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Manganese (II) chloride tetrahydrate: An efficient and environmentally benign nature catalyst for the synthesis of substituted dihydro-2-oxypyrroles at ambient temperature

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Abstract: In this present paper, we have reported an efficient, simple and environmentally benign nature methodology for the synthesis of substituted dihydro-2-oxypyrrole via a one-pot four-component domino condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature with excellent yields and short reaction times. Manganese (II) chloride tetrahydrate ($MnCl_2.4H_2O$) has been used as a mild, economical and environmentally friendly catalyst for preparation of substituted dihydro-2-oxypyrrole. The environmentally benign nature, simple, inexpensive and non-toxic catalyst, easily separated with no column chromatographic separation, high catalytic activity, highly efficient is an option for the simple synthesis of these rings.

Keywords: $MnCl_2.4H_2O$, Dihydro-2-oxypyrrole derivatives, Multi-component reaction, Efficient methodology.

Introduction

Multi -component domino reactions (MCRs) [1-5] has attracted much interest in the recent years. Because of their important benefits for example atom-economy, mild and environmentally-friendly, low-cost, one-pot, simple work-up. The MCRs has become one of the most important goals for organic researches.

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 anneexin A2-S100A10 proteinintraction [6], has been used as Pl-091 [7], many of number alkaloids with biological activities have pyrrole rings [8], cardiac cAMP phosphodiestrase [9]. In addition, these rings have been used HIV integrase [10] and they have also anti- cancer [11] activities and these rings have been used as UCS1025A [12], Oteromycin [13]. Some example containing a heterocyclic dihydro-2-oxypyrrole rings with biologically activities have been shown in Figure **1**.

Recently, several protocols for the preparation of these compounds have been reported that is including Brønsted or Lewis acid catalysts such as I_2 [14], $InCl_3$ [15], $[n\text{-}Bu_4N][HSO_4]$ [16], $Al(H_2PO_4)_3$ [17], AcOH [18], oxalic acid [19] and lime juice [20]. 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 substituted dihydro-2-oxypyrrole, we had attempted to report a simple,

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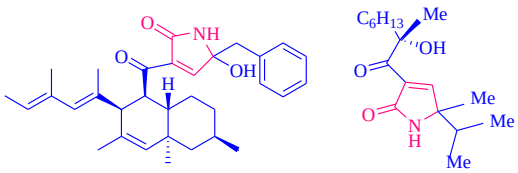
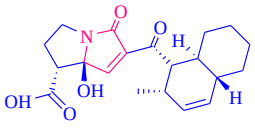
economical and environmental benign nature methodology for the preparation of these rings with one-pot, four condensation domino reaction using a mild and efficient catalyst and finally, we reported an efficient, mild and simple procedure for the synthesis of substituted dihydro-2-oxypyrrole through a one-pot four component reaction between amines (aromatic or aliphatic **1** and **3**), dialkyl acetylenedicarboxylate **2** and formaldehyde **4** in the presence of manganese (II) chloride tetrahydrate ($MnCl_2.4H_2O$) as an efficient and mild catalyst under ambient temperature in methanol (Scheme **1**).



Oteromycin

Pl-o91



UCS1025A

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

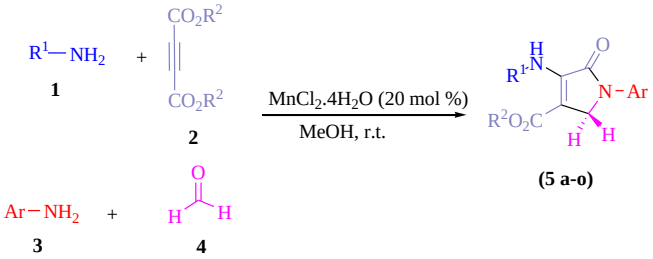
Results and discussion

The generality 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 various solvents was investigated for this protocol H_2O, CH_2Cl_2, $CHCl_3$, EtOH, MeOH, CH_3CN and among these solvents, MeOH found to be the best solvent for this methodology (Table **1**, entry 7) and the results are shown in Table **1**.

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 9h (Table **2**, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 20 mol % (0.039 g) (Table **2**, entry 5). The higher amount of catalyst did not increase the yields products (Table **2**, entry 6) and the results are summarized in Table **2**.

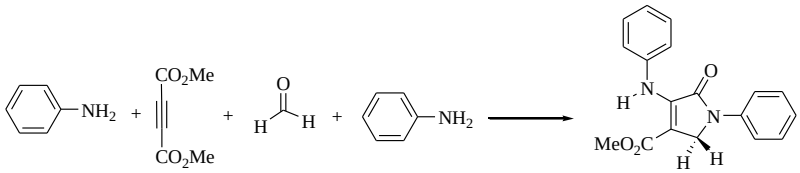
Finally, we reported Manganese (II) chloride Tetrahydrate (0.039 g) as a mild, efficient and environmentally benign nature catalyst for one-pot four-component reaction of amines (aromatic or aliphatic) dialkyl acetylenedicarboxylate and formaldehyde in MeOH as solvent at room temperature.

