

## Salicylic acid as a naturally green Brønsted acid catalyst for eco-friendly and simple synthesis of polysubstituted dihydro-2-oxypyrrroles under ambient temperature

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### Abstract

An efficient and environmental friendly methodology for the synthesis of polysubstituted dihydro-2-oxypyrrroles via a one-pot four-component domino condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at present of salicylic acid as an economical and naturally green Brønsted acid catalyst under ambient temperature with excellent yields and short reaction times is described. Green, natural, inexpensive and non-toxic catalyst, easily separated with no column chromatographic separation and highly efficient is an option for the simple synthesis of these rings.

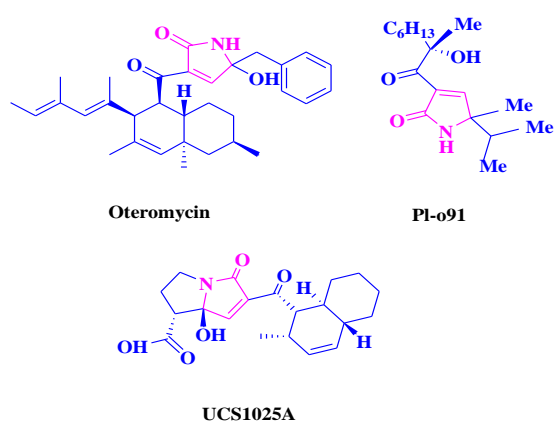
**Keywords:** Salicylic acid, Polysubstituted dihydro-2-oxypyrrroles, Naturally green catalyst, Multi-component reaction, Eco-friendly synthesis.

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## 1. Introduction

In recent years, green chemistry, has become to one of the best approach for and efficient preparation of organic compounds. The special benefits of green chemistry for the synthesis of heterocyclic compounds are using non-toxic substrate and environmentally benign nature. Herein, our recent studies focused on developing of using green catalyst [1-2] in the multi-component reactions [3-7].

Recently, the compound with pyrrole rings such as dihydro-2-oxypyrroles are attracting considerable interest because of their pharmaceutical and biological properties including inhibitors of the annexin A2-S100A10 protein interaction [8], has been used as PI-091 [9], many of number alkaloids with biological activities have pyrrole rings [10], cardiac cAMP phosphodiesterase [11]. In addition, these rings have been used HIV integrase [12] and they have also anti-cancer [13] activities and these rings have been used as UCS1025A [14], Oteromycin [15]. Some example containing a heterocyclic dihydro-2-oxypyrrole rings with biologically activities have been shown in Figure 1.

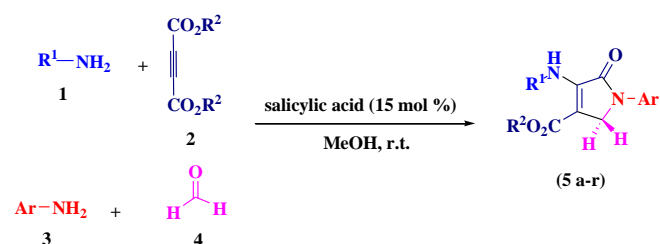


**Figure 1.** Biologically active compounds with dihydro-2-oxypyrrole rings.

Recently, several protocols for the preparation of these compounds have been reported that is including Lewis and Brønsted acid catalysts such as I<sub>2</sub> [16], InCl<sub>3</sub> [17], [n-Bu<sub>4</sub>N][HSO<sub>4</sub>] [18], Al(H<sub>2</sub>PO<sub>4</sub>)<sub>3</sub> [19], AcOH [20], Oxalic acid [21], ZrCl<sub>4</sub>[22], Cu(OAC)<sub>2</sub>.H<sub>2</sub>O[23]. Some of these methodologies have limitations such as toxic and expensive catalysts, long time reactions, low yields, use of strongly acidic conditions, difficulty work-up, high temperature.

