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$ZrCl_4$ as an efficient catalyst for one-pot four-component synthesis of polysubstituted dihydropyrrol-2-ones

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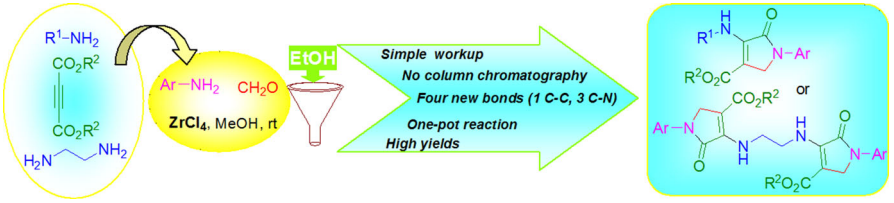
Abstract An efficient synthesis of polysubstituted dihydropyrrol-2-one derivatives via one-pot four-component domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in the presence of zirconium tetrachloride ($ZrCl_4$) is described. The presented methodology offers several advantages such as simplicity of operation, good to high yields, short reaction times, inexpensive and readily available starting material and catalyst. Furthermore, the products were obtained through simple filtering with no need for column chromatography.

Graphical abstract



Keywords Heterocycle · Dihydropyrrol-2-one · $ZrCl_4$ · Dialkyl acetylenedicarboxylate · Multi-component reaction

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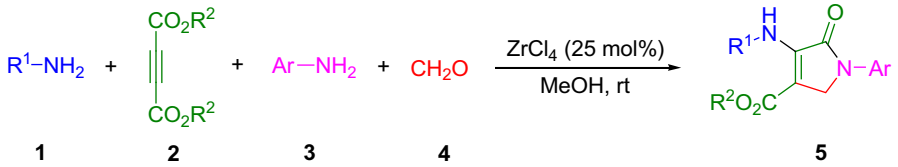
Introduction

Multi-component reactions (MCRs) play significant roles in organic chemistry as a result of the fact that a final product can be formed by means of the reaction between three or more different starting materials in a simple one-pot process [1]. In 1850, Strecker reported the synthesis of α-aminonitrile by a three-component reaction of ammonia, hydrocyanic acid and carbonyl compounds, which revealed the birth of MCRs [2]. Since then, numerous MCRs have been invented and their number is still growing. MCRs are advantageous compared to multistage syntheses due to their traits such as flexibility, no separation of intermediates and simple purification of products, atom-economy, time and energy savings, and environmental friendliness by considerably reducing amounts of solvents and associated waste. Also, MCRs are powerful tools in the modern drug discovery process and enable fast, automated, and high-throughput generation of 'drug-like' molecules [3–5].

Among nitrogen-containing heterocycles, dihydropyrrol-2-ones display a broad spectrum of biological and pharmacological activity as antitumor and anticancer agents [6], an HIV integrase inhibitor [7], a DNA polymerase inhibitor [8], a human cytomegalovirus (HCMV) protease inhibitor [9], and a human cytosolic carbonic anhydrase isozymes inhibitor [10]. The dihydro-2-oxypyrrole moiety was also found in various natural bioactive products, including pyrrocidine A, talaroconvolutin A, thiomarinol A4 and oteromycin [11–13]. These heterocycles are also important reagents as materials for the synthesis of organic complexes [14]. In view of the importance of dihydropyrrol-2-one derivatives, several methods have been developed to synthesize these useful heterocycles [15–20]. Recently, the literature has presented some methods to synthesise polysubstituted dihydropyrrol-2-ones via MCRs using catalysts such as acetic acid (AcOH), iodine (I_2) , benzoic acid, titanium dioxide (TiO_2) nanopowder, $Cu(OAc)_2{\cdot}H_2O$ and (S)-camphorsulfonic acid [21–27]. However, some of these methods displayed drawbacks, such as performing the reaction in the presence of 200 mol% catalyst at 70 °C and purification of products by preparative thin layer chromatography (TLC) [21], long reaction times [23], environmental pollution caused by utilization of chlorinated solvent under reflux conditions, and the need for column chromatography to purify the products [24]. Therefore, it is necessary to further develop an efficient, milder and convenient method to synthesis such important heterocycles.

During the past decade, the use of zirconium compound catalysts has received considerable attention in organic chemistry as a catalyst because of their important advantages, such as high catalytic activity, low toxicity, ease of handling and low cost [28, 29].

