Makara Journal of Science

Volume 23
Issue 1 *March*

Article 1

3-20-2019

Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures

Farzaneh Mohamadpour
Young Researchers and Elite Club, Shiraz Branch, Islamic Azad University, Shiraz 37195, Iran,
mohamadpour.f.7@gmail.com

Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures

Cover Page Footnote

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

Makara Journal of Science, 23/1 (2019), 1-8
doi: 10.7454/mss.v23i1.9687

Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures

Farzaneh Mohamadpour

Young Researchers and Elite Club, Shiraz Branch, Islamic Azad University, Shiraz 37195, Iran

*E-mail: mohamadpour.f.7@gmail.com

Received July 21, 2018 | Accepted January 22, 2019

Abstract

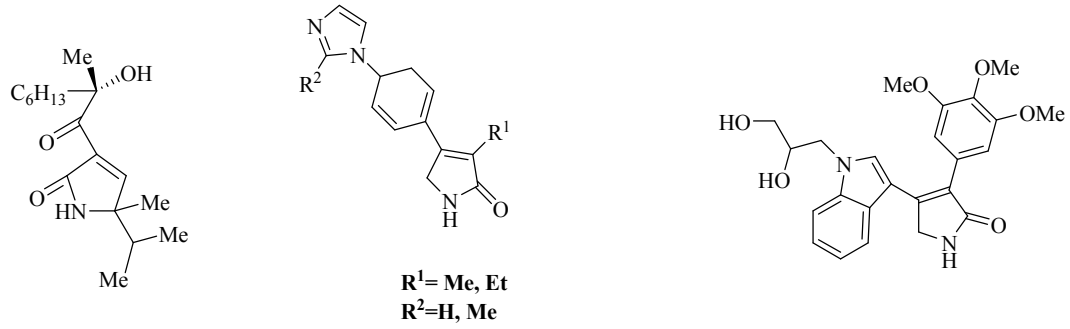
A convenient, expedient and efficient method for the synthesis of polysubstituted dihydro-2-oxypyrroles is described via the one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde, and amines (aromatic and aliphatic) at ambient temperature in the presence of Manganese (II) Nitrate Tetrahydrate ($Mn(NO_3)_2.4H_2O$) as a cost effective and inexpensive catalyst. The present methodology provides a simple and eco-safe procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles with some additional advantages, such as good to high yields, short reaction times, avoidance of hazardous or toxic catalysts, simplicity of operating and work-up procedures with no necessity for chromatographic purification steps.

Keywords: Polysubstituted dihydro-2-oxypyrroles, Manganese (II) Nitrate Tetrahydrate ($Mn(NO_3)_2.4H_2O$), eco-safe procedure, one-pot synthesis

Introduction

Synthesis of pyrrole rings has attracted great interest due to their biological and pharmaceutical properties. They have been used as human cytomegalovirus (HCMV) protease [1], CD45 protein tyrosinphosphatase [2], and an anti-cancer agent [3]. In addition, Thiomarinol A4 used as an antibiotic has pyrrole rings [4], and a number of alkaloids performing biological activities have pyrrole rings [5], which have been used as UCS1025A [6], and Oteromycin [7]. Furthermore, these rings have been used with HIV integrase [8], and they also have also herbicidal [9] properties. Some of those with biologically properties are shown in Figure 1.

In recent years, considerable attention has been paid to the design of an efficient and eco-friendly synthetic route through the use of multi-component domino reactions (MCRs) [10–13] due to their wide range of advantages, such as their atom-economy, simple work-up, mild and environmentally-friendly, one-pot, and low-cost. $Cu(OAc)_2.H_2O$ [14], $InCl_3$ [15], I_2 [16], AcOH [17], $[n\text{-}Bu_4N][HSO_4]$ [18], $Al(H_2PO_4)_3$ [19], oxalic acid [20], $ZrCl_4$ [21], Fe_3O_4@nano-cellulose–OPO_3H [22], -



