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Coupling of Amines, Dialkyl acetylenedicarboxylaes and Formaldehyde Promoted by Copper (II) Chloride: An Efficient Synthesis of Polysubstituted Dihydro-2-oxopyrrols

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Abstract

An environmental friendly synthetic route for copper (II) chloride dihydrate catalyzed one-pot multi-component synthesis of biologically active high substituted dihydro-2-oxypyrroles has developed. The non-toxic, low-cost catalyst and eco-friendly and good to high yields are the notable benefits for the efficient synthesis of these products.

Keywords: *Copper (II) chloride dihydrate, Polysubstituted dihydro-2-oxypyrroles, Multi-component reaction, Environmentally benign procedure.*

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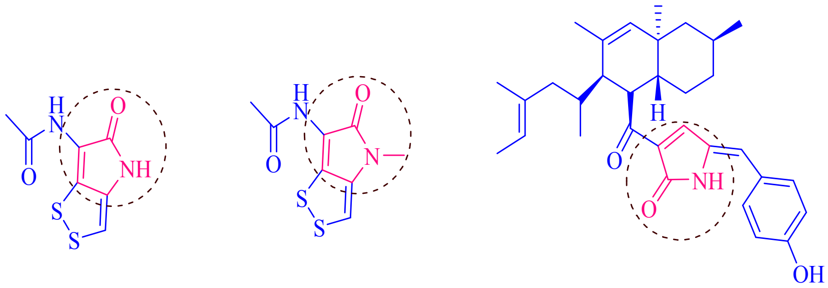
Introduction

In recent years, organic chemists have focused their attention towards green chemistry [1-6] for the synthesis of heterocyclic compounds by using of multi-component domino reactions (MCRs) [7] due to a broad range of notable advantages such as non-toxic substrate and environmental friendly. The compounds with pyrrole scaffold such as dihydro-2-oxypyrroles are attracting remarkable because of their medicinal and biological activities for example such as human cytomegalovirus (HCMV) protease [8], human cytosolic carbonic anhydrase isozymes [9], they have been used as Pl-091 [10], and cardiac cAMPphosphodiestrase [11], many of alkaloids with biological properties have pyrrole rings [12] are shown in Figure 1. Also these rings have been utilized as Oteromycin [13] and UCS1025A [14]. Some of them with biologically properties have been shown in Figure 1.



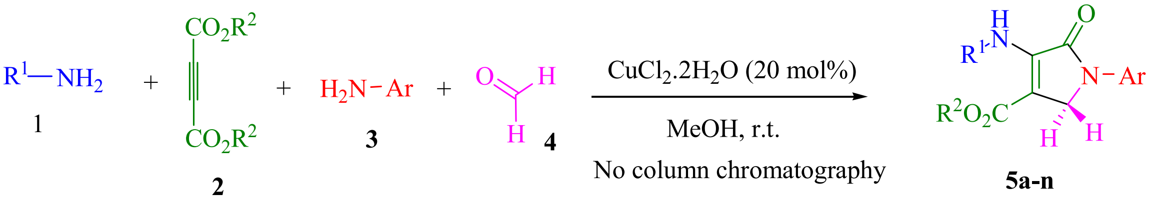
Holomycin Thiolutin Talaroconvolutin A

Figure1. Biologically active compounds with dihydro-2-oxypyrrole rings.

Recently, numerous methodologies for the preparation of these rings have been reported that is including Lewis and Brønsted acid catalysts such as I_2 [15], $InCl_3$ [16], $[n\text{-}Bu_4N][HSO_4]$ [17], $Al(H_2PO_4)_3$ [18], AcOH [19], $Cu(OAc)_2.H_2O$ [20], oxalic acid dihydrate [21], $ZrCl_4$ [22]. Some of these method have limitations such as long time reactions, low yields, use of strongly acidic conditions, high temperature, difficulty work-up, toxic and expensive catalysts. Furthermore, one of the source of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purity the products. In this present work, the products were obtained through simple filtering with no need column chromatographic.During the past decades, the use of copper compounds as environmental safe catalysts in organic synthesis have attracted great interest due to their notable advantages such as green, non-toxic, environmentally-friendly, easy to handle, highly efficient and low-cost [23, 24].