As a part of our program aimed at developing a new procedure for the preparation of dihydropyrrol-2-ones [30–35], in this work, we report an efficient and very facile synthesis of polyfunctionalized dihydropyrrol-2-ones via one-pot four-component reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in the presence of a catalytic amount of zirconium tetrachloride ($ZrCl_4$) in methanol at ambient temperature (Scheme 1).



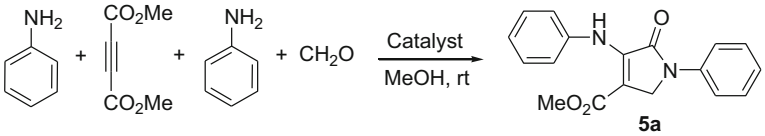
Scheme 1 Synthesis of polyfunctionalized dihydropyrrol-2-one **5**

Results and discussion

In order to establish the optimized reaction conditions, the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was chosen as a model reaction and carried out in the presence of 10 mol% of various potential catalysts, including $ZrOCl_2{\cdot}8H_2O$, $ZrCl_4$, $Zr(NO_3)_2$, $Bi(NO_3)_3{\cdot}5H_2O$, TiO_2 and Al_2O_3 at ambient temperature in methanol (Table 1). It was observed $ZrCl_4$ is superior, and produced the best yield of the desired product **5a**. A control experiment revealed that in the absence of the catalyst, only a trace amount of product **5a** was obtained.

Subsequently, a survey of solvents showed methanol to be the best choice. Low yields were obtained when the model reaction was performed in ethanol, H_2O, acetonitrile, CH_2Cl_2 and $CHCl_3$ (Table 2). To further optimize reaction conditions, we investigated the effect of the loading amount of $ZrCl_4$ on the model reaction in methanol (Table 2, entries 6-11). The optimum yield of product **5a** (84 %) was obtained in the presence of 25 mol% of $ZrCl_4$. By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower yield (Table 2, entry 7), while increasing the catalyst loading to 30 mol% has no significant effect on the product yield (Table 2, entry 11).

Table 1 Effect of different catalysts on the reaction of aniline, DMAD and formaldehyde



Entry	Catalyst	Time (h)	Yield (%)[a]
1	$ZrOCl_2{\cdot}8H_2O$	11	43
2	$ZrCl_4$	6	64
3	$Zr(NO_3)_2$	8	40
4	$Bi(NO_3)_3{\cdot}5H_2O$	8	37
5	TiO_2	8	39
6	Al_2O_3	8	26
7	None	12	Trace

Reaction conditions: Aniline (2 mmol), DMAD (1 mmol), formaldehyde (1.5 mmol), and catalyst (10 mol%) in methanol (3 mL) at ambient temperature

[a] Isolated yield

Table 2 Investigation of solvent effects and the amounts of $ZrCl_4$ on the model reaction of Table 1

Entry	Catalyst loading (mol%)	Solvent	Time (h)	Yield (%)[a]
1	10	EtOH	10	52
2	10	H_2O	16	10
3	10	MeCN	10	41
4	10	CH_2Cl_2	12	20
5	10	$CHCl_3$	12	23
6	10	MeOH	6	64
7	5	MeOH	7	47
8	15	MeOH	4	73
9	20	MeOH	4	80
10	25	MeOH	4	84
11	30	MeOH	4	85

Reaction conditions: Aniline (2 mmol), DMAD (1 mmol), formaldehyde (1.5 mmol), and $ZrCl_4$ in 3 mL of solvent at ambient temperature

[a] Isolated yield

To further explore the scope and limitation of this protocol, a variety of substituted anilines were reacted with dimethyl and/or diethyl acetylenedicarboxylate and formaldehyde under optimized conditions. The results are summarized in Table 3. The reaction was found to be compatible with various functional groups such as F, Cl, Br, Me and OMe. In all cases, the reaction proceeded smoothly to produce the desired product in high yield (Table 3, entries 1–11). Next, two different amines were employed for the synthesis of polysubstituted dihydropyrrol-2-ones **5 m-y**. Various aliphatic amines, including benzyl amine, 1-(pyridin-2-yl)methanamine, *n*-propyl amine, *n*-buthyl amine and cyclohexyl amine, were used in the reaction to afford the corresponding dihydropyrrol-2-one in good to high yields (Table 3, entries 12-25). In general, at the beginning of the reaction, the reagents were completely soluble in the reaction medium to form a homogeneous mixture. But, at the end of the reaction, the product was precipitated and separated by simple filtration. No column chromatography technique was used for product purification, thereby avoiding use of large amounts of volatile organic solvents, as the solvent is generally the main source of waste as well as environmental pollution.

