A one-pot multi-component synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates catalysed by oxalic acid dihydrate

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A simple synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates *via* one-pot multi-component reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in the presence of oxalic acid dihydrate (20 mol%) as catalyst in methanol is described. This homogeneous catalytic procedure offers advantages including mild reaction conditions, good to high yields, short reaction time, simple and readily available starting materials, easy work-up and there is no need for column chromatography.

Keywords: heterocycle, dihydropyrrol-2-one, oxalic acid dihydrate, dialkyl acetylenedicarboxylate, multi-component reaction

A number of biologically-active compounds and natural products contain the dihydropyrrol-2-one ring.[1–6] For example, dihydropyrrol-2-one derivatives act as HIV integrase,[7] antitumor and anticancer agents,[8] antibiotics,[9] vascular endothelial growth factor inhibitors,[10] modulators of $GABA_A$ receptors,[11] and nootropic agents.[12] Moreover, these heterocycles have been demonstrated as inhibitors for the protoporphyrinogen oxidase,[13] human cytomegalovirus (HCMV) protease,[14] annexin A2-S100A10 protein interaction,[15] human cytosolic carbonic anhydrase isozymes,[16] CD45 protein tyrosine phosphatase,[17] and DNA polymerase.[18]

Recently, two methods have been reported for the preparation of dihydropyrrol-2-ones involving one-pot multi-component reaction using catalysts, such as acetic acid[19] and molecular iodine.[20] Owing to the wide applications and significance of dihydropyrrol-2-one derivatives in organic synthesis, pharmacology and industry, there is still the need to develop an efficient, mild and environmentally benign protocol for the synthesis of these important compounds.

In continuation of our work on multi-component reactions,[21–24] we report here a simple and efficient synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates by means of one-pot, multi-component reaction between amines, dialkyl acetylenedicarboxylates and formaldehyde in the present of oxalic acid dihydrate (20 mol%) as a catalyst in methanol at ambient temperature (Scheme 1).

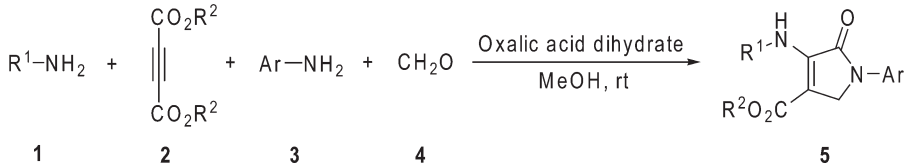
Results and discussion

First, we examined the feasibility of the reaction of aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde as a model in the presence of oxalic acid dihydrate as a catalyst for the preparation of desired dihydropyrrol-2-one **5a**. We screened the amount of catalyst and solvents to develop standard reaction conditions. As shown in Table 1, the use of 20 mol% of oxalic acid dihydrate resulted in the maximum yield (89%) in methanol at ambient temperature in 2h (Table 1, entry 7). In this reaction, a mixture of aniline (1 mmol) and DMAD (1 mmol) in MeOH was first stirred for 30 min. Then aniline (1 mmol), formaldehyde (1.5 mmol) and oxalic acid dihydrate (20 mol %) were added successively. While the all four reactants were added at once, the corresponding product was obtained in lower yield and required a longer reaction time. When the reaction was carried out in the absence of a catalyst, the product **5a** was obtained in trace amounts after 24 h.

Using these optimised experimental conditions, different aromatic amines were allowed to undergo a one-pot reaction with dimethyl and/or diethyl acetylenedicarboxylate and formaldehyde, to afford a series of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates in good to high yields (Table 2, entries 1–8). Anilines with various substituents such as, OMe, Me, F, Cl and Br were examined. The products were obtained in good yields. In order to explore the scope of this procedure, different functionalised dihydropyrrol-2-ones **5i–q** were synthesised *via* a one-pot four-component domino reaction using two different amines, dialkyl acetylenedicarboxylates and formaldehyde using optimum conditions (Table 2, entries 9–17). Aliphatic amines such as benzyl amine, *n*-propyl amine and *n*-butyl amine were employed in the reaction, affording the products in high yields.

The structures of products were characterised by IR, ^{1}H and ^{13}C NMR and elemental analysis. For example, the mass spectrum of **5c** displayed a molecular ion (M^+) at m/z = 344, which is consistent with the proposed structure. In the IR spectrum of **5c** the NH absorption band at 3284 cm^{-1} and two absorption bands at 1676 and 1649 cm^{-1}, which are related to two C=O stretching frequencies, revealed the significant functional groups in the product. The ^{1}H NMR spectrum of compound **5c** exhibited two singlets at δ 3.79 and 4.52 ppm for a methoxy group and CH_2 of the dihydropyrrol-2-one ring, respectively. The aromatic protons of **5c** were observed at δ 7.01–7.76 ppm as two multiplets and the NH proton was shown as a broad singlet at δ 8.05 ppm. The ^{13}C NMR spectrum of **5c** showed 13 distinct resonances consistent with the functionalised dihydropyrrol-2-one structure. A partial assignment of these resonances is given in the experimental section.