In this regard, we have reported synthesis of polysubstituted dihydro-2-oxypyrroles via one-pot, four condensation domino reactionbetween aromatic amines (**1** and **3**), dialkyl acetylenedicarboxylate **2** and formaldehyde **4** in the presence of copper (II) chloride dihydrate as an efficient catalyst under mild conditions.

(Scheme1).



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

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, ^{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 substituted dihydro-2-oxypyrroles **(5a-n)***

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; 0.045g) and copper (II) chloride dihydrate (0.034 g) were added and the reaction was stirred for appropriate time (Table 3). 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-n**). The catalyst is solvable in ethanol and was removed from the reaction mixture. All products were characterized by comparison of spectroscopic data (FT-IR, ^{1}HNMR). Spectra data of products are represented below:

Methyl 2,5-dihydro-2-oxo-1-phenyl-3-(phenylamino)-1H-pyrrole4-carboxylate ***(5a)***

Solid powder; yield: 84%; m.p. 153-155 °C;IR (KBr, cm^{-1}): ν 3264 (NH), 1692 (C=O), 1641 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (3H, s, OCH_3), 4.57 (2H, s, CH_2-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).

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

solid powder; yield: 75%; m.p. 176-178 °C; ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 4.50 (2H, s, CH_2-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).

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

solid powder; yield: 79%; m.p. 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (6H, s, $2CH_3$), 3.77 (3H, s, OCH_3), 4.52 (2H, s, CH_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).

Methyl 4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate ***(5f)***

solid powder; yield: 83%; m.p. 170-172 °C; IR (KBr, cm^{-1}): ν 3279 (NH), 1687 (C=O), 1642 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (3H, s, CH_3), 3.83 (6H, s, $2OCH_3$), 4.50 (2H, s, CH_2-N), 6.89 (4H, d, *J*=7.6 Hz, ArH), 7.13 (2H, s, ArH), 7.68 (2H, s, ArH), 8.03 (1H, s, NH).

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

solid powder; yield: 73%; m.p. 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 4.24 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.49 (2H, s, CH_2-N), 7.09 (2H, d, *J*=8.0 Hz, ArH), 7.27-7.75 (6H, m, ArH), 8.04 (1H, s, NH).

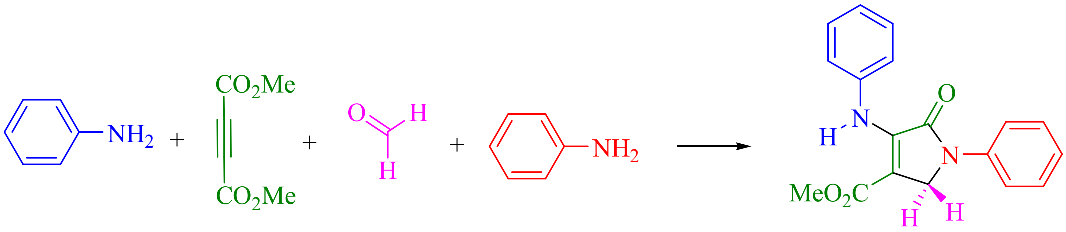
Ethyl 4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate ***(5m)*** solid powder; yield: 81%; m.p. 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 2.37 (6H, s, $2CH_3$), 4.23 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.53 (2H, s, CH_2-N),7.06 (2H, 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).

Results and discussion

The generality of this transformation, we investigated $CuCl_2.2H_2O$ catalyzed four component reaction between aniline (0.186 g), dimethyl acetylenedicarboxylate (DMAD) (0.14 g) and formaldehyde (0.045 g) as a model reaction under mild conditions for the synthesis of dihydro-2-oxypyrroles. In order to show the efficiency of catalyst in the current reaction, model reaction was performed in the absence of catalyst, which led to only a trace of product after 10 h (Table 1, entry 1).

Good yields were obtained in the presence of catalyst. The best amount of catalyst was 20 mol% (0.034 g) (Table 1, entry 5). The higher amount of catalyst did not increase the yields products (Table 1, entry 11) and the results are summarized in Table 1. The effect of various solvents was investigated for this protocol H_2O, CH_2Cl_2, $CHCl_3$, EtOH, MeOH, CH_3CN. Herein, reaction occurred efficiently to afford the corresponding dihydro-2-oxypyrroles in 84 % yield when 20 mol% $CuCl_2.2H_2O$ (0.034 g) was used in MeOH at room temperature (Table 1, entry 5).