PI-091 **(imidazolylphenyl) pyrrol-2-one** **VEGF-R**

Figure 1. Biologically Active Compounds with Dihydro-2-Oxypyrrole Rings

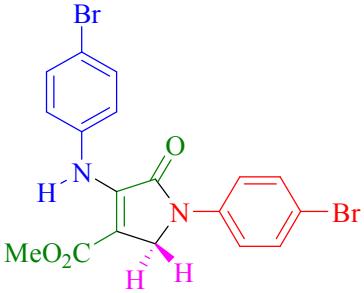
ethylenediammonium diformate (EDDF) [23], tartaric acid [24], Phthalic acid [25], and $ZnSO_4.7H_2O$ [26] can all be used as catalysts in this transformation. Some of these methodologies have limitations, such as using an expensive catalyst for the reflux condition, a longer reaction time, lower yield, tedious work-up procedure, or the use of a large amount of the catalyst. Thus, as part of our ongoing research program that aims for the development of efficient methodologies, we here report a mild and facile protocol for the synthesis of polysubstituted dihydro-2-oxypyrroles in the presence of $Mn(NO_3)_2.4H_2O$ as being a readily available and non-toxic catalyst, using a one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at ambient temperature.

Material and Methods

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

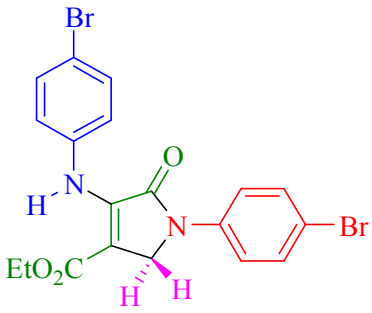
General procedure for preparation of polysubstituted dihydro-2-oxypyrroles (5a-q) [16]: A mixture of amine **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol) was stirred in MeOH (3 mL) for 15 min. Next, amine **3** (1.0 mmol), formaldehyde **4** (1.5 mmol), and $Mn(NO_3)_2.4H_2O$ (20 mol%) were added and the reaction was stirred for an appropriate time. After completion of the reaction (ascertained by thin layer chromatography, TLC), the mixture was separated by filtration, and the solid was washed with ethanol (3×2 mL) with no column chromatographic separation to give pure compounds (**5a-q**). The catalyst is soluble in ethanol and was thus removed from the reaction mixture. The products were characterized by comparison of the spectroscopic data (^{1}HNMR). The ^{1}HNMR data of the products were compared with the literature (Table 4). The spectra data of the products are represented below:

Methyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5c):



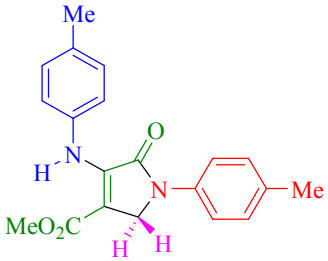
Yield: 78%; M.p. 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (3H, s, OCH_3), 4.52 (2H, s, $\underline{CH_2}$–N), 7.04 (2H, d, *J*= 11.2 Hz, ArH), 7.46 (2H, d, *J*= 11.6 Hz, ArH), 7.53 (2H, d, *J*= 12.0 Hz, ArH), 7.71 (2H, d, *J*= 12.0 Hz, ArH), 8.06 (1H, s, NH) ppm.

Ethyl 3-(4-bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5d):



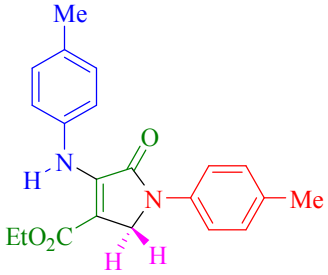
Yield: 79%; M.p. 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.29 (3H, t, *J*= 9.6 Hz, $OCH_2\underline{CH_3}$), 4.28 (2H, q, *J*= 9.6 Hz, $O\underline{CH_2}CH_3$), 4.53 (2H, s, $\underline{CH_2}$–N), 7.04 (2H, d, *J*= 11.6 Hz, ArH), 7.45 (2H, d, *J*= 11.2 Hz, ArH), 7.53 (2H, d, *J*= 12.0 Hz, ArH), 7.72 (2H, d, *J*= 11.6 Hz, ArH), 8.05 (1H, s, NH) ppm.

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



Yield: 86%; M.p. 178-179 °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) ppm.

