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Ascorbic acid: a naturally green and efficient catalyst for one-pot synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates under ambient temperature

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ABSTRACT
A naturally green and economical ascorbic acid synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates has been accomplished via one-pot four-condensation of dialkylacetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature. The notable advantages of the present procedure are green, natural and low-cost catalyst, operational simplicity, eco-friendly, environmentally benign nature, no necessity of chromatographic purification steps, short reaction times and good to high yields.
Keywords: *Ascorbic acid, Green catalyst, N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates, Multi-component reaction, One-pot procedure.*

1. INTRODUCTION
Compounds with pyrrole rings have been given much attention in recent years as they constitute important procedures forpromising drugs in the field of medicinal chemistry. Dihydro-2-oxypyrroles are such heterocyclic compounds that have shown biological and pharmaceutical properties for example such as for example human cytomegalovirus (HCMV) protease [1], CD45 protein tyrosinphosphatase [2], anti- cancer [3], they havebeen used as Thiomarinol A4 as antibiotic has pyrrole rings [4], many of number alkaloids with biological activities have pyrrole rings [5], and these rings have been used as UCS1025A [6], Oteromycin [7]. In addition, these rings have been used HIV integrase [8], and they have also herbicidal [9] activities. Due to the importance of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates, various methods for the synthesis of these compounds have been developed that is including Lewis and Brønsted acid catalysts such as ethylenediammoniumdiformate (EDDF) [10], $Cu(OAC)_2.H_2O$ [11], $InCl_3$ [12], Fe_3O_4@nano-cellulose–OPO_3H [13], I_2 [14], AcOH [15], $[n\text{-}Bu_4N][HSO_4]$ [16], $Al(H_2PO_4)_3$ [17], oxalic acid [18], $ZrCl_4$ [19], $BiFeO_3$ nanoparticles [20], nano-Fe_3O_4@SiO_2/$SnCl_4$ [21], $TiCl_4$/nano-sawdust [22], graphene oxide [23], $CoFe_2O_4$@SiO_2@IRMOF-3 [24], caffeine [25], glutamic acid [26], $ZnCl_2$ [27] and $Mn(NO_3)_2.4H_2O$ [28]. Some of limitations these methodologies are use of strongly acidic conditions, toxic and expensive catalysts, low yields, difficulty work-up and long times reactions.
Green catalyst for the synthesis of heterocyclic compounds has attracted considerable interest from both environmental and economically points in multi component reactions.
In recent years, the use of ascorbic acid (Figure 1) has received considerable attention in organic chemistry as a catalyst[29] because of its important advantages, such as green, natural, low-cost, high efficiently and also, it is well known that the ascorbic acid has many applications in the pharmacy and food. Because of the important antioxidant and metabolic functions of ascorbic acid it must, therefore, be incorporated as part of the human diet, and is known as vitamin C. L-ascorbic acid in plants, the main source of vitamin C for humans, is also an essential compounds for plants, with important roles as an antioxidant and as a modulator of plant development through hormone signaling [30].

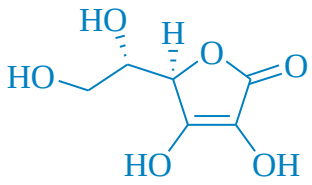


Figure 1. Structure of ascorbic acid.

Therefore, as a part of our research aimed at the development of synthetic methodologies using green catalysts [31-33] for preparation of organic compounds, and we report herein, a simple and clean protocol for the four-component synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates in the presence of ascorbic acid as a catalyst by reaction of dialkylacetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature. Efficient, green, natural and low-cost catalyst, good to high yields, short reaction times and eco-friendly that makes our protocol alternative in comparison to some of the earlier reported methods.

2. MATERIALS AND METHODS
General.
Melting points all compounds were determined using an Electrothermal 9100 apparatus. Also, nuclear magnetic resonance, ^1H 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 N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates (5a-o). A mixture of amine **1** (1.0 mmol) and dialkylacetylenedicarboxylate**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 ascorbic acid (0.026 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**). The catalyst is solvable in ethanol and was removed from the reaction mixture. All products were characterized by comparison of spectroscopic data (^{1}HNMR). Spectra data some known products are represented below:

Methyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5c). Yield: 81%; M.p. 173-175 °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).