Because of the above considerations and our interest in the development of synthesis of polysubstituted dihydro-2-

oxypyrroles, we had attempted to report a economical and simple methodology for the preparation of these rings with one-pot, four-condensation domino reaction using an efficient catalyst and finally, we reported an efficient and simple procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles through a one-pot four-component reaction between amines( aromatic or aliphatic **1** and **3**), dialkylacetylenedicarboxylate **2** and formaldehyde **4** in the presence of salicylic acid as an economical and naturally green Brønsted acid catalyst under ambient temperature in methanol (Scheme 1).



**Scheme 1.** Synthesis of polysubstituted dihydro-2-oxypyrroles.

Furthermore, one of the source of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purify the products. In this present work, products were obtained under ambient temperature and through simple filtering with no need column chromatographic separation.

## 2. Experimental

### General:

Melting points and IR spectra all compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Also, nuclear magnetic resonance, <sup>1</sup>H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with CDCl<sub>3</sub> as solvent. All reagents and solvents were purchased from Merck, Fluka and Across chemical companies were used without further purification.

### 2.1. General procedure for preparation of polysubstituted dihydro-2-oxypyrroles (5a-r):

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 salicylic acid (0.020 g) 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-r**). All products are characterized by comparison of spectroscopic data (FT-IR, <sup>1</sup>H NMR). Spectra data of products are represented below:

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

IR (KBr, cm<sup>-1</sup>): ν 3264 (NH), 1692 (C=O), 1641 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.76 (3H, s, OCH<sub>3</sub>), 4.57 (2H, s, CH<sub>2</sub>-N), 7.16-7.23 (4H, m, ArH), 7.35 (2H, t, J=7.8 Hz, ArH), 7.42 (2H, t, J=7.8 Hz, ArH), 7.81 (2H, d, J=8.0 Hz, ArH), 8.05 (1H, s, NH).

*Ethyl 1-phenyl-3-(phenylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5b)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.24 (3H, t, J=7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.24 (2H, q, J=7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.44 (2H, s, CH<sub>2</sub>-N), 7.15-7.23 (4H, m, ArH), 7.35 (2H, d, J=7.6 Hz, ArH), 7.41 (2H, d, J=7.6 Hz, ArH), 7.82 (2H, d, J=7.8 Hz, ArH), 8.01 (1H, s, NH).

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

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.78 (3H, s, OCH<sub>3</sub>), 4.50 (2H, s, CH<sub>2</sub>-N), 7.08 (2H, d, J=8.8 Hz, ArH), 7.30 (2H, d, J=8.4 Hz, ArH), 7.35 (2H, d, J=8.8 Hz, ArH), 7.72 (2H, d, J=8.8 Hz, ArH), 8.03 (1H, s, NH).

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

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.24 (3H, t, J=7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.24 (2H, q, J=7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.49 (2H, s, CH<sub>2</sub>-N), 7.09 (2H, d, J=8.0 Hz, ArH), 7.27-7.75 (6H, m, ArH), 8.04 (1H, s, NH).

*Methyl 4-(4-methoxyphenylamino)-1-(4-methoxy phenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5e)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.77 (3H, s, CH<sub>3</sub>), 3.83 (6H, s, 2OCH<sub>3</sub>), 4.50 (2H, s, CH<sub>2</sub>-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).

*Ethyl 4-(4-methoxyphenylamino)-1-(4-methoxy phenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5f)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.26 (3H, t, J=7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.83 (6H, s, 2OCH<sub>3</sub>), 4.23 (2H, q, J=7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.50 (2H, s, CH<sub>2</sub>-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).

*Methyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5i)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 3.79 (3H, s, OCH<sub>3</sub>), 4.52 (2H, s, CH<sub>2</sub>-N), 7.04 (2H, t, J=8.4 Hz, ArH), 7.08-7.16 (4H, m, ArH), 7.73-7.79 (2H, m, ArH), 8.05 (1H, s, NH).

*Methyl 4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5k)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 2.36 (6H, s, 2CH<sub>3</sub>), 3.77 (3H, s, OCH<sub>3</sub>), 4.52 (2H, s, CH<sub>2</sub>-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).