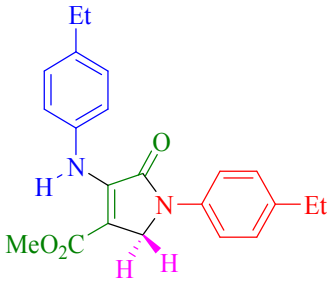
Ethyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5j):



Yield: 83%; M.p. 132-134 °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

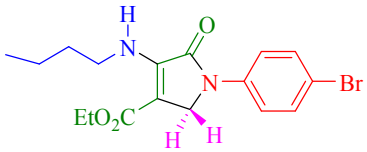
Hz, ArH), 7.21 (2H, d, *J*=8.4 Hz, ArH), 7.68 (2H, d, *J*=8.4 Hz, ArH), 8.01 (1H, s, NH) ppm.

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



Yield: 82%; M.p. 126-128 °C; IR (KBr): ν 3288 (N-H), 2964, 1675 (C=O), 1646 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.26 (6H, t, *J*=2.4 Hz, $2CH_2\underline{CH_3}$), 2.67 (4H, q, *J*=7.2 Hz, $2\underline{CH_2}CH_3$), 3.76 (3H, s, $2OCH_3$), 4.53 (2H, s, $C\underline{H_2}$-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); ^{13}C NMR (100 MHz, $CDCl_3$): 15.6, 15.7 ($2CH_2$-$\underline{CH_3}$), 28.3 and 28.4 ($2\underline{CH_2}$-CH_3), 48.3 (CH_2N), 51.3 (OCH_3), 101.9, 119.4, 123.1, 127.8, 128.5, 136.1, 136.4, 140.8, 141.3, 143.6 (C_{Ar}), 163.6 (C=O, amide), 165.1(C=O, ester); MS (EI) m/z (%): 364 (M^+, 59), 349 (1), 332 (10), 318 (4), 305 (100), 290 (1), 277 (7), 261 (4), 247 (2), 233 (2), 216 (13), 199 (2), 186 (1), 173 (14), 158 (12), 145 (3), 132 (18), 118 (10), 103 (12), 90 (8), 77 (21), 64 (2), 51 (4).

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

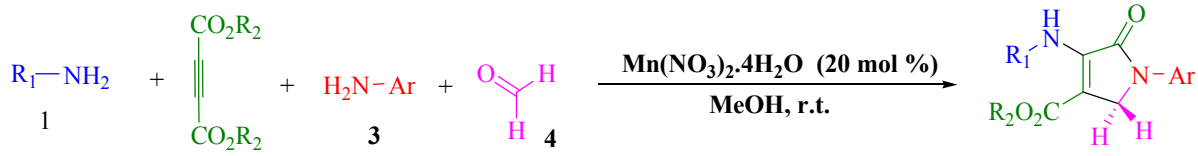


Yield: 81%; M.p. 93-95 °C; ^1H NMR (400 MHz, $CDCl_3$): 0.97 (3H, t, *J* = 7.2 Hz, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, $OCH_2\underline{CH_3}$), 1.43 (2H, sextet, *J* = 7.6 Hz, CH_2), 1.61 (2H, quintet, *J* = 7.6 Hz, CH_2), 3.87 (2H, t, *J* = 7.2 Hz, $\underline{CH_2}$-NH), 4.28 (2H, q, *J* = 7.2 Hz, $O\underline{CH_2}CH_3$), 4.40 (2H, s, $\underline{CH_2}$-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).

Results and Discussion

The generalizability of this four-condensation reaction was studied under optimized conditions and the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was investigation as a model reaction, and then the effect of different amounts of the catalyst in MeOH as the solvent was studied in this protocol. In the absence of the catalyst, a trace amount of this product was detected after 12 h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The most effective amount of the catalyst was 20 mol % (Table 1, entry 5). Higher amounts of catalyst did not increase the products' yields (Table 1, entry 12). The results are summarized in Table 1. The effect of various solvents was also investigated for this protocol, including H_2O, EtOH, CH_2Cl_2, $CHCl_3$ and CH_3CN. Of the solvents, MeOH was found to be the most effective for this methodology (Table 1, entry 5). Finally, a convenient, expedient and efficient procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles was described via the one-pot four-condensation of (aromatic or aliphatic **1** and **3**), dialkyl acetylenedicarboxylate **2** and formaldehyde **4** under ambient temperature in the presence of $Mn(NO_3)_2.4H_2O$ (Scheme 1). The results are summarized in Table 2.