Table1. Optimization of the reaction condition in the presence of different amounts of copper (II) chloride. dihydrate [a]



Entry	$CuCl_2.2H_2O$ (mol %)	Solvent	Time (h)	Isolated Yields (%)
1	Catalyst free	MeOH	10	Trace
2	5	MeOH	7	35
3	10	MeOH	6	53
4	15	MeOH	6	71

5	**20**	**MeOH**	**5**	**84**
6	20	Solvent free	8	46
7	20	H_2O	7	18
8	20	CH_2Cl_2	7	27
9	20	EtOH	5	54
10	20	$CHCl_3$	6	12
11	25	MeOH	5	86

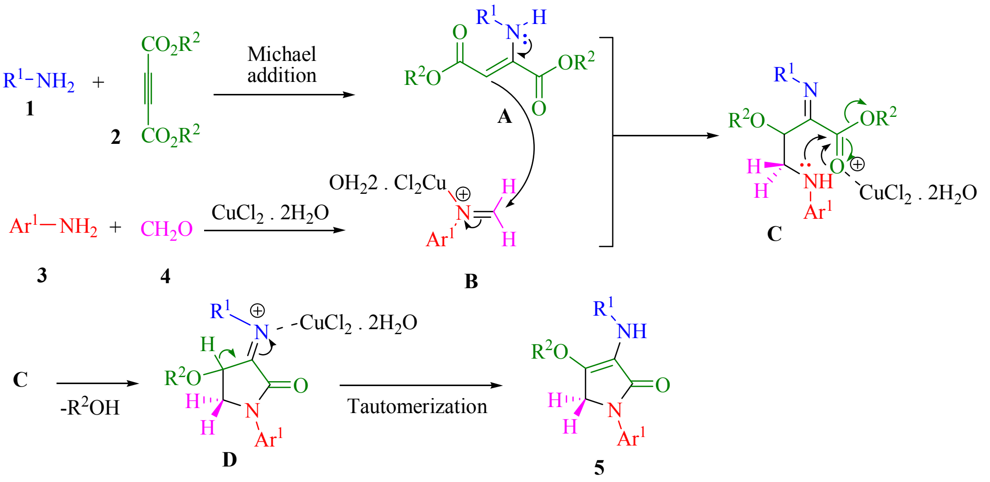
[a] Reaction conditions: aniline (2 mmol, 0.186 g), dimethyl acetylenedicarboxylate (1 mmol, 0.14 g) and formaldehyde (1.5 mmol, 0.045 g) and catalyst in various solvents at room temperature.

In order to study of this transformation, we have synthesis a series of polysubstituted dihydro-2-oxypyrroles with various aromatic amines with electron-releasing or electron-withdrawing groups, which gave excellent yields and the results, are shown in Table 2. Proposed mechanistic route for the synthesis of polysubstituted dihydro-2-oxypyrrolesin the presence of copper (II) chloride dihydrate are shown in scheme2.

Table 2. Synthesis of polysubstituted dihydro-2-oxypyrroles.

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	153-155	155-156 [15]
2	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5b**	6	77	172-174	171-173 [17]
3	4-F-C_6H_4	Me	4-F-C_6H_4	**5c**	5	88	160-162	163-165 [16]
4	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5d**	6	75	176-178	175-177 [17]
5	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5e**	5	79	178-180	177-178 [18]
6	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5f**	5	83	170-172	172-175 [17]
7	$PhCH_2$	Me	Ph	**5g**	4	81	139-141	140-141 [19]
8	Ph	Et	Ph	**5h**	5	80	136-138	138-140 [19]
9	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5i**	6	81	166-168	168-170 [17]
10	4-F-C_6H_4	Et	4-F-C_6H_4	**5j**	4.5	86	170-172	172-174 [17]
11	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5k**	6	73	169-171	169-171 [19]
12	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5l**	5	85	153-155	152-154 [18]
13	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5m**	6	81	131-133	131-132 [19]
14	$PhCH_2$	Et	Ph	**5n**	4.5	78	128-130	130-132 [19]

[a] Isolated yield.