*Ethyl 4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5l)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.25 (3H, t, J=7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.37 (6H, s, 2CH<sub>3</sub>), 4.23 (2H, q, J=7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>), 4.53 (2H, s, CH<sub>2</sub>-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).

*Methyl 3-(butylamino)-2,5-dihydro-2-oxo-1-phenyl-1H-pyrrole-4-carboxylate (5m)*

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.97 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 1.42 (sextet, 2H, J = 7.2 Hz, CH<sub>2</sub>), 1.64 (quintet, 2H, J = 7.2 Hz, CH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.85 (t, 2H, J = 7.2 Hz, CH<sub>2</sub>-NH), 4.45 (s, 2H, CH<sub>2</sub>-N), 6.85 (br s, 1H, NH), 7.18 (d, 1H, J = 7.6 Hz, ArH), 7.40 (d, 2H, J = 7.6 Hz, ArH), 7.73 (d, 2H, J = 7.6 Hz, ArH).

*Methyl 3-(butylamino)-1-(3,4-dichlorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5n)*

IR (KBr, cm<sup>-1</sup>): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.97 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>), 1.44 (sextet, 2H, J = 7.2 Hz, CH<sub>2</sub>), 1.63 (quintet, 2H, J = 7.2 Hz, CH<sub>2</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.87 (t, 2H, J = 7.2 Hz, CH<sub>2</sub>-NH), 4.39 (s, 2H, CH<sub>2</sub>-N), 6.75 (br s, 1H, NH), 7.46 (1H, d, J = 8.8 Hz, ArH), 7.67 (dd, 1H, J = 9.0, 2.8 Hz, ArH), 8.00 (d, 1H, J = 2.8 Hz, ArH).

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

IR (KBr, cm<sup>-1</sup>): ν 3320 (NH), 1699 (C=O), 1649 (C=O); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.97 (t, 3H, J = 7.2 Hz, CH<sub>3</sub>),

1.35 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.43 (sextet, 2H,  $J = 7.6$  Hz,  $\text{CH}_2$ ), 1.61 (quintet, 2H,  $J = 7.6$  Hz,  $\text{CH}_2$ ), 3.87 (t, 2H,  $J = 7.2$  Hz,  $\text{CH}_2\text{-NH}$ ), 4.28 (t, 2H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 6.72 (br s, 1H, NH), 4.40 (s, 2H,  $\text{CH}_2\text{-N}$ ), 7.52 (d, 2H,  $J = 8.8$  Hz, ArH), 7.71 (d, 2H,  $J = 8.8$  Hz, ArH).

*Methyl 3-(benzylamino)-1-phenyl-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5p)*

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.80 (s, 3H,  $\text{OCH}_3$ ), 4.48 (s, 2H,  $\text{CH}_2\text{-N}$ ), 5.10 (d, 2H,  $J = 6.4$  Hz,  $\text{CH}_2\text{-NH}$ ), 6.90 (br, 1H, NH), 7.18-7.41 (m, 8H, ArH), 7.73 (d, 2H,  $J = 8.0$  Hz, ArH).

*Methyl 3-(benzylamino)-1-(4-fluorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5q)*

IR (KBr,  $\text{cm}^{-1}$ ):  $\nu$  3320 (NH), 1697 (C=O), 1645 (C=O);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.80 (s, 3H,  $\text{OCH}_3$ ), 4.42 (s, 2H,  $\text{CH}_2\text{-N}$ ), 5.13 (d, 2H,  $J = 6.4$  Hz,  $\text{CH}_2\text{-NH}$ ), 6.91 (br s, 1H, NH), 7.09-7.13 (m, 2H, ArH), 7.29-7.39 (m, 5H, ArH), 7.71-7.75 (m, 2H, ArH).

*Ethyl 3-(benzylamino)-1-phenyl-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5r)*

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.29 (t, 3H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.24 (q, 2H,  $J = 7.2$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.44 (s, 2H,  $\text{CH}_2\text{-N}$ ), 5.11 (d, 2H,  $J = 6.4$  Hz,  $\text{CH}_2\text{-NH}$ ), 6.92 (br, 1H, NH), 7.19-7.38 (m, 8H, ArH), 7.73-7.75 (m, 2H, ArH).

