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Clean, facile and eco-friendly synthesis of biologically active N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates at present of maleic acid as an environmental friendly, readily and efficient catalyst under ambient temperature

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ABSTRACT

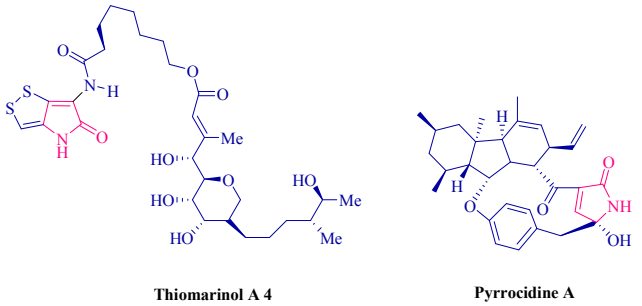
A clean, eco-friendly and simple synthetic route of biologically active N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates in the present of a catalytic amount of maleic acid as an environmental friendly, efficient and readily di-functional Brønsted acid catalyst via one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature has been accomplished. This present methodology has notable benefits such as highly efficient, inexpensive, easy-to-handle and non-toxic catalyst, one-pot, environmental benign nature, short reaction times, high to excellent yields, simplicity of operation with no necessity of chromatographic purification steps and eco-friendly and products have been characterized by melting points, FT-IR and ^{1}H NMR spectroscopy.

Keywords: *Maleic acid, Biologically active N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates, Multi-component reaction, Environmentally benign nature and eco-friendly procedure, Clean synthesis.*

1. INTRODUCTION

In the recent years, considerable attention has been paid to the design of efficient and environmental friendly synthetic route by using of multi component domino reactions (MCRs) [1-4] due to a wide range points such as atom-economy, simple work-up, mild and environmentally-friendly, one-pot and low-cost.

In recent years, pyrrole derivatives are a common structural motif in variety of natural and non-natural products. Their derivatives have been known to exhibit a wide range of pharmacological and biological properties such as human cytomegalovirus (HCMV) protease [5], human cytosolic carbonic anhydrase isozymes [6], they have been used as Pl-091 [7], and cardiac cAMPphosphodiestrase [8],many of number alkaloids with biological activities have pyrrole rings [9]. These rings have been used as UCS1025A [10], Oteromycin[11]. Some example containing a heterocyclic dihydro-2-oxypyrrole rings with biologically activities have been shown in Figure 1.

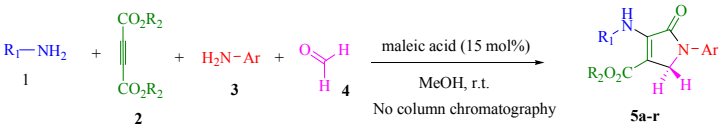


Thiomarinol A 4 Pyrrocidine A

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

Recently, numerous methodologies for the preparation of these rings have been reported that is including Lewis and Brønsted acid catalysts such as I_2 [12], $InCl_3$ [13], $[n\text{-}Bu_4N][HSO_4]$ [14], $Al(H_2PO_4)_3$ [15],AcOH[16], $Cu(OAc)_2.H_2O$ [17], Oxalic acid dehydrate [18], $ZrCl_4$ [19], *p*-TsOH.H_2O [20]. Some of these protocols have limitations such as toxic and expensive catalysts, long time reactions, low yields, use of strongly acidic conditions, difficulty work-up, high temperature.

Maleic acid (MA) is a very important chemical intermediate that find applications in nearly every field of industrial chemistry. Also it is an important raw material used in the manufacture of lubricant additives, unsaturated polyester resins, surface coatings, plasticizers, copolymers and agricultural chemicals [21, 22].



1 2 3 4 5a-r

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

Due to above considerations and our interest in the development of synthesis of N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates, we had attempted to report a simple and environmentally benign methodology for the preparation of these biologically active rings with one-pot, four condensation domino reaction using an environmental friendly and efficient catalyst and finally, we reported an clean, eco-friendly and simple procedure

for the synthesis of N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates through a one-pot four-component reaction between aromatic amines (1 and 3), dialkylacetylenedicarboxylate 2 and formaldehyde 4 in the presence of maleic acid as an environmentally benign, efficient and economical di-functional Brønsted acid catalyst under ambient temperature in methanol (Scheme1).

Efficient, readily, low-cost, easy-to-handle and non- toxic catalyst, high to excellent yields, short reaction times, one-pot and eco-friendly that makes our protocol alternative in comparison to some of the earlier reported methods.

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 separation.

2. EXPERIMENTAL SECTION

2.1. 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.