On the basis of above experimental results together with the related reports, a reasonable mechanism for the synthesis of functionalised dihydropyrrol-2-one **5** is depicted in Scheme 2.



Scheme 1 Synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylate **5**.

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Table 1 Optimisation of the reaction conditions for the synthesis of **5a**[a]

Entry	Catalyst/mol%	Solvent	Time/h	Yield/%[b]
1	10	MeOH	3	73
2	10	EtOH	4	66
3	10	MeCN	7	60
4	10	CH_2Cl_2	8	39
5	10	THF	7	43
6	15	MeOH	2	82
7	20	MeOH	2	89
8	25	MeOH	2	87
9	30	MeOH	2	88
10	No catalyst	MeOH	24	Trace

[a]Amount of materials in all reactions: aniline (2 mmol), DMAD (1 mmol), and formaldehyde (1.5 mmol).
[b]Isolated yield.

In summary, we have developed a facile and efficient one-pot multi-component synthesis of substituted dihydropyrrol-2-ones by coupling amines, dialkyl acetylenedicarboxylates and formaldehyde promoted by oxalic acid dihydrate as a homogeneous catalyst. This protocol is endowed with several advantages such as mild reaction conditions, clean reaction, simplicity in operation, no need to column chromatography, short reaction times and good to high yields.

Experimental

Melting points were recorded on an Electrothermal 9100 apparatus. IR spectra were obtained on a JASCO FT/IR-460 plus spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent and using TMS as internal reference at 400 and 100 MHz, respectively. The mass spectra were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionisation potential of 70 eV. Elemental analyses for C, H and N were performed using a Heraeus CHN–O-Rapid analyser. Chemicals were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

Synthesis of dihydropyrrol-2-one **5***; general procedure*

A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in MeOH (3 mL) was stirred for 30 min. Next, amine **3** (1 mmol), formaldehyde **4** (1.5 mmol) and oxalic acid dihydrate (20 mol %) were added in succession. The reaction mixture was stirred at ambient temperature for the appropriate time (see Table 2). After completion of the reaction (monitored by TLC), the solid precipitate was filtered off and washed with ethanol (3 × 2 mL) to give the pure product **5**.

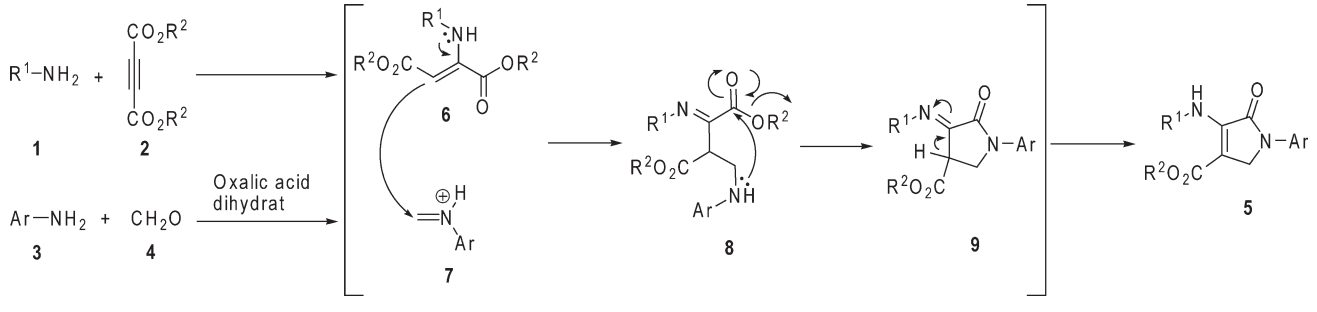
Methyl 3-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5c**): White solid, m.p. 163–165 °C. IR (KBr) (λ_{max}, cm^{-1}): 3284 (NH), 1676, 1649; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.79 (3H, s, OCH_3), 4.52 (2H, s, CH_2), 7.01–7.16 (6H, m, ArH), 7.73–7.76 (2H, m, ArH), 8.05 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 48.3, 51.4, 115.1 (d, J_{CF} = 23.0 Hz), 115.9 (d, J_{CF} = 22.0 Hz), 121.0 (d, J_{CF} = 7.0 Hz), 125.1 (d, J_{CF} = 8.0 Hz), 134.4 (d, J_{CF} = 3.0 Hz), 134.7 (d, J_{CF} = 2.0 Hz), 143.4, 153.7 (d, J_{CF} = 33.0 Hz), 161.2 (d, J_{CF} = 32.0 Hz), 163.5, 164.8; MS, (*m/z*, %): 345 (M+1, 10), 344 (M^+, 70), 313 (7), 285 (100), 257 (25), 163 (27), 137 (12), 123 (30), 109 (10), 95 (50), 69 (33), 57 (30); Anal. Calcd for $C_{18}H_{14}F_2N_2O_3$: C, 62.79; H, 4.10; N, 8.14. Found: C, 63.13; H, 4.23; N, 8.29%.