### 3. Results and discussion

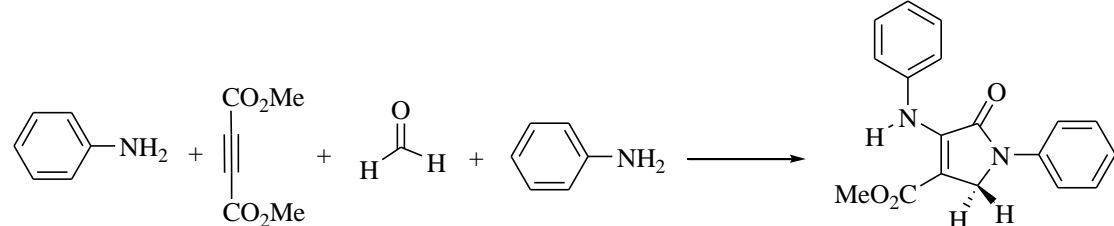
The generality of this four component condensation was studied under optimized conditions and the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was investigated as a model reaction and then the effect of different amount of catalyst was also studied in this protocol and in the absence of catalyst, a trace amount of this product was detected after 7h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol % (0.020 g) (Table 1, entry 4). The higher amount of catalyst did not increase the yields products (Table 1, entry 5) and the results are summarized in Table 1.

And also, the effect of various solvents was investigated for this protocol  $\text{H}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ , EtOH, MeOH,  $\text{CH}_3\text{CN}$  and among these solvents, MeOH found to be the best solvent for this methodology (Table 1, entry 4) and the results are shown in Table 2.

Finally, we reported salicylic acid (0.020 g) as an economical, naturally green catalyst for one-pot four-component condensation of amines (aromatic or aliphatic) dialkyl acetylenedicarboxylate and formaldehyde in MeOH as solvent at room temperature.

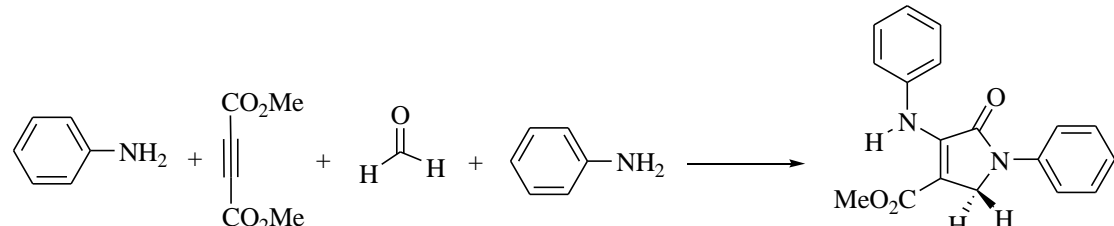
In order to study of this procedure, the various substituted anilines, dimethyl and diethyl acetylenedicarboxylate and formaldehyde were employed successfully to generate the desired polysubstituted dihydro-2-oxypyrroles under ambient temperature in MeOH that gave excellent yields and the results are shown in Table 3 and the proposed mechanism for the synthesis of polysubstituted dihydro-2-oxypyrroles are shown in scheme 2.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of polysubstituted dihydro-2-oxypyrroles are shown in Table 4. This study reveals that salicylic acid has shown its extraordinary potential to be an alternative natural, green and efficient catalyst for the one-pot synthesis of these heterocyclic compounds, in addition to excellent yields and short reaction times are the notable advantages this present methodology.

**Table 1.** Optimization of the reaction condition in the presence of different amounts of salicylic acid<sup>a</sup>


Entry	Salicylic acid (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	7	5a	trace
2	5	7	5a	47
3	10	5	5a	58
<b>4</b>	<b>15</b>	<b>4</b>	<b>5a</b>	<b>91</b>
5	20	4	5a	92

<sup>a</sup> Reaction conditions: aniline (2.0 mmol), dialkyl acetylenedicarboxylate (1.0 mmol) and formaldehyde (1.5 mmol) and catalyst at room temperature.