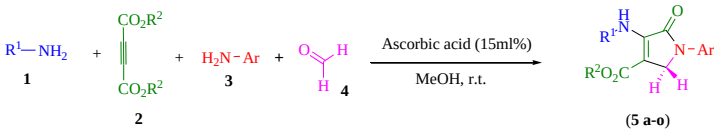
Ethyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5d). Yield: 77%; M.p. 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (3H, t, *J*=7.2Hz, $CH_2\underline{CH}_3$), 3.83 (6H, s, $2OCH_3$), 4.23 (2H, q, *J*=7.2 Hz, $\underline{CH}_2CH_3$), 4.50 (2H, s, $C\underline{H}_2$-N), 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).

Methyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5g). Yield: 82%; 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, $C\underline{H}_2$-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).

Ethyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5h). Yield: 84%; M.p. 128-130 °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), 7.69 (2H, d, *J*=8.4 Hz, ArH), 8.01 (1H, s, NH).

3. RESULTS

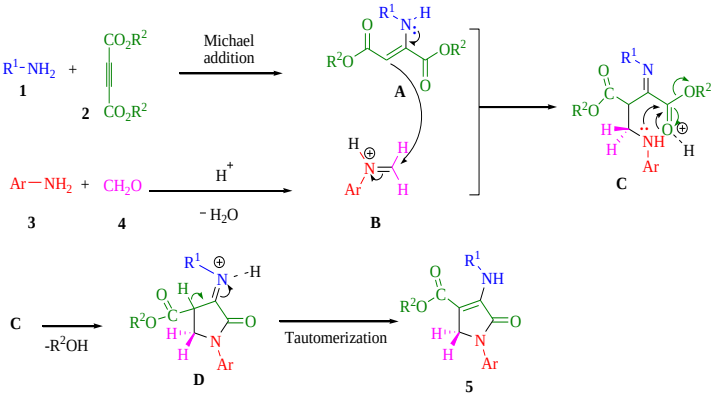
We have studied a green, eco-friendly and simple methodology for one-pot synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylatesthrough a four-component reaction between amines(aromatic or aliphatic **1** and **3**), dialkylacetylenedicarboxylate**2** and formaldehyde **4** under ambient temperature in methanol (Scheme1)**.**



Scheme 1. Synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates.

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 8h (Table 1, entry 1).Good yields were obtained in the presence of catalyst. The best amount of catalyst was 15 mol % (0.026g) (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. Also the effect of various solvents was investigated for this protocol H2O, EtOH, MeOH, CH3CN, CHCl3, CH2Cl2 and among these solvents, MeOH was found to be the best solvent for this methodology (Table 2, entry 4) and the results are shown in Table 2. Finally, we reported ascorbic acid (0.026 g) as a green and efficient catalyst for economical, environmental benign nature and clean one-pot four-component reaction of amines (aromatic or aliphatic) dialkylacetylenedicarboxylate and formaldehyde in MeOH as solvent under ambient temperature.

In order to study of this procedure, we have synthesis a series of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates with the type of aromatic or aliphatic amines with electron-donating or electron-withdrawing groups such as Cl, F, Me, OMe,… and dialkylacetylenedicarbixylate with formaldehyde under ambient temperature in MeOH which gave excellent yields and the results are shown in Table 3. And proposed mechanistic route for the synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates in the presence of ascorbic acid isshown in scheme 2.