The proposed mechanism for the synthesis of polysubstituted dihydro-2-oxypyrroles in the presence of $Mn(NO_3)_2.4H_2O$ is illustrated in scheme **2**. First, an amine (**1**) reacts with dialkyl acetylenedicarboxylate (**2**) to yield intermediate **A**. Second, condensation between amine **3** and formaldehyde **4** in the presence of $Mn(NO_3)_2.4H_2O$ produces imine **B**. Intermediate **A**



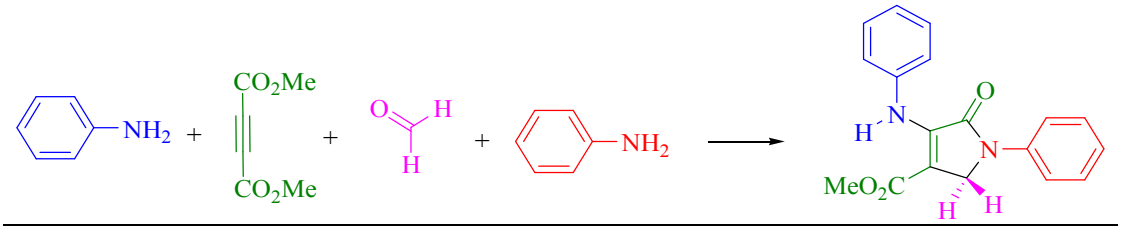
R^1 = C_6H_5, 4-Br-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 4-Et-C_6H_4, n-C_4H_9, $PhCH_2$.

R^2 = CH_3, C_2H_5.

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

Figure 1. Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

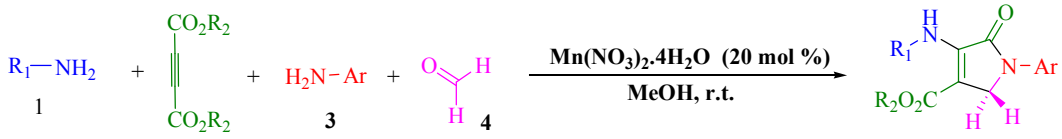
Table 1. Optimization of the Reaction Conditions in the Presence of Different Amounts of $Mn(NO_3)_2.4H_2O$ and Different Solvents in the Synthesis of 5a [a]



Entry	$Mn(NO_3)_2.4H_2O$ (mol%)	Solvent	Time (h)	Isolated Yields (%)
1	Catalyst free	MeOH	12	trace
2	5	MeOH	9	26
3	10	MeOH	7	43
4	15	MeOH	6	68
5	**20**	**MeOH**	**5**	**84**
6	20	Solvent free	8	35
7	20	EtOH	5	67
8	20	H_2O	8	28
9	20	CH_2Cl_2	10	18
10	20	$CHCl_3$	10	13
11	20	CH_3CN	7	39
12	25	MeOH	5	84

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

Table 2. Synthesis of Dihydro-2-Oxypyrrole Derivatives



1 **2** **3** **4** **5a-q**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	M.p. °C	Lit. M.p. °C
1	Ph	Me	Ph	**5a**	5	84	154-156	155-156[16]
2	Ph	Et	Ph	**5b**	5	82	140-141	138-140[17]
3	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5c**	7	78	176-178	175-177[18]
4	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5d**	7	79	167-169	169-171[17]
5	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5e**	5	85	175-177	172-175[18]
6	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5f**	5	81	153-155	152-154[19]
7	4-F-C_6H_4	Me	4-F-C_6H_4	**5g**	4	87	161-163	163-165[20]
8	4-F-C_6H_4	Et	4-F-C_6H_4	**5h**	4	88	170-172	172-174[18]
9	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5i**	4	86	178-179	177-178[16]
10	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5j**	4	83	132-134	131-132[17]
11	4-Et-C_6H_4	Me	4-Et-C_6H_4	**5k**	4	82	126-128	124-125[22]
12	n-C_4H_9	Me	Ph	**5l**	4	84	58-60	60[16]
13	n-C_4H_9	Me	3,4-Cl_2-C_6H_3	**5m**	6	78	96-98	97-99[19]
14	n-C_4H_9	Et	4-Br-C_6H_4	**5n**	5	81	93-95	94-96[19]
15	$PhCH_2$	Me	Ph	**5o**	6	85	141-143	140-141[17]
16	$PhCH_2$	Me	4-F-C_6H_4	**5p**	5	87	165-167	166-168[19]
17	$PhCH_2$	Et	Ph	**5q**	6	84	128-130	130-132[17]

[a] Isolated yield.