Encouraged by these results, we improved the reaction scope by using ethane-1,2-diamine as a reactant. The four-component (pseudo seven-component) reaction of ethane-1,2-diamine, dialkyl acetylenedicarboxylates, aromatic amines and formaldehyde (with mole ratio: 1:2:2:2) was carried out under optimal conditions (Scheme 2). The corresponding bis-dihydropyrrol-2-ones **7a-j** were obtained in satisfactory yields (Table 4).

It is noted that the polysubstituted dihydropyrrol-2-ones can be obtained by changing the sequence of amine addition (Scheme 3). For this aim, first a mixture of aniline (1 mmol) and DMAD (1 mmol) in methanol (2 mL) was stirred for 20 min. Next, a mixture of benzyl amine (1 mmol), formaldehyde and $ZrCl_4$ (25 mol%) in methanol (2 mL) was added dropwise. After completion of the reaction, the target product **5z** was obtained in moderate yield (67 %).

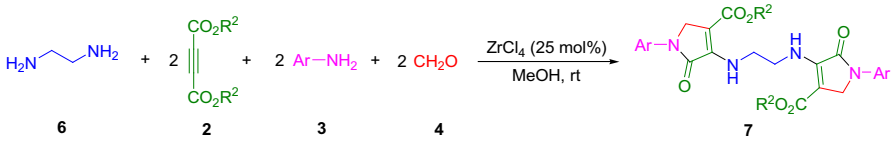
The structure of the products was characterized by their melting points and infrared (IR) and nuclear magnetic resonance (NMR) spectral data, which were then compared with those of authentic samples. As an unknown compound, the structure

Table 3 Synthesis of polysubstituted dihydropyrrol-2-ones **5a-y**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	Mp (lit. mp) [Ref.][a]
1	Ph	Me	Ph	**5a**	4	84	153–155 (155–156) [22]
2	4-F-C_6H_4	Me	4-F-C_6H_4	**5b**	3.5	85	164–166 (163–165) [30]
3	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5c**	4	85	170–172 (173–174) [22]
4	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5d**	3	83	180–182 (179–180) [22]
5	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5e**	4	81	168–170 (168–170) [22]
6	Ph	Et	Ph	**5f**	3.5	83	133–135 (138–140) [21]
7	4-F-C_6H_4	Et	4-F-C_6H_4	**5g**	4	84	171–173 (172–173) [21]
8	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5h**	3	82	168–170 (168–170) [32]
9	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5i**	4	80	164–166 (169–171) [21]
10	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5j**	4	84	128–130 (131–132) [21]
11	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5k**	6	73	153–155 (152–154) [31]
12	$PhCH_2$	Me	Ph	**5l**	3.5	85	138–140 (140–141) [21]
13	$PhCH_2$	Me	4-Cl-C_6H_4	**5m**	3	81	142–144 (147–148) [22]
14	$PhCH_2$	Me	4-Br-C_6H_4	**5n**	3.5	86	118–120 (120–121) [22]
15	$PhCH_2$	Et	4-Br-C_6H_4	**5o**	4	85	114–116 (New product)
16	$PhCH_2$	Me	4-Me-C_6H_3	**5p**	3	83	144–146 (144–146) [33]
17	C_5H_4N-2-CH_2	Me	4-Br-C_6H_4	**5q**	7.5	63	159–161 (159–161) [34]
18	C_5H_4N-2-CH_2	Me	4-Me-C_6H_3	**5r**	7	61	106–108 (106–108) [32]
19	Cyclohexyl	Me	4-Cl-C_6H_4	**5s**	3.5	79	120–122 (124–125) [22]
20	Cyclohexyl	Et	Ph	**5t**	3	82	103–105 (107–108) [21]
21	*n*-C_3H_7	Et	Ph	**5u**	4	84	76–78 (78–79) [21]
22	*n*-C_4H_9	Me	Ph	**5v**	4	80	61–63 (60) [22]
23	*n*-C_4H_9	Me	4-F-C_6H_4	**5w**	3.5	82	81–83 (81–83) [33]
24	*n*-C_4H_9	Me	4-Cl-C_6H_4	**5x**	3	83	91–93 (92–94) [34]
25	*n*-C_4H_9	Et	4-Br-C_6H_4	**5y**	4	82	94–96 (94–96) [30]

