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One-pot Synthesis of Polysubstituted Dihydro-2-oxypyrroles Catalyzed by Vanadium (V) oxide

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Abstract

A mild and efficient synthesis of polysubstituted dihydro-2-oxypyrroles has been developed for the one-pot, four-component domino condensation of dialkyl acetylenedicarboxylate, formaldehyde and aromatic amines using Vanadium (V) oxide as the catalyst at ambient temperature. The use of Vanadium (V) oxide makes this process simple, more convenient, and environmentally friendly.

Keywords: *Vanadium (V) oxide, Dihydro-2-oxypyrrole derivatives, Multi-component reactions, Eco-friendly.*

Introduction

In the past few decades, studies in multi-component reactions (MCRs) [1-5] is an important goal for organic researches. Because of their important advantages such as atom-economy, mild and environmentally-friendly, low-cost, eco-friendly, one-pot, simple work-up MCRs is useful tools for the synthesis of heterocyclic compounds with biological and pharmaceutical activities such as dihydro-2-oxypyrroles.

Because of their pharmaceutical and biological activities, in recent years, the compound with pyrrole rings such as dihydro-2-oxypyrroles are an important class of heterocyclic compounds, such as DNA polymerase inhibitors [6] , has been used as P1-091 [7] , and Thiomarinol A4 as antibiotic has pyrrole rings [8], many of number alkaloids with biological activities have pyrrole rings [9], human cytomegalovirus(HCMV) protease [10], human cytosolic carbonic anhydrase isozymes [11], CD45 protein tyrosinphosphatase [12], cardiac cAMPphosphodiestrase [13]. In addition, these rings have been used HIV integrase [14], protoporphyrinogen oxidase

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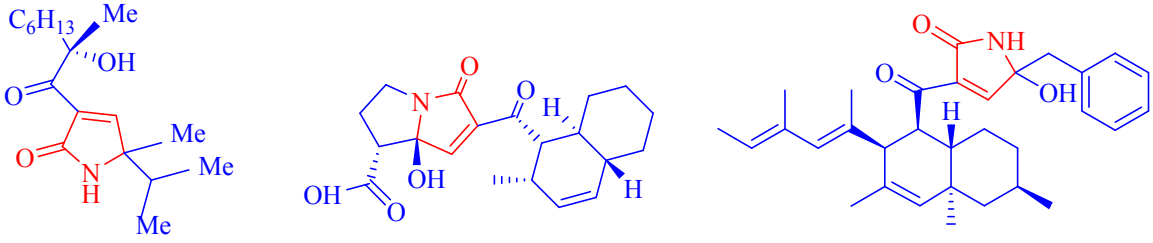
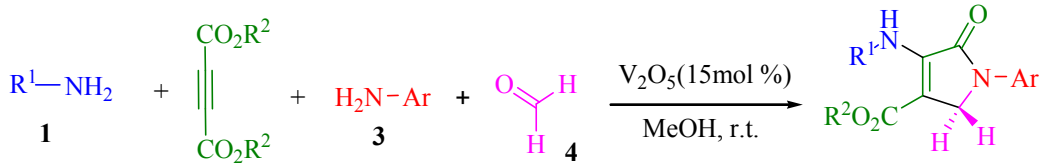
and herbicidal [15], modulators of GABAA receptors [16] and they have also anti- cancer [17], activities and these rings have been used as UCS1025A [18] and Oteromycin [19]. Some example containing heterocyclic dihydro-2-oxypyrrole rings with biologically activities have been shown in Figure 1.