Ethyl 1-(4-bromophenyl)-3-(butylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5q**): White solid, m.p. 94–96 °C. IR (KBr) (λ_{max}, cm^{-1}): 3323 (NH), 2955, 2934, 2870, 1698, 1647; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.97 (3H, t, *J* = 7.2 Hz, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.43 (2H, sextet, *J* = 7.6 Hz, CH_2), 1.61 (2H, quintet, *J* = 7.6 Hz, CH_2), 3.87 (2H, t, *J* = 7.2 Hz, $C\underline{H}_2$–NH), 4.28 (2H, t, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.40 (2H, s, $C\underline{H}_2$–N), 6.72 (1H, br, NH), 7.52 (2H, d, *J* = 8.8 Hz, ArH), 7.71 (2H, d, *J* = 8.8 Hz, ArH); ^{13}C NMR

Table 2 The synthesis of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylate **5**

Entry	R^1	R^2	Ar	Product	Time/h	Yield/%[a]	M.p./°C	Lit. m.p./°C[Ref,b]
1	Ph	Me	Ph	**5a**	2	89	154–156	155–156[20]
2	Ph	Et	Ph	**5b**	2	87	136–138	138–140[19]
3	4-F–C_6H_4	Me	4-F–C_6H_4	**5c**	2	85	163–165	This work
4	4-Cl–C_6H_4	Me	4-Cl–C_6H_4	**5d**	2	88	170–172	173–174[20]
5	4-Br–C_6H_4	Et	4-Br–C_6H_4	**5e**	2	89	168–170	169–171[19]
6	4-OMe–C_6H_4	Me	4-OMe–C_6H_4	**5f**	3	77	172–174	176–177[20]
7	4-Me–C_6H_4	Me	4-Me–C_6H_4	**5g**	2	88	178–180	177–178[20]
8	4-Me–C_6H_4	Et	4-Me–C_6H_4	**5h**	2.5	85	129–131	131–132[19]
9	Ph–CH_2	Me	Ph	**5i**	2	82	142–144	140–141[19]
10	Ph–CH_2	Et	Ph	**5j**	2.5	84	126–128	130–132[19]
11	Ph–CH_2	Me	4-Br–C_6H_4	**5k**	2	85	119–121	120–121[20]
12	Ph–CH_2	Me	4-Cl–C_6H_4	**5l**	3	85	147–149	147–148[20]
13	Ph–CH_2	Me	4-OMe–C_6H_4	**5m**	5	73	124–126	129–130[20]
14	*n*-C_3H_7	Et	Ph	**5n**	2.5	88	76–78	78–79[19]
15	*n*-C_4H_9	Me	4-Br–C_6H_4	**5o**	3	84	110–112	108–109[20]
16	*n*-C_4H_9	Me	Ph	**5p**	3	85	60–62	60[20]
17	*n*-C_4H_9	Et	4-Br–C_6H_4	**5q**	2	87	94–96	This work

[a]Isolated yield.
[b]All known products have been reported previously in the literature and were characterised by comparison of IR and NMR spectra with those of authentic samples.



Scheme 2 Proposed mechanism for preparation of N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5**.

(100 MHz, $CDCl_3$): δ_C 13.8, 14.5, 19.8, 33.4, 42.8, 47.8, 59.8, 98.1, 117.7, 120.6, 132.0, 137.9, 164.6, 165.5; MS, (*m/z*, %): 382 (M+2, 38), 380 (M^+, 38), 353 (16), 351 (16), 337 (44), 307 (100), 293 (41), 291 (42), 184 (20), 182 (20), 157 (16), 98 (18), 80 (17), 66 (29), 55 (33); Anal. Calcd for $C_{17}H_{21}BrN_2O_3$: C, 53.55; H, 5.55; N, 7.35. Found: C, 53.88; H, 5.71; N, 7.54%.

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