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Citric acid as a green and naturally biodegradable catalyst promoted convenient synthesis of polysubstituted dihydro-2-oxypyrrole derivatives via four-condensation reaction of dialkylacetylenedicarboxylate, formaldehyde and amines

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ABSTRACT
Citric acid is found to be a green and naturally biodegradable catalyst for one-pot, four-condensation of dialkylacetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) to afford the corresponding polysubstituted dihydro-2-oxypyrrole derivatives under ambient temperature. The remarkable features of this one-pot procedure are green and low-cost catalyst, high yields, short reaction times, simplicity of operation and work-up procedures, the availability and easy to handle of this solid acid catalyst, avoidance of hazardous or toxic catalyst and mild reaction conditions.
Keywords: *Polysubstituted dihydro-2-oxypyrroles, Citric acid, Green and naturally biodegradable catalyst, Mild reaction conditions*.

1. INTRODUCTION
Citric acid exists in greater than trace amounts in a variety of fruits and vegetables, most notably citrus fruits. Lemons and limes have particularly high concentrations of the acid; it can constitute as much as 8% of the dry weight of these fruits (about 47 g/L in the juices) [1]. Citric acid was first isolated by KarlsScheels in 1874, in England, from the lemon juice imported from Italy. Citric acid is the most important acid produced in tonnage and is extensively used in food and pharmaceutical industries. Citric acid can be used as a pH-regulating additive in granules and the tablet matrix in enteric-coated formulations for colon-specific drug delivery [2]. In addition to, single-use citric acid sachets have been used as an inducement to get heroin users to exchange their dirty needles for clean needles in an attempt to decrease the spread of HIV and hepatitis [3].Synthesis of the pyrrole rings has attracted great interests due to biological and pharmaceutical properties. They have been used as human cytomegalovirus(HCMV) protease [4], CD45 protein tyrosinphosphatase [5], anti-cancer [6], also, Thiomarinol A4 as antibiotic has pyrrole rings [7], many of number alkaloids with biological activities have pyrrole rings [8], and these rings have been used as UCS1025A [9], Oteromycin [10]. In addition, these rings have been used HIV integrase [11], and they have also herbicidal [12] activities. Some of them with biological properties have been shown in Figure 1.
In recent decades, a number of methodologies for preparation of these compounds have been reported that is including various catalysts such as $Cu(OAc)_2.H_2O$ [13], $InCl_3$ [14], I_2 [15], AcOH [16], $[n\text{-}Bu_4N][HSO_4]$ [17], $Al(H_2PO_4)_3$ [18], oxalic acid [19], $ZrCl_4$ [20], ethylenediammoniumdiformate (EDDF) [21], Fe_3O_4@nano-cellulose–OPO_3H [22], $BiFeO_3$ nanoparticles [23], nano-Fe_3O_4@SiO_2/$SnCl_4$ [24], $TiCl_4$/nano-sawdust [25], grapheneoxide [26], $CoFe_2O_4$@SiO_2@IRMOF-3 [27], caffeine [28], glutamic acid [29], $ZnCl_2$ [30] and $Mn(NO_3)_2.4H_2O$ [31]. Some of these methodologies have limitations such as difficult work-up, toxic and expensive catalysts, low yields, use of strongly acidic conditions, long time reactions and high temperature. Thus, as part of our ongoing research program on the development of efficient and environmentally friendly methodologies [32-34], herein, we report a convenient, one-pot and mild procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles in the presence of citric acid as a green and readily available catalyst via a one-pot four-condensation of dialkylacetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at ambient temperature. The advantages of citric acid as a mild and green acidic catalyst in organic synthesis are environmental friendly, highly efficient, inexpensive and non-toxic.