Pl-o91 UCS1025A Oteromycin

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

In recent decades, a number of methodologies for preparation of these compounds have been reported that is including Lewis and Brønsted acid catalysts such as I_2 [20], $NiCl_2$ [21], heterogeneous TiO_2 nanopowder [22], $InCl_3$ [23], [*n*-Bu_4N][HSO_4] [24], $Al(H_2PO_4)_3$ [25], AcOH [26], Cu(OAC)2.H_2O [27], Oxalic acid [28], $ZrCl_4$ [29]. 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. Therefore, the study of mild catalysts and how their effect on environment is an aim in our recent researches and because of specially pharmaceutical and biological properties these compounds, the development of simple methodology and environmentally safe for the synthesis of these compounds has become the most important goal of our researches and finally, we have been reported vanadium (V) oxide as an inorganic, mild and efficient catalyst for the synthesis of polysubstituted dihydro-2-oxypyrrole through a one-pot four-component reaction between aromatic amines (1 and 3), dialkyl acetylenedicarboxylate 2 and formaldehyde 4 in the presence of vanadium (V) oxide as an efficient catalyst under ambient temperature in methanol (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 polysubstituted dihydro-2-oxypyrroles (***5a-l***)*

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 vanadium (V) oxide (0.027 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-l**). 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 4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2, 5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (***5a***)*

Yellow solid, M.p. 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s, CH_3), 3.83 (6H, s, $2OCH_3$), 4.50 (2H, s, CH_2-N), 6.89 (4H, d, *J*=17.6 Hz, ArH), 7.13 (1H, s, ArH), 7.68 (1H, s, ArH), 8.03 (^{1}H, s, NH).

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

Yellow solid, M.p. 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (3H, t, *J*=7.2Hz, CH_2CH_3), 3.83 (6H, s, $2OCH_3$), 4.23 (2H, q, *J*=7.2 Hz, CH_2CH_3), 4.50 (2H, s, CH_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 (^{1}H, s, NH).

Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl) -2,5-dihydro-5-oxo-1H-pyrrole3-carboxylate (5d)

Yellow solid, M.p. 169-171°C. IR (KBr) (kmax, cm^{-1}): 3,320 (NH), 2,991, 1,698, 1,640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.27 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.52 (2H, s, CH_2-N), 7.09 (2H, d, *J*=8.8 Hz, ArH), 7.29 (2H, d, *J* = 8.4 Hz, ArH), 7.37 (2H,d,*J* = 8.8 Hz,ArH), 7.76 (2H,d,*J* = 8.8 Hz,ArH), 8.07 (1H, s, NH).

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

Yellow solid, M.p. 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (3H, s, OCH_3), 4.52 (2H, s, CH_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 (^{1}H, s, NH).

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

Yellow solid, M.p. 154-156 °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).

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

Yellow solid, M.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 4.24 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 4.44 (2H, s, CH_2-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-methylphenylamino)-1-(4-methylphenyl)-2, 5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (***5i***)*

Yellow solid, M.p. 177-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (3H, 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).

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

Yellow solid, M.p. 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J*=7.2 Hz, CH_2CH_3), 2.37 (6H, s, $2CH_3$), 4.23 (2H, q, *J*=7.2 Hz, $2CH_2CH_3$), 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).

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

Yellow solid, M.p. 173-175 °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 (^{1}H, s, NH).

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

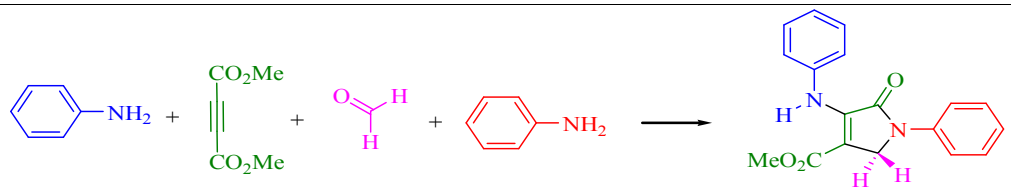
Yellow solid, M.p. 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 4.24 (2H, q, *J*=7.2 Hz, OCH_2CH_3),

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 (^{1}H, s, NH).

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 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 12h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol % (0.027 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.

Table 1. Optimization of the reaction condition in the presence of different amounts of vanadium (V) oxide[a].