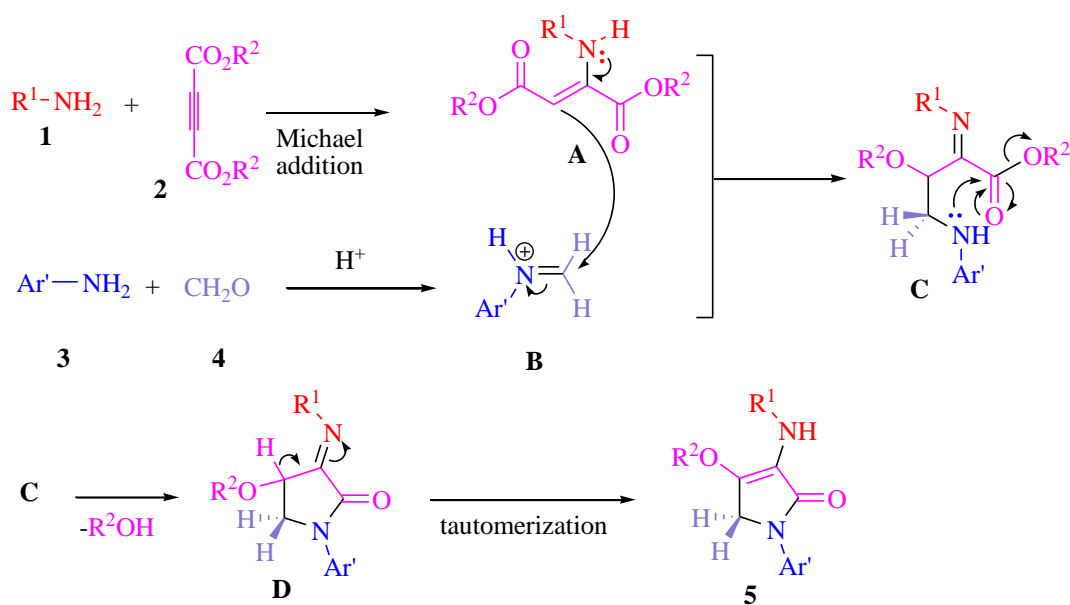
**Table 2.** Optimization of the reaction condition in the presence of different solvents by using of salicylic acid (15 mol%)<sup>a</sup>


Entry	Solvent	Time (h)	Product	Isolated Yields (%)
1	Solvent free	7	5a	38
2	H <sub>2</sub> O	8	5a	24
3	EtOH	4	5a	62
<b>4</b>	<b>MeOH</b>	<b>4</b>	<b>5a</b>	<b>91</b>
5	CH <sub>3</sub> CN	8	5a	46
6	CHCl <sub>3</sub>	7.5	5a	18
7	CH <sub>2</sub> Cl <sub>2</sub>	8	5a	15

<sup>a</sup> Reaction conditions: aniline (2.0 mmol), dialkyl acetylenedicarboxylate (1.0 mmol) and formaldehyde (1.5 mmol) and catalyst in various solvents at room temperature.