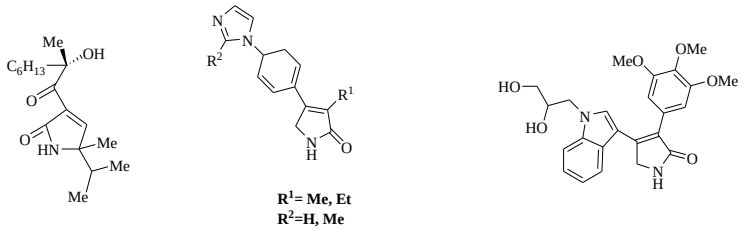


Figure 1. Biologically active compounds with dihydro-2-oxypyrrole rings.

2. MATERIALS AND METHODS
General.
Melting points all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ^1H 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 polysubstituted dihydro-2-oxypyrroles (5a-u). A mixture of amine **1** (1.0 mmol) and dialkylacetylenedicarboxylate**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 citric 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-u**). 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 the known products are represented below:

Methyl4-(4-ethylphenylamino)-1-(4-ethylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (Table 1, entry 9):

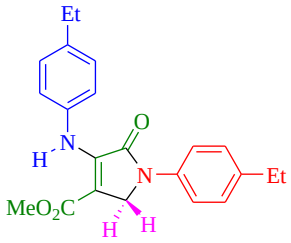


Figure 2. Methyl4-(4-ethylphenylamino)-1-(4-ethylphenyl)-2,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate

Yield: 80%; M.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (6H, t, *J*=2.4 Hz, $2CH_2CH_3$), 2.67 (4H, q, *J*=7.2 Hz, $2CH_2CH_3$), 3.76 (3H, s, $2OCH_3$), 4.53 (2H, s, CH_2-N),7.09 (2H, d, *J*=8.4 Hz, ArH), 7.17 (2H, d, *J*=8.4 Hz, ArH), 7.24 (2H, d, *J*=8.8 Hz, ArH),7.70 (2H, d, *J*=8.8 Hz, ArH), 8.05(1H, s, NH).

Ethyl 1-(4-bromophenyl)-3-(butylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate(Table 1, entry 14):

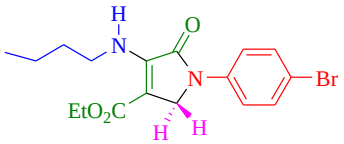


Figure 3. Ethyl 1-(4-bromophenyl)-3-(butylamino)-2,5-dihydro-2-oxo-1*H*-pyrrole-4-carboxylate

Yield: 76%; M.p. 95-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 0.97 (3H, t, *J* = 7.2 Hz, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 1.43 (2H, sextet, *J* = 7.6 Hz, CH_2), 1.61 (2H, quintet, *J* = 7.6 Hz, CH_2), 3.87 (2H, t, *J* = 7.2 Hz, CH_2-NH), 4.28 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 4.40 (2H, s, CH_2-N), 6.72 (1H, br s, NH), 7.52 (2H, d, *J* = 8.8 Hz, ArH), 7.70 (2H, d, *J* = 8.8 Hz, ArH).

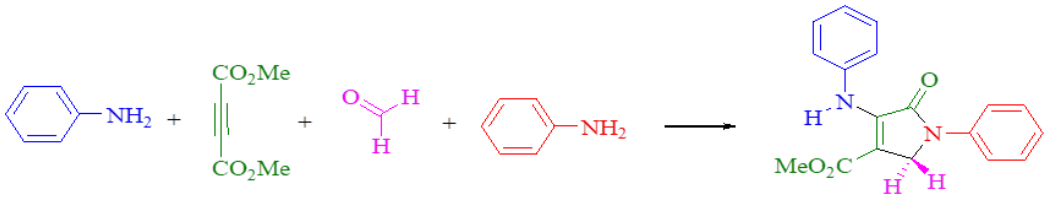


Figure 4. Methyl 1-phenyl-3-(phenylamino)-2,5-dihydro-2-oxo-1*H*pyrrole-4-carboxylate (5f)