Isolated yield

[a] Literature references for known compounds



Scheme 2 Synthesis of substituted bis-dihydropyrrol-2-ones **7**

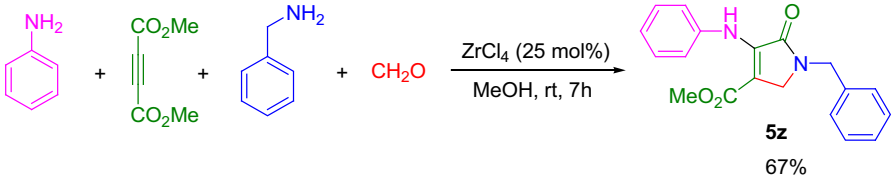
of **5o** also was fully characterized by IR, proton (^1H) and carbon 13 (^{13}C) NMR, mass spectra as well as elemental analysis, and its structural assignment is described below. The IR spectrum of **5o** showed three absorption bands at 3307, 1698 and 1640 cm^{-1} due to the NH and carbonyl groups, respectively. The ^1H NMR spectrum of compound **5o** exhibited a triplet and a quartet at 1.34 ($J = 7.2$ Hz) and 4.27 ($J = 7.2$ Hz) ppm for an ethoxy group. The methylene protons of

Table 4 Preparation of polysubstituted bis-dihydropyrrol-2-ones **7a-j**

Entry	R^2	Ar	Product	Time (h)	Yield (%)[a]	M.p. (lit. m.p.)[Refs.][a]
1	Me	Ph	**7a**	7	84	148–150 (149–151) [32]
2	Et	4-Me-C_6H_4	**7b**	5.5	84	210–212 (210–212) [32]
3	Me	4-F-C_6H_4	**7c**	6	85	197–199 (199–201) [32]
4	Et	3,4-Cl_2-C_6H_3	**7d**	6	81	206–208 (206–208) [32]
5	Et	4-Br-C_6H_4	**7e**	5.5	83	175–177 (174–176) [34]
6	Me	4-Br-C_6H_4	**7f**	7	82	207–209 (New product)
7	Et	4-Cl-C_6H_4	**7g**	6	80	211–213 (New product)
8	Et	Ph	**7h**	8	81	159–161 (158–160) [35]
9	Et	4-OMe-C_6H_4	**7i**	6	70	222–224 (219–221) [35]
10	Me	4-Cl-C_6H_4	**7j**	7	85	202–204 (202–204) [35]

Isolated yield

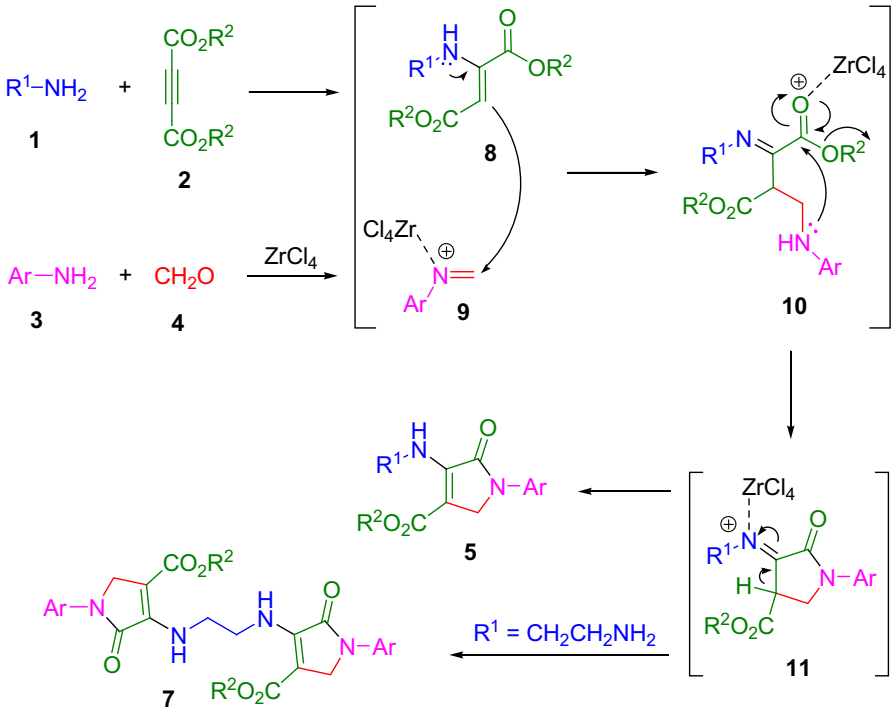
[a] Literature references for known compounds