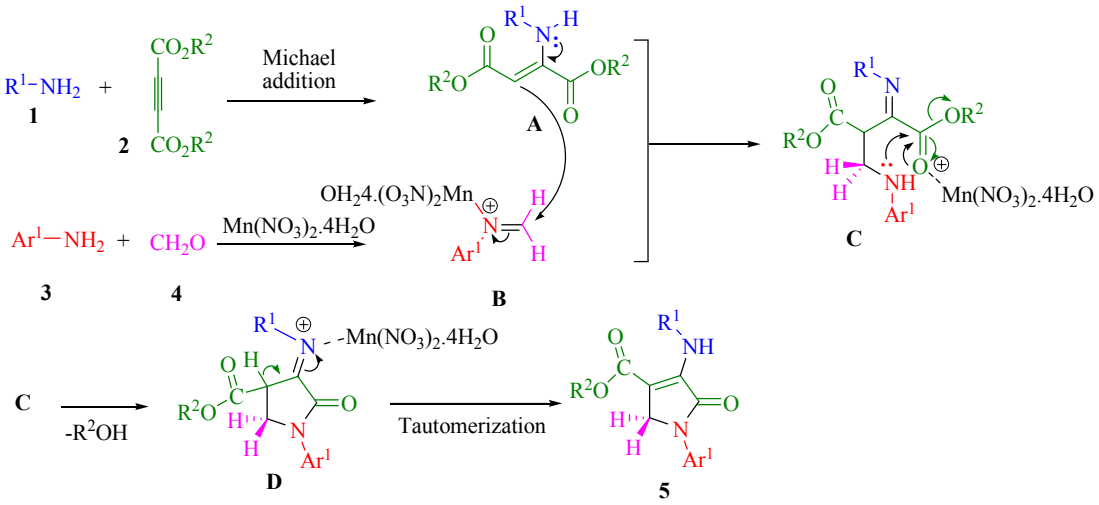


Figure 2. Proposed Mechanistic Route for the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

Table 3. Comparison of the Catalytic Ability of Some of the Catalysts as Reported in the Literature for use in the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

Entry	Compound	Catalyst	Conditions	Time/Yield (%)	Reference
1	**5a**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6h/91	[14]
2	**5a**	$InCl_3$	MeOH, r.t.	3h/85	[15]
3	**5a**	I_2	MeOH, r.t.	1 h/82	[16]
4	**5a**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/88	[18]
5	**5a**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[19]
6	**5a**	$ZrCl_4$	MeOH, r.t.	4 h/84	[21]
7	**5a**	EDDF	EtOH, Reflux	3 h/89	[23]
8	**5a**	$Mn(NO_3)_2.4H_2O$	MeOH, r.t.	5 h/84	This work
9	**5b**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5h/85	[14]
10	**5b**	$InCl_3$	MeOH, r.t.	3h/85	[15]
11	**5b**	I_2	MeOH, r.t.	1 h/81	[16]
12	**5b**	$[n\text{-}Bu_4N][HSO_4]$	MeOH, r.t.	4 h/86	[18]
13	**5b**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[19]
14	**5b**	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[21]
15	**5b**	EDDF	EtOH, Reflux	3.5 h/84	[23]
16	**5b**	$Mn(NO_3)_2.4H_2O$	MeOH, r.t.	5 h/82	This work

Table 4. Comparison of ^{1}HNMR Data for the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