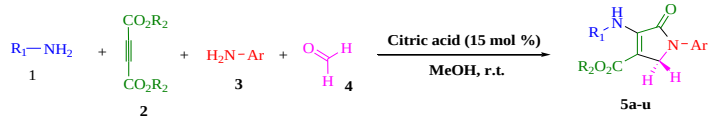
Table 1. Optimization of the reaction condition in the presence of different amounts of citric acid and different solvents on the synthesis of 5f [a]

Entry	Citric acid (mol %)	Solvent	Time, h	Isolated Yields (%)
1	Catalyst free	MeOH	10	**trace**
2	5	MeOH	6	**38**
3	10	MeOH	4	**65**
4	**15**	**MeOH**	**3**	**84**
5	15	Solvent free	6	**40**
6	15	EtOH	4	**72**
7	15	H_2O	6	**21**
8	15	CH_2Cl_2	7	**25**
9	15	$CHCl_3$	7	**29**
10	15	CH_3CN	5	**52**
11	15	DMF	5	**46**
12	20	MeOH	3	**85**

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

3. RESULTS

The generality of this four-condensation reaction was studied under optimized conditions and the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde (Figure 4) was investigation as a model reaction and then the effect of different amount of catalyst in MeOH as solvent was studied in this protocol and in the absence of catalyst, a trace amount of this product was detected after 10 h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol % (Table 1, entry 4). The higher amount of catalyst did not increase the yields products (Table 1, entry 12) and the results are summarized in Table 1. Also, the effect of various solvents was investigated for this protocol EtOH, H_2O, CH_2Cl_2, $CHCl_3$, CH_3CN and DMF among these solvents, MeOH was found to be the best solvent for this methodology (Table 1, entry 4). Finally, a convenient, expedient and efficient procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles was described via one-pot four-condensation of (aromatic or aliphatic **1** and **3**), dialkylacetylenedicarboxylate**2** and formaldehyde **4** under ambient temperature in the presence of citric acid (Scheme 1) and the results are summarized in Table 2.



R^1 = n-C_4H_9, 4-OMe-C_6H_4, $PhCH_2$, C_6H_5, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-Br-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4.

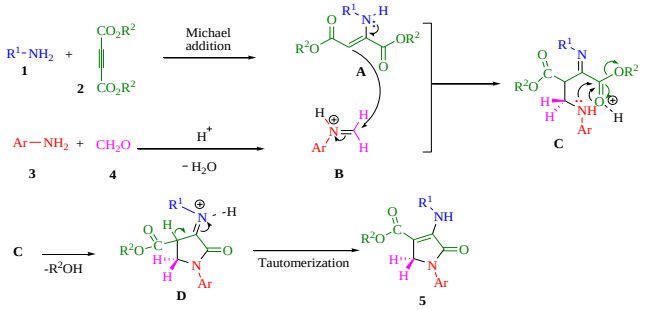
R^2 = CH_3, C_2H_5.

Ar = 4-Cl-C_6H_4, 3, 4-Cl_2-C_6H_3, 4-OMe-C_6H_4, C_6H_5, 4-F-C_6H_4, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-Br-C_6H_4.

Scheme1. Synthesis of polysubstituted dihydro-2-oxypyrroles.

Proposed mechanism for the synthesis of functionalized dihydro-2-oxypyrrole derivatives in the presence of citric acid are shown in scheme 2. Firstly, the reaction of amine **1** with dialkylacetylenedicarboxylate**2** lead to dialkyl 2-(alkyl/arylamino) fumarate **A**. Secondly, condensation between amine **3** and formaldehyde **4** in the present of citric acid produce imine **B**. Dialkyl 2-(alkyl/arylamino) fumarate **A** possesses an enamine character and, thus, can readily react with imine **B** to in the present of citric acid generate intermediate **C**. Cyclization reaction of intermediate **C** lead to intermediate **D**, that in the final step tautomerizes to the corresponding functionalized dihydro-2-oxypyrroles **5**.