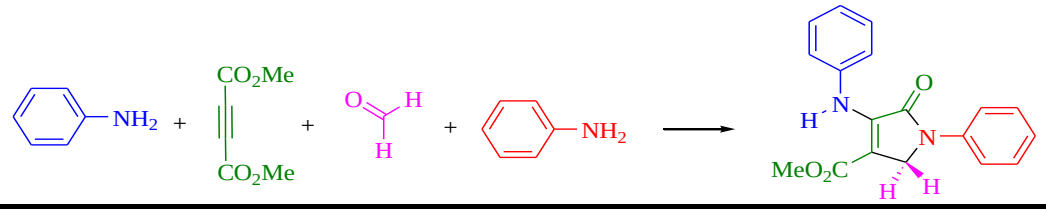


Scheme 2. Proposed mechanistic route for the synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates.

4. CONCLUSIONS

In summary, a green and clean methodology for the one-pot synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates using ascorbic acid as the catalyst is described. The present protocol provides economic and efficient method for the synthesis of these compounds. Several notable advantages over the existing methods including green, low-cost and available catalyst, environmentally friendly, short reaction times, operational simplicity, good to high yields and purification of products without the need of column chromatography.

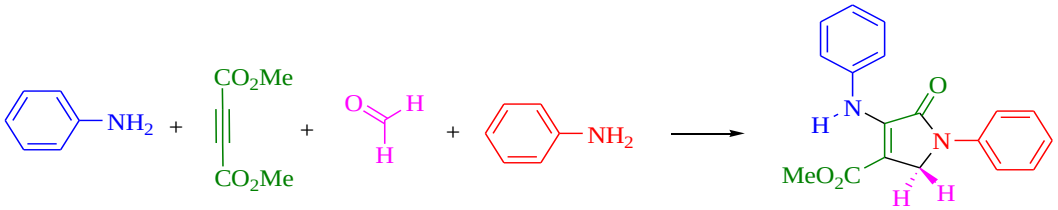
Table 1. Optimization of the reaction condition in the presence of different amounts of ascorbic acid [a].



Entry	Ascorbic acid (mol %)	Time (h)	Product	Isolated Yields (%)
1	Catalyst free	8	5a	trace
2	5	7	5a	53
3	10	6	5a	69
4	**15**	**4**	**5a**	**87**
5	20	4	5a	89

[a] Reaction conditions: aniline (2.0 mmol), dialkylacetylenedicarboxylate (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 ascorbic acid (15mol%)[a].



Entry	Solvent	Time (h)	Product	Isolated Yields (%)
1	Solvent free	6	5a	43
2	H_2O	6.5	5a	29
3	EtOH	4	5a	68
4	**MeOH**	**4**	**5a**	**87**
5	CH_3CN	**7**	5a	56
6	$CHCl_3$	7.5	5a	27
7	CH_2Cl_2	8	5a	23

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

Table 3. Synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates.

Entry	R^1	R^2	Ar^1	Product	Time (h)	Yield (%)[a]	M.p. ˚C	Lit. M.p. ˚C
1	Ph	Me	Ph	**5a**	4	87	155-157	155-156[14]
2	Ph	Et	Ph	**5b**	4	84	139-141	138-140[15]
3	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5c**	4.5	81	173-175	172-175[16]
4	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5d**	5	77	154-156	152-154[17]
5	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5e**	6	79	171-173	171-173[16]
6	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5f**	6	75	170-172	168-170[16]
7	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5g**	4	82	178-180	177-178[14]
8	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5h**	4.5	84	128-130	131-132[15]
9	4-F-C_6H_4	Me	4-F-C_6H_4	**5i**	4	89	164-166	163-165[18]
10	4-F-C_6H_4	Et	4-F-C_6H_4	**5j**	4	85	172-174	172-174[16]
11	$PhCH_2$	Me	Ph	**5k**	5	83	140-142	140-141[15]
12	$PhCH_2$	Et	Ph	**5l**	5	82	129-131	130-132[15]
13	$PhCH_2$	Me	4-F-C_6H_4	**5m**	4.5	89	166-168	166-168[17]
14	n-C_4H_9	Me	Ph	**5n**	5	86	60-62	60[14]
15	n-C_4H_9	Et	4-Br-C_6H_4	**5o**	6	78	92-94	94-96[17]

[a] Isolated yield.

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