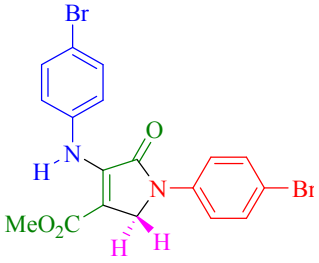
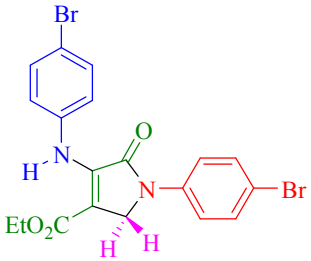
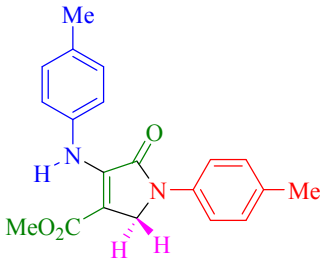
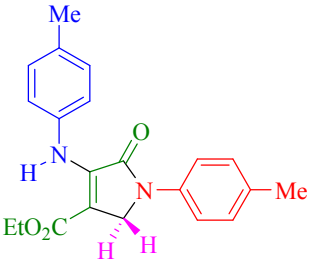
Entry	Product	H Shift (found)	H Shift (lit)	Reference
1	**5c** 	3.81 (3H, s, OCH_3) 4.52 (2H, s, $\underline{CH_2}$–N) 8.06 (1H, s, NH)	3.79 (3H, s, NH) 4.48 (2H, s, $\underline{CH_2}$-N) 8.06 (1H, s, OCH_3)	14

Table 4. ***Continue***

Entry	Product	H Shift (found)	H Shift (lit)	Reference
2	**5d** 	1.29 (3H, t, *J*= 9.6 Hz, $OCH_2\underline{CH_3}$) 4.28 (2H, q, *J*= 9.6 Hz, $O\underline{CH_2}CH_3$) 4.53 (2H, s, $\underline{CH_2}$–N) 8.05 (1H, s, NH)	1.29 (3H, t, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 4.27 (2H, q, *J* = 7.1 Hz, $O\underline{CH_2}CH_3$) 4.52 (2H, s, $\underline{CH_2}$-N) 8.05 (1H, s, NH)	14
3	**5i** 	2.36 (6H, s, $2CH_3$) 3.77 (3H, s, OCH_3) 4.52(2H, s, $C\underline{H_2}$-N) 8.03 (1H, s, NH)	2.38 (6H, d, $2CH_3$) 3.77 (3H, s, OCH_3) 4.50 (2H, s, $\underline{CH_2}$-N) 8.06 (1H, s, NH)	14
4	**5j** 	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) 8.01 (1H, s, NH)	1.25 (3H, t, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 2.37 (6H, s, $2CH_3$) 4.24 (2H, q, *J* = 7.1 Hz, $O\underline{CH_2}CH_3$) 4.51 (2H, s, $\underline{CH_2}$-N) 8.04 (1H, s, NH)	14

possesses an enamine character and can thus readily react with imine **B** in the presence of $Mn(NO_3)_2.4H_2O$ to generate intermediate **C**. The cyclization of intermediate **C** yields intermediate **D**, which tautomerizes to the corresponding polysubstituted dihydro-2-oxypyrroles (**5**) in the final step.

A comparison of the catalytic ability of some of the catalysts as reported in the literature for the synthesis of polysubstituted dihydro-2-oxypyrroles is shown in Table 3. In Table 4, the ^{1}HNMR data for the products is compared with that in the literature. This study reveals that $Mn(NO_3)_2.4H_2O$ has shown extraordinary potential as an alternative, inexpensive, eco-safe, and efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds. In addition, good to high yields and short reaction times are other notable advantages of this present methodology.

Conclusions

In conclusion, we have introduced a simple and efficient protocol for the synthesis of a wide range of biologically and pharmacologically polysubstituted dihydro-2-oxypyrroles in the presence of Manganese (II) Nitrate Tetrahydrate ($Mn(NO_3)_2.4H_2O$) via a one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at room temperature conditions. The promising advantages of the methodology presented are its generalizability, the avoidance of hazardous byproducts in production, good to high yields, short reaction times, clean reaction profiles and ease of product isolation.

Acknowledgments

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

References

[1] Borthwick, A.D., Crame, A.J., Ertl, P.F., Exall, A.M., Haley, T.M., Hart, G.J., et al. 2002. 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. J. Med. Chem. 45(1): 1-18, doi: 10.1021/jm0102203.