Also, comparison of catalytic ability some of catalysts reported in the literature for the synthesis of polysubstituted dihydro-2-oxypyrroles are shown in Table 3. This study reveals that citric acidhas shown its extraordinary potential to be an alternative natural, green, readily available, mildly acidic and highly efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds, in addition, high yields and short reaction times are the notable advantages this present methodology.



Scheme 2. Proposed mechanistic route for the synthesis of polysubstituted dihydro-2-oxypyrrole derivatives.

Table 2. Synthesis of dihydro-2-oxypyrrole derivatives.

Entry	R^1	R^2	Ar	Product	Time,h	Isolated yield, %	M.p. °C	Lit. M.p. °C
1	n-C_4H_9	Me	4-Cl-C_6H_4	**5a**	3	83	91-93	**91-93**[21]
2	n-C_4H_9	Me	3,4-Cl_2-C_6H_3	**5b**	3.5	76	99-101	**97-99**[18]
3	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5c**	3	87	171-173	**172-175**[17]
4	n-C_4H_9	Me	Ph	**5d**	2.5	89	60-62	**60**[15]
5	$PhCH_2$	Me	Ph	**5e**	3.5	82	138-140	**140-141**[16]
6	Ph	Me	Ph	**5f**	3	84	155-157	**155-156**[15]
7	n-C_4H_9	Me	4-F-C_6H_4	**5g**	2	88	80-82	**81-83**[22]
8	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5h**	3	85	175-177	**177-178**[15]
9	4-Et-C_6H_4	Me	4-Et-C_6H_4	**5i**	3.5	80	124-126	**124-125**[22]
10	$PhCH_2$	Me	4-F-C_6H_4	**5j**	3	85	168-170	**166-168**[18]
11	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5k**	4	81	175-177	**175-177**[17]
12	4-F-C_6H_4	Me	4-F-C_6H_4	**5l**	2	90	165-167	**163-165**[19]
13	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5m**	3.5	79	170-172	**171-173**[17]
14	n-C_4H_9	Et	4-Br-C_6H_4	**5n**	4	76	95-97	**94-96**[18]
15	Ph	Et	Ph	**5o**	3	85	136-138	**138-140**[16]
16	4-F-C_6H_4	Et	4-F-C_6H_4	**5p**	2	92	174-176	**172-174**[17]
17	$PhCH_2$	Et	Ph	**5q**	2.5	78	131-133	**130-132**[16]
18	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5r**	3.5	83	129-131	**131-132**[16]
19	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5s**	4	75	170-172	**169-171**[16]
20	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5t**	4	76	168-169	**168-170**[17]
21	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5u**	3.5	84	151-153	**152-154**[18]

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

Entry	Compound	Catalyst	Conditions	Time/Yield (%)	References
1	**5a**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6h/91	[13]
2	**5a**	$InCl_3$	MeOH, r.t.	3h/85	[14]
3	**5a**	I_2	MeOH, r.t.	1 h/82	[15]
4	**5a**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/88	[17]
5	**5a**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[18]
6	**5a**	$ZrCl_4$	MeOH, r.t.	4 h/84	[20]
7	**5a**	EDDF	EtOH, Reflux	3 h/89	[21]
8	**5a**	Citric acid	MeOH, r.t.	3 h/84	This work
9	**5b**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5h/85	[13]
10	**5b**	$InCl_3$	MeOH, r.t.	3h/85	[14]
11	**5b**	I_2	MeOH, r.t.	1 h/81	[15]
12	**5b**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/86	[17]
13	**5b**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[18]
14	**5b**	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[20]
15	**5b**	EDDF	EtOH, Reflux	3.5 h/84	[21]
16	**5b**	Citric acid	MeOH, r.t.	3 h/85	This work

4. CONCLUSIONS

In summary, the use of citric acid as a green and naturally biodegradable catalyst for facile preparation of polysubstituted dihydro-2-oxypyrrole derivatives *via* one-pot four-condensation reaction of dialkylacetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at ambient temperature is studied. The use of green, readily available, easy to handle, non-toxic and inexpensive catalyst, high yields, short reaction times, simple work-up with no necessity of chromatographic purification steps provides a sustainable procedure compared to conventional methods.