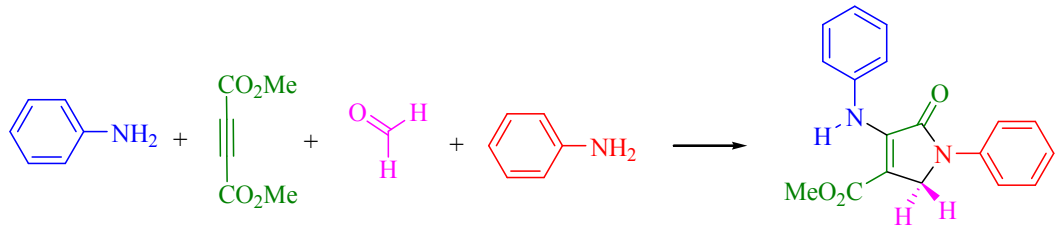


Entry	V_2O_5 (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	12	5g	trace
2	5	8	5g	26
3	10	8	5g	45
4	15	6	5g	81
5	20	6	5g	83

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

Also the effect of various solvents was investigated for this protocol, EtOH, MeOH, H2O, CH2Cl2, CHCl3, CH3CN and among these solvents, MeOH was found to be the best solvent for this methodology and the results are shown in Table 2 (Table 2, entry 3).

Table 2. Optimization of the reaction condition in the presence of different solvents by using of V_2O_5 (15 mol%) [a].



Entry	Catalyst (mol%)	Solvent	Time (h)	Product	Isolated Yields (%)
1	V_2O_5	Solvent free	7	5g	39
2	V_2O_5	EtOH	6	5g	62
3	V_2O_5	MeOH	6	5g	81
4	V_2O_5	H_2O	8	5g	26
5	V_2O_5	CH_2Cl_2	**8**	5g	19
6	V_2O_5	$CHCl_3$	8	5g	23
7	V_2O_5	CH_3CN	6	5g	41

[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.

Finally, we reported vanadium (V) oxide (0.027 g) as a mild an inorganic catalyst for efficient, environmental benign nature and eco-friendly one-pot four-component reaction of aromatic amines, dialkyl acetylenedicarboxylate and formaldehyde in MeOH as solvent under ambient temperature.

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

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	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5a**	6	78	174-176	172-175 [19]
2	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5b**	6	74	150-152	152-154 [20]
3	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5c**	5	71	171-173	171-173 [19]
4	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5d**	5	67	169-171	168-170 [19]
5	4-F-C_6H_4	Me	4-F-C_6H_4	**5e**	3	82	163-165	163-165 [23]
6	4-F-C_6H_4	Et	4-F-C_6H_4	**5f**	3	75	173-175	172-174 [19]
7	Ph	Me	Ph	**5g**	6	81	154-156	155-156 [15]
8	Ph	Et	Ph	**5h**	6	74	140-142	138-140 [21]
9	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5i**	3	85	177-179	177-178 [15]
10	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5j**	3	77	129-131	131-132 [21]
11	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5k**	4	69	173-175	175-177 [19]
12	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5l**	4	67	167-169	169-171 [21]

[a]Isolated yield.

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 Vanadium (V) oxide has shown its extraordinary potential to be an alternative efficient and inorganic catalyst for the one-pot synthesis of these heterocyclic compounds, in addition to good yields and short reaction times are the notable advantages this present methodology.

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	I_2	MeOH, r.t.	1 h/82	[20]
2	$InCl_3$	MeOH, r.t.	3h/85	[23]
3	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/88	[24]
4	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[25]
5	$Cu(OAC)_2.H_2O$	MeOH, r.t.	6 h/91	[27]
6	$ZrCl_4$	MeOH, r.t.	4 h/84	[29]
7	V_2O_5	MeOH, r.t.	6 h/81	This work

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

Conclusion

In summary, in this protocol, the use of vanadium (V) oxide as an inorganic, mild and efficient catalyst for the one-pot, four-component synthesis of polysubstituted dihydro-2-oxypyrrole from starting materials is reported. Some advantages this methodology are using of mild and non-toxic catalyst, inexpensive, eco-friendly, environmentally benign nature, short reaction times with no column chromatographic separation and good to high yields.

Acknowledgments

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