[2] Li, W.R., Lin, S.T., Hsu, N.M., Chern, M.S. 2002. Efficient total synthesis of pulchellalactam, a CD45 protein tyrosine phosphatase inhibitor. J. Org. Chem. 67(14): 4702-4706, doi: 10.1021/jo010828j.

[3] Lampe, Y.L., Chou, R.G., Hanna, R.G., DiMeo, S.V., Erhardt, P.W., Hagedorn, A.A., Ingebretsen, W.R., Cantor, E. 1993. (Imidazolylphenyl) pyrrol-2- one inhibitors of cardiac cAMPphosphodiesterase. J. Med. Chem. 36(8): 1041-1047, doi: 10.1021/jm00060a012.

[4] Shiozawa, H., Takahashi, S. 1994. Configurational studies on thiomarinol. J. Antibiot. 47(7): 851-853.

[5] Chen, Y., Zeng, D.X., Xie, N., Dang, Y.Z. 2005. 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. J. Org. Chem. 70(13): 5001-5005, doi: 10.1021/jo050236r.

[6] Grunwald, C., Rundfeldt, C., Lankau, H.J., Arnold, T., Hofgen, N., Dost, R., et al. 2006. Synthesis, pharmacology, and structure-activity relationships of novel Imidazolones and Pyrrolones as modulators of GABAA receptors. J. Med. Chem. 49(6): 1855-1866, doi: 10.1021/jm0509400.

[7] Singh, S.B., Goetz, M.A., Jones, E.T., Billes, G.F., Giacobbe, R.A., Herranz, L. et al. 1995. A novel antagonist of endothelin receptor. J. Org. Chem. 60(21): 7040-7042, doi: 10.1021/jo00126a071.

[8] Kawasuji, T., Fuji, M., Yoshinaga, T., Sato, A., Fujiwara, T., Kiyama, R. 2007. 3-Hydroxy-1, 5-dihydro-pyrrol-2-one derivatives as advanced inhibitors of HIV integrase. J. Bioorg. Med. Chem. 15(16): 5487-5492, doi: https://doi.org/10.1016/j.bmc.2007.05.052.

[9] Zhang, L., Tan, Y., Wang, N.X., Wu, Q.Y., Xi, Z., Yang, G.F. 2010. Design, syntheses and 3D-QSAR studies of novel N-phenyl pyrrolidin-2-ones and N-phenyl-1H-pyrrol-2-ones as protoporphyrinogen oxidase inhibitors. J. Bioorg. Med. Chem. 18(22): 7948-7956, doi: https://doi.org/10.1016/j.bmc.2010.09.036.

[10] Mohamadpour, F. 2018. Development of an Environment-Friendly and Solvent-Free Synthetic Route for the Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones/Thiones Using $La(NO_3)_3.6H_2O$ as an Efficient Catalyst. Makara. J. Sci. 22(3): 142-148, doi: 10.7454/mss.v22i3.9899.

[11] Mohamadpour, F., Lashkari, M. 2018. 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(1H)-ones/thiones derivatives under nsolvent-free conditions. J. Serb. Chem. Soc. 83(6): 673-684, doi: https://doi.org/10.2298/JSC170712041M.

[12] Mohamadpour, F. 2018. 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. Polycycl. Aromat. Comp. 1-12 doi: https://doi.org/10.1080/10406638.2018.1472111.

[13] Mohamadpour, F. 2018. Ascorbic acid as a natural green, highly efficient and economical catalyst promoted one-pot facile synthesis of 12-aryltetrahydrobenzo[*a*]xanthenes, 1,8-dioxooctahydroxanthenes and 14-aryl-14*H*-dibenzo[*a, j*] xanthenes under solvent-free conditions. U.P.B. Sci. Bull. Series B. 80(2): 101-116.

[14] Lv, L., Zheng, S., Cai, X., Chen, Z., Zhu, Q., Liu, S. 2013. Development of Four-Component Synthesis of Tetra- and Pentasubstituted Polyfunctional Dihydropyrroles: Free Permutation and Combination of Aromatic and Aliphatic Amines. J. Acs. Comb. Sci. 15(4): 183-192, doi: 10.1021/co300148c.