5. REFERENCES

1. Penniston, K.L.; Nakada, S.Y.; Holmes, R.P.;Assimos, D.G.Quantitative Assessment of Citric Acid in Lemon Juice, Lime Juice, and Commercially-Available Fruit Juice Products. *Journal of Endourology* **2008**, *22*, *567*-570, https://doi.org/10.1089/end.2007.0304.
2. Nykänen, P.; Sten, T.; Jürjenson, H.; Veski,P.; Marvola, M. Citric acid as a pH-regulating additive in granules and the tablet matrix in enteric-coated formulations for colon-specific drug delivery. *Pharmazi e***2004**, *59*, 268-273.
3. Matheson, C.; Anthony, G.B.; Bond, C.; Rossi, M.K. Assessing and prioritizing the preferences of injecting drug users in needle and syringe exchange service development. *Journal of Public Health* **2008**, *30*, 133-138, https://doi.org/10.1093/pubmed/fdn030.
4. Borthwick, A.D.; Crame, A.J.; Ertl, P.F.; Exall, A.M.; Haley, T.M.; Hart, G.J.; Mason, A.M.; Pennell, M.K.; Singh, O.M.P.; Weingarten, G.G.; Woolven, J.M. 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* **2002**, *45*, 1-18, https://doi.org/10.1021/jm0102203.
5. Li, W.R.; Lin, S.T.; Hsu, N.M.; Chern, M.S. Efficient total synthesis of pulchellalactam, a CD45 protein tyrosine phosphatase inhibitor. *Journal of Organic Chemistry* **2002**, *67*, 4702-4706, https://doi.org/10.1021/jo010828j.
6. Lampe, Y.L.; Chou, R.G.; Hanna, R.G.; DiMeo, S.V.; Erhardt, P.W.; Hagedorn, A.A.; Ingebretsen, W.R.; Cantor, E. (Imidazolylphenyl) pyrrol- 2- one inhibitors of cardiac cAMPphosphodiesterase. *Journal of Medicinal Chemistry* **1993**, *36*, 1041-1047, https://doi.org/10.1021/jm00060a012.
7. Shiozawa, H.; Takahashi, S. Configurational studies on thiomarinol. *Journal of Antibiotics* **1994**, *47*, 851-853, https://doi.org/10.7164/antibiotics.47.851.
8. Chen, Y.; Zeng, D.X.; Xie, N.; Dang, Y.Z. 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* **2005**, *70*, 5001-5005, https://doi.org/10.1021/jo050236r.
9. Grunwald, C.; Rundfeldt, C.; Lankau, H.J.; Arnold, T.; Hofgen, N.; Dost, R.; Egerland, U.; Hofmann, H.J.; Unverferth, K. Synthesis, pharmacology, and structure-activity relationships of novel Imidazolones and Pyrrolones as modulators of GABAA receptors. *Journal of Medicinal Chemistry* **2006**, *49*, 1855-1866, https://doi.org/10.1021/jm0509400.
10. Singh, S.B.; Goetz, M.A.; Jones, E.T.; Billes, G.F.; Giacobbe, R.A.; Herranz, L.; Stevens Miles, S.; Williams, D.L.; Stevens-Miles, S.; Williams, D.L. a novel antagonist of endothelin receptor. *Journal of Organic Chemistry* **1995**, *60*, 7040-7042, https://doi.org/10.1021/jo00126a071.
11. Kawasuji, T.; Fuji, M.; Yoshinaga, T.; Sato, A.; Fujiwara, T.; Kiyama, R. 3-Hydroxy-1, 5-dihydro-pyrrol-2-one derivatives as advanced inhibitors of HIV integrase. *Bioorganic & Medicinal Chemistry* **2007**, *15*, 5487-5492, https://doi.org/10.1016/j.bmc.2007.05.052.
12. Zhang, L.; Tan, Y.; Wang, N.X.; Wu, Q.Y.; Xi, Z.; Yang, G.F. 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* **2010**, *18*, 7948-7956, https://doi.org/10.1016/j.bmc.2010.09.036.
13. Lv, L.; Zheng, S.; Cai, X.; Chen, Z.; Zhu, Q.; Liu, S. Development of Four-Component Synthesis of Tetra- and PentasubstitutedPolyfunctionalDihydropyrroles: Free Permutation and Combination of Aromatic and Aliphatic Amines. *ACS Combinatorial Science* **2013**, *15*, 183-192, **https://doi.org**/10.1021/co300148c.
14. Sajadikhah, S.S.; Maghsoodlou, M.T.; Hazeri, N. 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* **2014**, *25*, 58-60, http://dx.doi.org/10.1016%2Fj.cclet.2013.10.010.