**Table 3.** Salicylic acid catalyzed synthesis of polysubstituted dihydro-2-oxypyrrroles.

Entry	R <sup>1</sup>	R <sup>2</sup>	Ar <sup>1</sup>	Product	Time (h)	Yield (%) <sup>a</sup>	M.p. °C	Lit. M.p. °C
1	Ph	Me	Ph	<b>5a</b>	4	91	153-155	155-156 <sup>16</sup>
2	Ph	Et	Ph	<b>5b</b>	4	89	141-143	138-140 <sup>20</sup>
3	4-Br-C <sub>6</sub> H <sub>4</sub>	Me	4-Br-C <sub>6</sub> H <sub>4</sub>	<b>5c</b>	5	81	172-175	175-177 <sup>18</sup>
4	4-Br-C <sub>6</sub> H <sub>4</sub>	Et	4-Br-C <sub>6</sub> H <sub>4</sub>	<b>5d</b>	5	78	167-169	169-171 <sup>20</sup>
5	4-OMe-C <sub>6</sub> H <sub>4</sub>	Me	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>5e</b>	5	86	171-173	172-175 <sup>18</sup>
6	4-OMe-C <sub>6</sub> H <sub>4</sub>	Et	4-OMe-C <sub>6</sub> H <sub>4</sub>	<b>5f</b>	5.5	82	150-152	152-154 <sup>19</sup>
7	4-Cl-C <sub>6</sub> H <sub>4</sub>	Me	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5g</b>	6	81	172-174	171-173 <sup>18</sup>
8	4-Cl-C <sub>6</sub> H <sub>4</sub>	Et	4-Cl-C <sub>6</sub> H <sub>4</sub>	<b>5h</b>	6.5	78	170-172	168-170 <sup>18</sup>
9	4-F-C <sub>6</sub> H <sub>4</sub>	Me	4-F-C <sub>6</sub> H <sub>4</sub>	<b>5i</b>	3.5	92	161-164	163-165 <sup>21</sup>
10	4-F-C <sub>6</sub> H <sub>4</sub>	Et	4-F-C <sub>6</sub> H <sub>4</sub>	<b>5j</b>	4	89	173-175	172-174 <sup>18</sup>
11	4-Me-C <sub>6</sub> H <sub>4</sub>	Me	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>5k</b>	4	87	177-180	177-178 <sup>16</sup>
12	4-Me-C <sub>6</sub> H <sub>4</sub>	Et	4-Me-C <sub>6</sub> H <sub>4</sub>	<b>5l</b>	4	83	130-132	131-132 <sup>20</sup>
13	n-C <sub>4</sub> H <sub>9</sub>	Me	Ph	<b>5m</b>	5	89	61-63	60 <sup>16</sup>
14	n-C <sub>4</sub> H <sub>9</sub>	Me	3,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>5n</b>	4	82	95-97	97-99 <sup>19</sup>
15	n-C <sub>4</sub> H <sub>9</sub>	Et	4-Br-C <sub>6</sub> H <sub>4</sub>	<b>5o</b>	6	82	93-95	94-96 <sup>19</sup>
16	PhCH <sub>2</sub>	Me	Ph	<b>5p</b>	4	85	139-141	140-141 <sup>20</sup>
17	PhCH <sub>2</sub>	Me	4-F-C <sub>6</sub> H <sub>4</sub>	<b>5q</b>	4.5	87	167-170	166-168 <sup>19</sup>
18	PhCH <sub>2</sub>	Et	Ph	<b>5r</b>	5	83	128-130	130-132 <sup>20</sup>

<sup>a</sup> Isolated yield.**Scheme 2.** Proposed mechanistic route for the synthesis of polysubstituted dihydro-2-oxypyrrroles

**Table 4.** Comparison of catalytic ability some of catalysts reported in the literature for synthesis of polysubstituted dihydro-2-oxypyrrroles <sup>a</sup>

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	I <sub>2</sub>	MeOH, r.t.	1 h/82	[16]
2	InCl <sub>3</sub>	MeOH, r.t.	3h/85	[17]
3	[n-Bu <sub>4</sub> N][HSO <sub>4</sub> ]	MeOH, r.t.	4 h/88	[18]
4	Al(H <sub>2</sub> PO <sub>4</sub> ) <sub>3</sub>	MeOH, r.t.	5 h/81	[19]
5	ZrCl <sub>4</sub>	MeOH, r.t.	4 h/84	[22]
6	Cu(OAC) <sub>2</sub> .H <sub>2</sub> O	MeOH, r.t.	6 h/91	[23]
7	salicylic acid	MeOH, r.t.	4 h/91	This work

<sup>a</sup> Based on the four-component reaction of aniline, dimethylacetylenedicarboxylate, formaldehyde.

#### 4. Conclusion

In summary, a simple and efficient methodology for the one-pot, four-component synthesis of polysubstituted dihydro-2-oxypyrrroles by using of salicylic acid as a natural, mild and economical catalyst are reported.

This methodology has an important advantages including green, natural, mild, inexpensive and non-toxic catalyst, one-pot, eco-friendly, short reaction times, good yields, environmental friendly and simple work up with no column chromatographic separation.