Scheme 3 Synthesis of dihydropyrrol-2-one **5z** by changing the sequence of amine addition

dihydropyrrol-2-one ring were observed as a singlet at 4.41 ppm. A doublet at 5.12 ppm ($J = 6.4$ Hz) appeared for methylene protons of a benzyl amine moiety. The NH proton was exhibited as a broad singlet at δ 6.90 ppm. The aromatic protons were observed as two multiplets and two doublets at 7.28-7.33, 7.36-7.37, 7.52 ($J = 8.8$ Hz) and 7.70 ($J = 8.8$ Hz) ppm, respectively. The ^{13}C NMR spectrum of this compound showed 15 distinct resonances in agreement with the suggested structure, and partial assignment of these resonances is given in the experimental section. The mass spectrum of **5o** displayed a molecular ion peak (M^+) at $m/z = 414$, and also peak M + 2 at $m/z = 416$ due to the presence of a bromine atom within this compound, which was consistent with the proposed structure.

A possible reaction mechanism for the formation of dihydropyrrol-2-ones is presented based on the reported literature [21, 22]. Firstly, the reaction of amine **1** (or **6**) with dialkyl acetylenedicarboxylate **2** lead to intermediate **8.** Secondly, condensation between amine **3** and formaldehyde **4** in the presence of $ZrCl_4$ produce imine **9**. Intermediate **8** possesses an enamine character and, thus, can readily react with imine **9** to generate intermediate **10**. Cyclization reaction of intermediate **10** lead to intermediate **11**, that in the final step tautomerizes to the corresponding mono- or bis-dihydro-2-oxopyrroles **5** or **7** (Scheme 4).



Scheme 4 Proposed mechanism for the formation of compounds **5** and **7**

To show the efficiency and the applicability of the present work for the synthesis of polysubstituted dihydropyrrol-2-ones, we compared results of $ZrCl_4$ with previously reported catalysts in the synthesis of compounds **5a**, **5f** (Table 5). The results clearly show that $ZrCl_4$ can act as an effective and efficient catalyst with respect to yields and reaction times.

Experimental

General

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

Table 5 Comparison of $ZrCl_4$ with reported catalysts for the synthesis of polysubstituted dihydropyrrol-2-ones

Entry	Compound	Conditions	Time (h)	Yield (%)	Ref.
1	**5a**	I_2 (10 mol%), MeOH, r.t.	1	82	[22]
		$Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol), benzaldehyde (2 mmol, as additive), MeOH, r.t.	6	91	[25]
		$Al(H_2PO_4)_3$ (0.1 g), MeOH, r.t.	5	81	[31]
		p-TsOH·H_2O (15 mol%), MeOH, r.t.	3	84	[34]
		$ZrCl_4$ (25 mol%), MeOH, r.t.	4	84	–
2	**5f**	AcOH (2 mmol), EtOH, 70 °C	4	85	[21]
		I_2 (10 mol%), MeOH, r.t.	1	81	[22]
		$Cu(OAc)_2{\cdot}H_2O$ (0.4 mmol), benzaldehyde (2 mmol, as additive), MeOH, r.t.	5	85	[25]
		$Al(H_2PO_4)_3$ (0.1 g), MeOH, r.t.	5	80	[31]
		p-TsOH·H_2O (15 mol%), MeOH, r.t.	4	84	[34]
		$ZrCl_4$ (25 mol%), MeOH, r.t.	3.5	83	–

General procedure for the synthesis of polysubstituted dihydropyrrol-2-one 5 and bis-dihydropyrrol-2-one 7 For product **5**, a mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in methanol (3 mL) was stirred for 20 min. Then, aromatic amine **3** (1 mmol), formaldehyde **4** (37 % solution; 1.5 mmol) and $ZrCl_4$ (25 mol%) were added successively. For compound **7**, the stoichiometric amounts of amine **6**, dialkyl acetylenedicarboxylate **2**, amine **3** and formaldehyde **4** are 1, 2, 2 and 3 mmol, respectively. The reaction mixture was stirred at ambient temperature for an appropriate time. After reaction completion (monitored by TLC), the solid precipitate was filtered off and washed with ethanol (3 × 2 mL) to afford the pure products **5** or **7**. Physical and spectral data for the new compounds are presented below.