15. Khan, A.T.; Ghosh, A.; Khan, M. One-pot four-component domino reaction for the synthesis of substituted dihydro-2-oxypyrrole catalyzed by molecular iodine. *Tetrahedron Letters* **2012**, *53*, 2622-2626, https://doi.org/10.1016/j.tetlet.2012.03.046.
16. Zhu, Q.; Jiang, H.; Li, J.; Liu, S.; Xia, C.; Zhang, M. Concise and versatile multicomponent synthesis of multisubstitutedpolyfunctionaldihydropyrroles. *Journal of Combinatorial Chemistry* **2009**, *11*, 685-696, https://doi.org/10.1021/cc900046f.
17. Sajadikhah, S.S.; Hazeri, N. Coupling of amines, dialkylacetylenedicarboxylaes and formaldehyde promoted by [n-Bu_4N][HSO_4]: an efficient synthesis of highly functionalized dihydro-2-oxopyrrols and bis-dihydro-2-oxopyrroles. *Research on Chemical Intermediates* **2014**, *40*, 737-748, https://doi.org/10.1007/s11164-012-0998-7.
18. Sajadikhah, S.S.; Hazeri, N.; Maghsoodlou, M.T.; HabibiKhorasani, S.M.; Beigbabaei, A.; Willis. A.C. $Al(H_2PO_4)_3$ 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* **2013**, *10*, 863-871, https://doi.org/10.1007/s13738-013-0222-8.
19. Sajadikhah, S.S.; Hazeri, N.; Maghsoodlou, M.T. A one-pot multi-component synthesis of N-aryl-3-aminodihydropyrrl-2-one-4-carboxylate catalyzed by oxalic acid dehydrate. *Journal of Chemical Research* **2013**, *37*, 40-42, https://doi.org/10.3184/174751912X13547952669204.
20. Sajadikhah, S.S.; Maghsoodlou, M.T.; Hazeri, N.; Mohamadian-Souri, S. $ZrCl_4$ as an efficient catalyst for one-pot four-component synthesis of polysubstituted dihydropyrrol-2-ones. *Research on Chemical Intermediates* **2016**, *42*, 2805-2814, https://doi.org/10.1007/s11164-015-2178-z.
21. Zarei, M.; Sajadikhah, S.S. Green and facile synthesis of dihydropyrrol-2-ones and highly substituted piperidines using ethylenediammoniumdiformate (EDDF) as a reusable catalyst. *Research on Chemical Intermediates* **2016**, *42*, 7005-7016, https://doi.org/10.1007/s11164-016-2512-0**.**
22. Salehi, N.; Mirjalili, B.B.F. Synthesis of highly substituted dihydro-2-oxopyrroles using Fe_3O_4@nano-cellulose–OPO_3H as a novel bio-based magnetic nanocatalyst. *RSC Advances* **2017**, *7*, 30303-30309, https://doi.org/10.1039/C7RA04101B.
23. Singh**,** H.; Rajput**,** J.K. Chelation and calcination promoted preparation of perovskite-structured $BiFeO_3$ nanoparticles: a novel magnetic catalyst for the synthesis of dihydro-2-oxypyrroles. *Journal of Materials Science* **2018**, 53, 3163–3188,https://doi.org/10.1007/s10853-017-1790-2.
24. Mirjalilia, B.B.F.; Araqia, R.; Mohajeri, S.A. A simple and green approach for the synthesis of substituted dihydro-2-oxypyrroles catalyzed by nano-Fe_3O_4@SiO_2/$SnCl_4$superparamagnetic nanoparticles. *Iranian Journal of Catalysis* **2019**, *9*, 11-19.