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## Reference

- [1] M. Kangani, N. Hazeri, M.T. Mghsoodlou, S.M. Habibi-khorasani, S. Salahi, *Res. Chem. Intermed.*, 41 (2015) 2513-2519.
- [2] S. Salahi, M.T. Maghsoodlou, N. Hazeri, M. Lashkari, *Chin. J. Catal.*, 36 (2015) 1023-1028
- [3] M. Agha Baba Zadeh, R. Hosein Zadeh, S. Zakhireh, *Journal of Applied Chemistry.*, 10 (2015) 61-72.
- [4] M. Bitaraf, A. Amoozadeh, *Journal of Applied Chemistry.*, 10 (2015) 109-116
- [5] R. Kazemi Rad, J. Azizian, *Journal of Applied Chemistry.*, 10 (2015) 61-68.
- [6] A. Hasan Pour, R. Hosein Zadeh, Kh. Ghorban Pour, J. Abolhasani, Y. Moosaei Oskooei, *Journal of Applied Chemistry.*, 10 (2015) 51-64.
- [7] N. Kokabi, S. Otokesh, A. Amoozadeh, E. Klouri, *Journal of Applied Chemistry.*, 9 (2014) 31-38
- [8] T.R.K Reddy, C. Li, X.J. Guo, *J. Med. Chem.*, 54 (2011) 2080-2094.
- [9] R. Shiraki, A. Sumino, K. Tadano, S. Ogawa, *Tetrahedron Lett.*, 36 (1995) 5551-5554
- [10] Y. Chen, D.X. Zeng, N. Xie, Y.Z. Dang, *J. Org. Chem.*, 70 (2005) 5001-5005
- [11] Y. L. Lampe, R.G. Chou, R.G. Hanna, S.V. DiMeo, P.W. Erhardt, A.A. Hagedorn, W.R. Ingebretsen, E. Cantor, *J. Med. Chem.*, 36 (1993) 1041-1047
- [12] T. Kawasuji, M. Fuji, T. Yoshinaga, A. Sato, T. Fujiwara, R. Kiyama, *J. Bioorg. Med. Chem.*, 15 (2007) 5487-5492
- [13] W.R. Li, S.T. Lin, N.M. Hsu, M.S. Chern, *J. Org. Chem.*, 67 (2002) 4702-4206.
- [14] B.B. Snider, B.J. Neubert, *J. Org. Chem.*, 69 (2004) 8952-8955.
- [15] S.B. Singh, M.A. Goetz, E.T. Jones, G.F. Billes, R.A. Giacobbe, L. Herranz, S. Stevens Miles, D.L. Williams, *J. Org. Chem.*, 60 (1995) 7040-7042.
- [16] A.T. Khan, A. Ghosh, M. Musawwer Khan, *Tetrahedron Lett.*, 53 (2012) 2622-2626.
- [17] S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, *J. Chin. Chem. Lett.*, 25 (2014) 58-60.
- [18] S.S. Sajadikhah, N. Hazeri, *J. Res. Chem. Intermed.*, 40 (2014) 737-748.
- [19] S.S. Sajadikhah, N. Hazeri, M.T. Maghsoodlou, S.M. HabibiKhorasani., A. Beigbabaei, A. C. Willis., *J. Iran. Chem. Soc.*, 10 (2013) 863-871.
- [20] Q. Zhu, H. Jiang, J. Li, S. Liu, C. Xia, M. Zhang, *J. Comb. Chem.*, 11 (2009) 685-696.
- [21] S.S. Sajadikhah, N. Hazeri, M.T. Maghsoodlou, *J. Chem. Res.*, 37 (2013) 40-42.
- [22] S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, S. Mohamadian-Souri, *Res. Chem. Intermed.*, (2015) DOI: 10.1007/s11164-015-2178-z.
- [23] L. Lv, S. Zheng, X. Cai, Z. Chen, Q. Zhu, S. Liu, *J. Acs. Comb. Sci.*, 15 (2013) 183-192.