2.2. General procedure for preparation of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates (5a-r).

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 maleic acid (0.017 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**). 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: 93%; M.p. 154-156 °C; IR (KBr, cm^{-1}): ν 3264 (NH), 1692 (C=O), 1641 (C=O); ^{1}H NMR (400 MHz, CDCl3): 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 3-(benzylamino)-1-phenyl-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate**(5c)***

Solid powder; Yield: 89%; M.p. 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 4.48 (s, 2H, CH_2-N), 5.10 (d, 2H, *J* = 6.4 Hz, CH_2-NH), 6.90 (br, 1H, NH), 7.18-7.41 (m, 8H, ArH), 7.73 (d, 2H, *J* = 8.0 Hz, ArH).

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

Solid powder; Yield: 86%; M.p. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 4.24 (q, 2H, *J* = 7.2 Hz, OCH_2CH_3), 4.44 (s, 2H, CH_2-N), 5.11 (d, 2H, *J*=6.4 Hz, CH_2-NH), 6.92 (br, 1H, NH), 7.19-7.38 (m, 8H, ArH), 7.73-7.75 (m, 2H, ArH).

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

Solid powder; Yield: 91%; M.p. 165-167 °C; IR (KBr, cm^{-1}): ν 3320 (NH), 1697 (C=O), 1645 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ*3.80 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2-N), 5.13 (d, 2H, *J* = 6.4 Hz, CH_2-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).

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

Solid powder; Yield: 94%; M.p. 59-61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.97 (t, 3H, *J* = 7.2 Hz, CH_3), 1.42 (sextet, 2H, *J* = 7.2 Hz, CH_2), 1.64 (quintet, 2H, *J* = 7.2 Hz, CH_2), 3.82 (s, 3H, OCH_3), 3.85 (t, 2H, *J* = 7.2 Hz, CH_2-NH), 4.45 (s, 2H, CH_2-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).

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

Solid powder; Yield: 84%; M.p. 92-94 °C; IR (KBr, cm^{-1}): ν 3320 (NH), 1699 (C=O), 1649 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 0.97 (t, 3H, *J* = 7.2 Hz, CH_3), 1.35 (t, 3H, *J* = 7.2 Hz, OCH_2CH_3), 1.43 (sextet, 2H, *J* = 7.6 Hz, CH_2), 1.61 (quintet, 2H, *J* = 7.6 Hz, CH_2), 3.87 (t, 2H, *J* = 7.2 Hz, CH_2-NH), 4.28 (t, 2H, *J* = 7.2 Hz, OCH_2CH_3), 6.72 (br s, 1H, NH), 4.40 (s, 2H, CH_2-N), 7.52 (d, 2H, *J* = 8.8 Hz, ArH), 7.71 (d, 2H, *J* = 8.8 Hz, ArH).

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

Solid powder; Yield: 89%; M.p. 176-179 °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).

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

Solid powder; Yield: 88%; M.p. 132-134 °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).

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

Solid powder; Yield: 81%; M.p. 166-169 °C; IR (KBr) (k_{max}, cm^{-1}): 3,320 (NH), 2,991, 1,698, 1,640; ^{1}H NMR (400 MHz, CDCl3): 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-methoxyphenylamino)-1-(4-methoxy phenyl)-2, 5-dihydro-5-oxo-1H-pyrrole-3-carboxylate **(5m)***

Solid powder; Yield: 89%; M.p. 174-176 °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 4-(4-methoxyphenylamino)-1-(4-methoxy phenyl)-2, 5-dihydro-5-oxo-1H-pyrrole-3-carboxylate ***(5n)***

Solid powder; Yield: 83%; M.p. 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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 (1H, s, NH).

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

Solid powder; Yield: 92%; M.p. 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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 (1H, s, NH).

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

Solid powder; Yield: 83%; M.p. 175-177 °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).

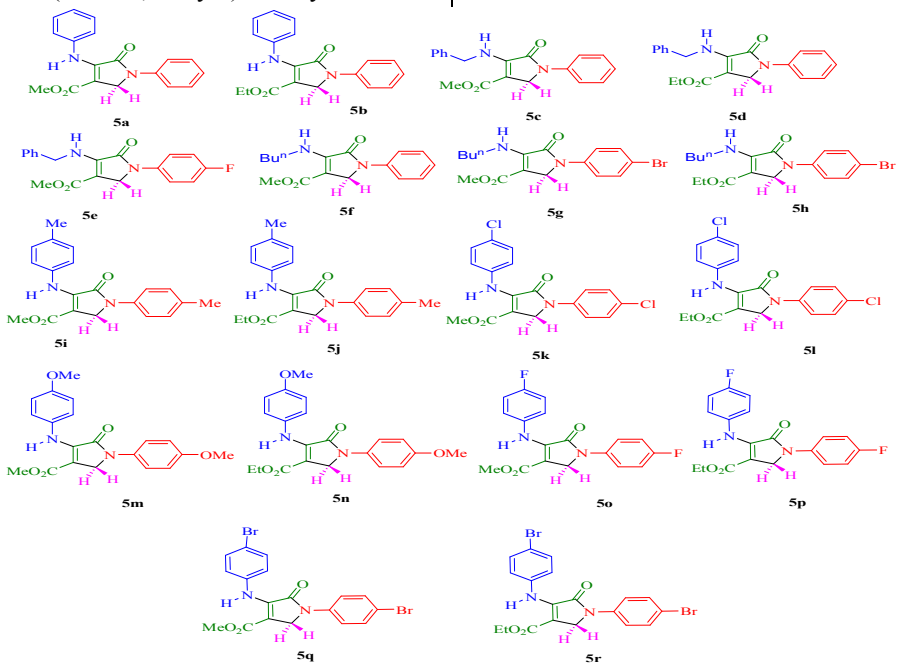
*Ethyl 3-(4-bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate****(5r)***