25. Gholami, A.; Khabnadideh, S.; Ghasemi, Y.; Mirjalili, B.B.F.; Shahmoradi, R.; Zamani, L. $TiCl_4$/nano-sawdust as an Efficient Biocatalyst for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles as Antimicrobial Agents. *British Journal of Pharmaceutical Research* **2017**, *16*, 1-14, https://doi.org/10.9734/BJPR/2017/33030.
26. Bavadi, M.; Niknam, K. Synthesis of functionalized dihydro-2-oxopyrroles using graphene oxide as heterogeneous catalyst. *Molecular Diversity* **2018**, 22, 561–573, https://doi.org/10.1007/s11030-017-9809-9.
27. Zhang, J.N.; Yang, X.H.; Guo, W.J.; Wang, B.; Zhang, Z.H. Magnetic metal-organic framework $CoFe_2O_4$@SiO_2@IRMOF-3 as an efficient catalyst for one-pot synthesis of functionalized dihydro-2- oxopyrroles. *Synlett* **2017**, *28*, 734–740. https://doi.org/10.1055/s-0036-1588924.
28. Mohamadpour, F. Caffeine as a naturally green and biodegradable catalyst promoted convenient and expedient synthetic route for the synthesis of polysubstituted dihydro-2-oxypyrroles. *Bulletin of the Chemical Society of Ethiopia* **2019**, *33*, 149-158, https://dx.doi.org/10.4314/bcse.v33i1.15.
29. Mohamadpour,F. Glutamic acid as green and bio-based α-amino acid catalyst promoted one-pot access to polyfunctionalized dihydro-2-oxypyrroles. *Journal of the Serbian Chemical Society* **2019**, https://doi.org/10.2298/JSC180720006M.
30. Mohamadpour, F. $ZnCl_2$-catalyzed four-component domino reaction for one-pot eco-safe and convenient synthesis of polysubstituted dihydro-2-oxopyrroles at ambient temperature. *Chemistry and Chemical Technology* **2019**, *13*, 157–162, https://doi.org/10.23939/chcht13.02.157.
31. Mohamadpour, F. Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures. *Makara Journal of Science* **2019**, *23*, 1-8, https://doi.org/10.7454/mss.v23i1.9687.
32. Mohamadpour, F. Green and Convenient One-Pot Access to PolyfunctionalizedPiperidine Scaffolds via Glutamic Acid Catalyzed Knoevenagel-Intramolecular [4+2] aza-Diels-Alder Imin-Based Multi-Component Reaction Under Ambient Temperature. *Polycyclic Aromatic Compounds* **2018**, https://doi.org/10.1080/10406638.2018.1472111.
33. Mohamadpour, F. Synthesis of Pyran-Annulated Heterocyclic Systems Catalyzed by Theophylline as a Green and Bio-Based Catalyst. *Polycyclic Aromatic Compounds* **2019**, https://doi.org/10.1080/10406638.2019.1575246.
34. Mohamadpour, F.; Lashkari, M. 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/thiones derivatives under solvent-free conditions. *Journal of the Serbian Chemical Society* **2018**, *83*, 673–684, https://doi.org/10.2298/JSC170712041M.

6. ACKNOWLEDGEMENTS

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