[15] Sajadikhah, S.S., Maghsoodlou, M.T., Hazeri, N. 2014. A simple and efficient approach to one-pot synthesis of mono- and bis-N-aryl-3-aminodihidropyrrol-2-one-4-carboxylate catalyzed by $InCl_3$. J. Chin. Chem. Lett. 25(1): 58-60, doi: https://doi.org/10.1016/j.cclet.2013.10.010.

[16] Khan, A.T., Ghosh, A., Musawwer K.M. 2012. One-pot four-component domino reaction for the synthesis of substituted dihydro-2-oxypyrrole catalyzed by molecular iodine. Tetrahedron Lett. 53(21): 2622-2626, doi: https://doi.org/10.1016/j.tetlet.2012.03.046.

[17] Zhu, Q., Jiang, H., Li, J., Liu, S., Xia, C., Zhang, M. 2009. Concise and versatile multicomponent synthesis of multisubstituted polyfunctional dihydropyrroles. J. Comb. Chem. 11(4): 685-696, doi: 10.1021/cc900046f.

[18] Sajadikhah, S.S., Hazeri, N. 2014. 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. Res. Chem. Intermed. 40(2): 737-748, doi: https://doi.org/10.1007/s11164-012-0998-7.

[19] Sajadikhah, S.S., Hazeri, N., Maghsoodlou, M.T., Habibi Khorasani, S.M., Beigbabaei, A., Willis, A.C. 2013. $Al(H_2PO_4)_3$ as an efficient and reusable catalyst for the multi-component synthesis of highly functionalized piperidines and dihydro-2-oxypyrroles. J. Iran. Chem. Soc. 10(5): 863-871, doi: https://doi.org/10.1007/s13738-013-0222-8.

[20] Sajadikhah, S.S., Hazeri, N., Maghsoodlou, M.T. 2013. A one-pot multi-component synthesis of N-aryl-3-aminodihydropyrrl-2-one-4-carboxylate catalyzed by oxalic acid dehydrate. J. Chem. Res.

37(1): 40-42, doi: https://doi.org/10.3184/174751912X13547952669204.

[21] Sajadikhah, S.S., Maghsoodlou, M.T., Hazeri, N., Mohamadian-Souri, S. 2016. $ZrCl_4$ as an efficient catalyst for one-pot four-component synthesis of polysubstituted dihydropyrrol-2-ones. Res. Chem. Intermed. 42(4): 2805-2814, doi: https://doi.org/10.1007/s11164-015-2178-z.

[22] Salehi, N., Mirjalili, B.B.F. 2017. Synthesis of highly substituted dihydro-2-oxopyrroles using Fe_3O_4@nano-cellulose–OPO_3H as a novel bio-based magnetic nanocatalyst. RSC Adv. 7(48): 30303-30309, doi: 10.1039/C7RA04101B.

[23] Zarei, M., Sajadikhah, S.S. 2016. Green and facile synthesis of dihydropyrrol-2-ones and highly substituted piperidines using ethylenediammonium diformate (EDDF) as a reusable catalyst. Res. Chem. Intermed. 42(9): 7005-7016, doi: https://doi.org/ 10.1007/s11164-016-2512-0.

[24] Mohamadpour, F., Maghsoodlou, M.T., Heydari, R., Lashkari, M. 2017. 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. Iran. J. Sci. Technol. Trans. Sci. 41(3): 843-849, doi: 10.1007/s40995-016-0049-0.

[25] Mohamadpour, F., Lashkari, M., Maghsoodlou, M.T., Heydari, R. 2018. Phthalic acid: a green, biodegradable and environmentally benhgn nature difunctional Bronsted acid catalyst for the one-pot synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-one derivatives and substituted dihydro-2-oxypyrroles. J. Chil. Chem. Soc. 63(1): 3811-3818.

[26] Mohamadpour, F. 2018. $ZnSO_4.7H_2O$ Catalyzed One-pot and Facile Synthesis of Highly Substituted Dihydro-2-oxopyrroles at Room Temperature. Makara. J. Sci. 22(2): 82-88, doi: 10.7454/mss.v22i2.8792.