Solid powder; Yield: 85%; M.p. 171-173 °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).

3. RESULTS SECTION

At the outset, the one-pot four-component reaction of aniline (2 mmol), dimethyl acetylenedicarboxylate (DMAD) (1 mmol) and formaldehyde (1.5 mmol) was tested in methanol (3 ml) as a model reaction at ambient temperature.

And a control experiment revealed that in the absence of the catalyst, only a trace amount of product **5a** was obtained (Table 1, entry 1). To further optimize reaction conditions, we investigated the effect of the loading amount of maleic acid on the model reaction in methanol (Table 1). The optimum yield of product **5a** (93%) was obtained in the presence of 15 mol% (0.017 g) of maleic acid (Table 1, entry 4). By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower yield (Table 1, entry 2). While increasing the catalyst loading to 20 mol% has no significant effect on the product yield (Table 1, entry 11). Subsequently, a survey of solvents showed methanol to be the best choice (Table 1, entry 4). Low yields were obtained when the model reaction was performed in EtOH, H_2O, CH_3CN, CH_2Cl_2, $CHCl_3$ (Table 1). Thus, a variety of other anilines (aromatic and aliphatic) containing electron-withdrawing or –donating group were reacted with dimethy or diethyl acethylenedicarboxylate and formaldehyde under the optimized conditions (Scheme 2) and the results are summarized in Table 3. The substituted on the benzene ring such as Cl, Br, F, Me and OMe were tolerated during the reaction. In all cases, the reaction proceeded smoothly to generate the corresponding N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates in high yield. The structure of the products was characterized by their melting points, FT-IR and nuclear magnetic resonance (^{1}H NMR) spectral data, which were then compared with those of authentic samples.



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

Table1. Optimization of the reaction condition on the synthesis of **5a**[a].

Entry	maleic acid(mol %)	Solvent	Time (h)	Isolated Yields (%)
1	Catalyst free	MeOH	6	Trace
2	5	MeOH	6	51
3	10	MeOH	5	78
4	**15**	**MeOH**	**4**	**93**
5	15	Solvent free	6	37
6	15	EtOH	4	75
7	15	H_2O	8	24
8	15	CH_3CN	7	42
9	15	CH_2Cl_2	7	26
10	15	$CHCl_3$	7	22
11	20	MeOH	4	94

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

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

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	M.p. °C	Lit. M.p. °C
1	Ph	Me	Ph	**5a**	4	93	154-156	155-156[12]
2	Ph	Et	Ph	**5b**	4	91	140-142	138-140[16]
3	$PhCH_2$	Me	Ph	**5c**	3.5	89	141-143	140-141[16]
4	$PhCH_2$	Et	Ph	**5d**	4	86	130-132	130-132[16]
5	$PhCH_2$	Me	4-F-C_6H_4	**5e**	3	91	165-167	166-168[15]
6	n-C_4H_9	Me	Ph	**5f**	3	94	59-61	60[12]
7	n-C_4H_9	Me	4-Br-C_6H_4	**5g**	3.5	87	175-177	175-177[14]
8	n-C_4H_9	Et	4-Br-C_6H_4	**5h**	3.5	84	92-94	94-96[19]
9	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5i**	3	89	176-179	177-178[12]
10	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5j**	3	88	132-134	131-132[16]
11	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5k**	4	85	171-173	170-172[19]
12	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5l**	4.5	81	166-169	168-170[19]
13	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5m**	3	89	174-176	172-175[14]
14	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5n**	4	83	151-153	153-155[19]
15	4-F-C_6H_4	Me	4-F-C_6H_4	**5o**	3	92	162-164	164-166[19]
16	4-F-C_6H_4	Et	4-F-C_6H_4	**5p**	3	93	173-175	172-174[14]
17	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5q**	4	83	175-177	175-177[14]
18	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5r**	4	85	171-173	169-171[16]

[a]Isolated yield.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates are shown in Table 3. Also ^{1}HNMR data of products have been compared with literature (Table 4). This study reveals that maleic acid has shown its extraordinary potential to be an alternative readily, mild, efficient and environmental friendly catalyst for one-pot simple and clean synthesis of these biologically active heterocyclic compounds, in addition to high to excellent yields are the notable advantages this present methodology.