Ethyl 3-(benzylamino)-1-(4-bromophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5o) White solid; mp: 114–116 °C; IR (KBr, cm^{-1}): *ν* 3307 (NH), 1698 (C = O), 1640 (C = O); ^1H NMR (400 MHz, $CDCl_3$): *δ* 1.34 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$) 4.27 (q, *J* = 7.2 Hz, 2H, $OC\underline{H_2}CH_3$), 4.41 (s, 2H, $C\underline{H_2}$–N), 5.12 (d, *J* = 6.4 Hz, 2H, $C\underline{H_2}$–NH), 6.90 (br, 1H, NH), 7.28–7.33 (m, 1H, ArH), 7.36–7.37 (m, 4H, ArH), 7.52 (d, *J* = 8.8 Hz, 2H, ArH), 7.70 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.5, 46.6, 47.8, 60.0, 97.8, 117.7, 120.5, 127.4, 127.5, 128.7, 132.0, 137.8, 139.4, 164.5 (C = O), 165.1 (C = O); MS (EI, 70 eV): *m/z* (%) 416 (M + 2, 21), 414 (M^+, 21), 387 (31), 385 (29), 365 (25), 363 (23), 341 (15), 261 (17), 184 (6), 157 (5), 105 (10), 91 (100), 65 (15). Anal. Calcd. for $C_{20}H_{19}BrN_2O_3$: C 57.84, H 4.61, N 6.75; Found: C 58.02, H 4.67, N 6.80.

Bis-(methyl 1-(4-bromophenyl)-3-(methyleneamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate) (7f) Pale yellow solid; mp: 207–209 °C; IR (KBr, cm^{-1}): ν 3305 (NH), 1698 (C = O), 1637 (C = O); ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.68 (s, 6H, $2OC\underline{H_3}$), 4.12–4.16 (m, 4H, $2C\underline{H_2}$–NH), 4.26 (s, 4H, $2C\underline{H_2}$–N), 6.77 (br s, 2H, 2NH), 7.48 (d, *J* = 8.8 Hz, 4H, ArH), 7.63 (d, *J* = 8.8 Hz, 4H, ArH); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 43.9, 47.7, 51.1, 117.8, 120.4, 132.0, 137.7, 164.4 (C = O), 165.0 (C = O); MS (EI, 70 eV): *m/z* (%) 648 (M^+, 1), 368 (10), 236 (16), 152 (10), 111 (25), 97 (50), 83 (56), 69 (80), 57 (100); Anal. Calcd. for $C_{26}H_{24}Br_2N_4O_6$: C 48.17, H 3.73, N 8.64; Found: C 48.50, H 3.91, N 8.55.

Bis-(ethyl 1-(4-chlorophenyl)-3-(methyleneamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate) (7g) White solid, mp: 211-213 °C; IR (KBr, cm^{-1}): ν 3338 (NH), 1697 (C = O), 1641 (C = O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J = 6.8 Hz, 6H, $2OCH_2\underline{CH_3}$), 4.15 (br s, 8H, $2O\underline{CH_2}CH_3$ and $2C\underline{H_2}$–NH), 4.31 (s, 4H, $2C\underline{H_2}$–N), 6.73 (br s, 2H, 2NH), 7.35 (d, J = 8.0 Hz, 4H, ArH), 7.71 (d, J = 8.4 Hz, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 44.0, 47.9, 59.9, 98.5, 117.8, 120.2, 129.1, 130.0, 137.3, 164.5 (C = O), 165.3 (C = O); MS (EI, 70 eV): *m/z* (%) 588 (M + 2, 5), 686 (M^+, 8), 540 (6), 494 (8), 368 (6), 306 (100), 293 (33), 280 (15), 247 (70), 233 (51), 221 (45), 192 (14), 164 (12), 138 (30), 111 (25), 91 (34), 66 (44), 59 (27). Anal. Calcd. for $C_{28}H_{28}Cl_2N_4O_6$: C 57.25, H 4.80, N 9.54; Found: C 57.54, H 4.89, N 9.79.

Conclusion

In summary, we have described an efficient and simple strategy for the synthesis of polysubstituted dihydropyrrol-2-ones and bis-dihydropyrrol-2-ones using $ZrCl_4$ as a catalyst in methanol at ambient temperature. The important aspects of this multi-component heteroannulation are simple operations under mild conditions, good to high yields, and readily available starting material and catalyst. Furthermore, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution.

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