlou, R. Heydari, M. Lashkari*, "Tartaric Acid: A Naturally Green and Efficient Di-Functional Brønsted Acid Catalyst for the One-Pot Four-Component Synthesis of Polysubstituted Dihydropyrrol-2-Ones at Ambient Temperature", Iranian Journal of Science and Technology, Transactions A: Science, **vol. 41**, no. 3, 2016, pp. 843-849.

[24]. *J.L. Thompson JL, M. Hinton*, "Antibacterial activity of formic and propionic acids in the diet of hens on Salmonellas in the crop", British Poultry Science, **vol. 38**, no. 1, 1997, pp. 59-65.