Table 3. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of N-aryl-3- aminodihydropyrrol-2-one-4-carboxylates.

Entry	Compound	Catalyst	Conditions	Time/Yield (%)	Refreences
1	**5a**	I_2	MeOH, r.t.	1 h/82	[12]
2	**5a**	$InCl_3$	MeOH, r.t.	3h/85	[13]
3	**5a**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/88	[14]
4	**5a**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/81	[15]
5	**5a**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6h/91	[17]
6	**5a**	$ZrCl_4$	MeOH, r.t.	4 h/84	[19]
7	**5a**	*p*-TsOH.H_2O	MeOH, r.t.	3h/84	[20]
8	**5a**	maleic acid	MeOH, r.t.	4 h/93	This work
9	**5b**	I_2	MeOH, r.t.	1 h/81	[12]
10	**5b**	$InCl_3$	MeOH, r.t.	3h/85	[13]
11	**5b**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4 h/86	[14]
12	**5b**	$Al(H_2PO_4)_3$	MeOH, r.t.	5 h/80	[15]
13	**5b**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5h/85	[17]
14	**5b**	$ZrCl_4$	MeOH, r.t.	3.5 h/83	[19]
15	**5b**	*p*-TsOH.H_2O	MeOH, r.t.	4h/84	[20]
16	**5b**	maleic acid	MeOH, r.t.	4 h/91	This work

Table 4. Comparison of ^{1}H-NMR data.

Entry	Product	H Shift (found)	H Shift (lit)	Ref.
1	**5a**	3.76 (3H, s, OCH_3) 4.57 (2H, s, $\underline{CH_2}$-N) 8.05 (1H, s, NH)	3.74 (3H, s, OCH_3) 4.53 (2H, s, $\underline{CH_2}$-N) 8.08 (1H, s, NH)	17
2	**5i**	2.36 (6H, s, $2CH_3$) 3.77 (3H, s, OCH_3) 4.52 (2H, s, $\underline{CH_2}$-N) 8.03 (1H, s, NH)	2.38 (6H, d, $2CH_3$) 3.77 (3H, s, OCH_3) 4.50 (2H, s, $\underline{CH_2}$-N) 8.06 (1H, s, NH)	17
3	**5j**	1.25 (3H, t, *J*=7.2 Hz, $OCH_2\underline{CH_3}$) 2.37 (6H, s, $2CH_3$) 4.23 (2H, q, *J*=7.2 Hz, $O\underline{CH_2}CH_3$) 4.53 (2H, s, $\underline{CH_2}$-N) 8.01 (1H, s, NH)	1.25 (3H,t, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 2.37 (6H,s, $2CH_3$) 4.24 (2H,q, *J* = 7.1 Hz, $O\underline{CH_2}CH_3$) 4.51 (2H,s, $\underline{CH_2}$-N) 8.04 (1H, s, NH)	17
4	**5q**	3.78 (3H, s, OCH_3) 4.50 (2H, s, $\underline{CH_2}$-N) 8.03 (1H, s, NH)	3.79 (3H,s, NH) 4.48 (2H, s, $\underline{CH_2}$-N) 8.06 (1H, s, OCH_3)	17
5	**5r**	1.24 (3H, t, *J*=7.0 Hz, $OCH_2\underline{CH_3}$) 4.24 (2H, q, *J*=7.2 Hz, $O\underline{CH_2}CH_3$) 4.49 (2H, s, $\underline{CH_2}$-N) 8.04 (1H, s, NH)	1.29 (3H,t, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$) 4.27 (2H, q, *J* = 7.1 Hz, $O\underline{CH_2}CH_3$) 4.52 (2H, s, $\underline{CH_2}$-N) 8.05 (1H, s, NH)	17

4. CONCLUSIONS

In summary, an efficient, clean and eco-friendly protocol for the one-pot, four-component synthesis of biologically activeN-aryl-3- aminodihydropyrrol-2-one-4-carboxylates by using of maleic acid as an environmental friendly and readily di-functional Brønsted acid catalyst is reported. The present procedure provides economic and simple methodology for the synthesis of these heterocyclic compounds. And offers several notable advantages over the exiting methods including low-cost, available and non-toxic catalyst, environmental friendly, short reaction times, operational simplicity, high to excellent yields and purification of products without need of column chromatography.

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