In order to study of this procedure, we have synthesis a series of dihydro-2-oxypyrrole derivatives with the type of aromatic or aliphatic amines with electron-donating or electron- with drawing groups such as Cl, Br, F, Me, OMe,… and dialkyl acetylenedicarbixylate with formaldehyde under ambient temperature in MeOH which gave excellent yields and the results are shown in Table **3**.



Scheme 1: Synthesis of substituted dihydro-2-oxypyrroles.

Table 1: Optimization of the reaction condition in the presence of different solvents.[a]

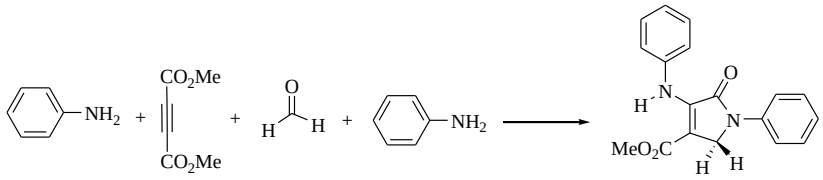


Entry	Catalyst (mol%)	Solvent	Time (h)	Product	Isolated Yields (%)
1	$MnCl_2.4H_2O$ (20 mol%)	Solvent free	9	5a	36
2	$MnCl_2.4H_2O$ (20 mol%)	EtOH	6	5a	58
3	$MnCl_2.4H_2O$ (20 mol%)	H_2O	8	5a	27
4	$MnCl_2.4H_2O$ (20 mol%)	CH_3CN	7	5a	41

5	$MnCl_2.4H_2O$ (20 mol%)	CH_2Cl_2	9	5a	26
6	$MnCl_2.4H_2O$ (20 mol%)	$CHCl_3$	8	5a	17
7	**$MnCl_2.4H_2O$ (20 mol%)**	**MeOH**	**5**	**5a**	**81**

[a] 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 2: Optimization of the reaction condition in the presence of different amounts of manganese (II) chloride tetrahydrate.



Entry	$MnCl_2.4H_2O$ (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	9	5a	trace
2	5	8	5a	29
3	10	7	5a	45
4	15	5	5a	67
5	**20**	**5**	**5a**	**81**
6	25	5	5a	83

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

Table 3: Synthesis of dihydro-2-oxypyrrole derivatives.

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	M.p. °C	Lit. M.p. °C
1	Ph	Me	Ph	**5a**	5	81	156-158	155-156 [14]
2	Ph	Et	Ph	**5b**	5	79	137-139	138-140 [18]
3	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5c**	5.5	83	173-174	171-173 [16]
4	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5d**	6	82	167-169	168-170 [16]
5	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5e**	5	86	175-177	172-175 [16]
6	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5f**	5	84	151-153	152-154 [17]
7	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5g**	4	85	176-178	177-178 [14]
8	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5h**	4.5	82	129-131	131-132 [18]
9	4-F-C_6H_4	Me	4-F-C_6H_4	**5i**	3.5	89	163-165	163-165 [19]
10	4-F-C_6H_4	Et	4-F-C_6H_4	**5j**	4	87	174-176	172-174 [16]
11	$PhCH_2$	Me	Ph	**5k**	3	89	139-141	140-141 [18]
12	$PhCH_2$	Et	Ph	**5l**	3	85	132-134	130-132 [18]
13	n-C_4H_9	Me	Ph	**5m**	3	84	59-61	60 [14]
14	n-C_4H_9	Me	3,4-Cl_2-C_6H_3	**5n**	4	81	96-98	97-99 [17]
15	n-C_4H_9	Et	4-Br-C_6H_4	**5o**	3.5	83	94-96	94-96 [17]

[a] Isolated yield.

Conclusion

In summary, we have reported a simple and efficient methodology for the one-pot, four-component synthesis of substituted dihydro-2-oxypyrrole by using of manganese (II) chloride tetrahydrate ($MnCl_2.4H_2O$) as a mild, economical and efficient catalyst. This methodology has an important advantages including mild, inexpensive and non-toxic catalyst, one-pot, eco-friendly, environmental friendly, high catalytic activity,

short reaction times and good yields, simple work up with no column chromatographic separation.

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-o):***

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 $MnCl_2.4H_2O$ (0.039 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-o**). All products were characterized by comparison of spectroscopic data (FT-IR, ^{1}HNMR). Spectra data of selected and known products are represented below:

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

Pale yellow solid, yield: (86%), mp. 175-177 °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).

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

Pale yellow solid, yield: (84%), mp. 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, $\underline{CH}_2CH_3$), 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).

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

White solid, yield: (85%), mp. 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (3H, 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).

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

White solid, yield: (82%), mp. 129-131 °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, $2\underline{CH}_2CH_3$), 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), 8.00 (1H, s, NH).

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

White solid, yield: (89%), mp. 163-165 °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), 7.73-7.79 (2H, m, ArH), 8.05 (1H, s, NH).

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