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

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

Entry	product	Catalyst	Conditions	Time/Yield (%)	References
1	5a	I_2	MeOH, r.t.	1 h/82	[15]
2	5a	$InCl_3$	MeOH, r.t.	3h/85	[16]
3	5a	$[n-Bu_4N][HSO_4]$	MeOH, r.t.	4 h/88	[17]
4	5a	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[18]
5	5a	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6 h/91	[20]
6	5a	$ZrCl_4$	MeOH, r.t.	4 h/84	[22]
7	5a	$CuCl_2.2H_2O$	MeOH, r.t.	5h/84	This work
8	5h	I_2	MeOH, r.t.	1 h/81	[15]
9	5h	$InCl_3$	MeOH, r.t.	3h/85	[16]
10	5h	$[n-Bu_4N][HSO_4]$	MeOH, r.t.	4 h/86	[17]
11	5h	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[18]
12	5h	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5 h/85	[20]
13	5h	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[22]
14	5h	$CuCl_2._2H_2O$	MeOH, r.t.	5h/80	This work

[a] Based on the four-component reaction of aniline, dimethylacetylenedicarboxylate, formaldehyde.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of polysubstituted dihydro-2-oxypyrroles are shown in Table 3. Also ^{1}HNMR data of products have been compared with literature (Table 4). This study reveals that copper (II) chloride dihydrate has shown its extraordinary potential to be an alternative efficient and environmental friendly catalyst for the one-pot clean synthesis of these biologically active heterocyclic compounds, in addition to good to high yields are the notableadvantages this present methodology.

Table 4. Comparison of ^{1}HNMR data.

Entry	Product	H Shift (found)	H Shift (lit)	References
1	**5a**	3.76 (3H, s, OCH_3) 4.57 (2H, s, CH_2-N) 8.05 (1H, s, NH)	3.74 (3H, s, OCH_3) 4.53 (2H, s, CH_2-N) 8.08 (1H, s, NH)	[20]
2	**5d**	3.78 (3H, s, OCH_3) 4.50 (2H, s, CH_2-N) 8.03 (1H, s, NH)	3.79 (3H,s, NH) 4.48 (2H, s, CH_2-N) 8.06 (1H, s, OCH_3)	[20]
3	**5e**	2.36 (6H, s, $2CH_3$) 3.77 (3H, s, OCH_3) 4.52 (2H, s, CH_2-N) 8.03 (1H, s, NH)	2.38 (6H, d, $2CH_3$) 3.77 (3H, s, OCH_3) 4.50 (2H, s, CH_2-N) 8.06 (1H, s, NH)	[20]
4	**5k**	1.24 (3H, t, J=7.0 Hz, OCH_2CH_3) 4.24 (2H, q, J=7.2 Hz, OCH_2CH_3) 4.49 (2H, s, CH_2-N) 8.04 (1H, s, NH)	1.29 (3H,t, J = 7.1 Hz, OCH_2CH_3) 4.27 (2H, q, J = 7.1 Hz, OCH_2CH_3) 4.52 (2H, s, CH_2-N) 8.05 (1H, s, NH)	[20]
5	**5m**	1.25 (3H, t, J=7.2 Hz, OCH_2CH_3) 2.37 (6H, s, $2CH_3$) 4.23 (2H, q, J=7.2 Hz, OCH_2CH_3) 4.53 (2H, s, CH_2-N) 8.01 (1H, s, NH)	1.25 (3H,t, J = 7.1 Hz, OCH_2CH_3) 2.37 (6H,s, $2CH_3$) 4.24 (2H,q, J = 7.1 Hz, OCH_2CH_3) 4.51 (2H,s, CH_2-N) 8.04 (1H, s, NH)	[20]

Conclusion

In summary, a clean and eco-friendly protocol for the one-pot, four-component synthesis of biologically active polysubstituted dihydro-2-oxypyrroles by using of copper (II) chloride dihydrate as an environmental friendlyand efficient catalyst is reported. This methodology has notable advantages including low-cost and non-toxic catalyst, one-pot, good to high yields and simple work up with no need to column chromatography.

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