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A simple and efficient approach to one-pot synthesis of mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates catalyzed by $InCl_3$

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ABSTRACT

An efficient and straightforward procedure has been developed for the synthesis of highly substituted mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates *via* a one-pot, four-component domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in the presence of $InCl_3$ (20 mol%) in MeOH at ambient temperature. The salient advantages of this method are mild reaction conditions, environmentally benign, high to excellent yields, shorter reaction times, easy operation and no column chromatographic separation.

1. Introduction

In recent years, growing attention has been paid to the synthesis of *N*-heterocycles due to diverse biological and pharmaceutical applications [1–3]. In this respect, the presence of pyrrol-2-ones (5-lactams or γ-lactams) in pharmaceuticals and natural products has continued to stimulate a great deal of interest in the development of new methodologies for their synthesis [4–6]. There are several bioactive natural molecules with a pyrrol-2-one moiety, such as holomycin and thiolutin [7], thiomarinol A4 [8], oteromycin [9], pyrrocidine A [10], quinolactacin C [11], and ypaoamide [12]. On the other hand, dihydropyrrol-2-ones have been successfully used as peptidomimetic [13], HIV integrase [14], herbicidals [15], DNA polymerase inhibitors [16], caspase-3 inhibitors [17] cytotoxic and antitumor agents [18], antibiotics [19], and also inhibitors of the annexin A2-S100A10 protein interaction [20]. Recently, a few methods have been reported for the synthesis of highly substituted dihydropyrrol-2-ones using one-pot, four-component reactions in the presence of catalyst, such as AcOH, I_2, benzoic acid, TiO_2 nanopowder or $Cu(OAc)_2{\cdot}H_2O$ [21–25]. However, some of these methods have drawbacks, such as high temperature and utilize a chlorinated solvent. Therefore, the development of a milder and more efficient route for one-pot synthesis of these important heterocycles is still in demand.

In continuation of our ongoing studies for the preparation of heterocyclic compounds, in particular, highly substituted dihydropyrrol-2-ones [26–31], herein we report a simple and efficient procedure for the synthesis of mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5** and **6** *via* one-pot, four-component domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde. The reaction was performed in the presence of catalytic amounts of $InCl_3$ (20 mol%) in MeOH at room temperature (Scheme 1).

2. Experimental

Melting points were taken on an Electrothermal 9100 apparatus. IR spectra were obtained on a JASCO FT/IR-460 plus spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avanve instrument with $CDCl_3$ as solvent and using TMS as internal reference at 400 MHz and 100 MHz, respectively. Chemicals were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

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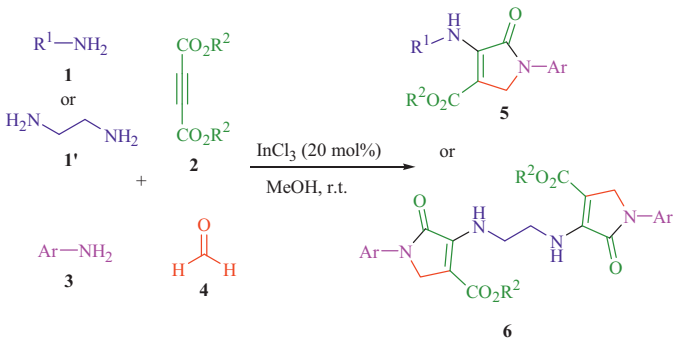


Scheme 1. Synthesis of mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates.

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

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	$InCl_3$ (10)	EtOH	4	63
2	$InCl_3$ (10)	MeOH	3.5	75
3	$InCl_3$ (10)	H_2O	6	21
4	$InCl_3$ (5)	MeOH	5	59
5	$InCl_3$ (15)	MeOH	3	81
6	$InCl_3$ (20)	MeOH	3	85
7	$InCl_3$ (25)	MeOH	3	85
8	ZnO (20)	MeOH	8	39
9	$Zn(OAc)_2{\cdot}2H_2O$ (20)	MeOH	10	33
10	$NiCl_2$ (20)	MeOH	7	61
11	$ZnCl_2$ (20)	MeOH	7	57
12	–	MeOH	24	Trace

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

General procedure for the synthesis of mono- and bis-N-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5** and **6**: A mixture of amine **1** or **1′** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol for product **5**, 2 mmol for product **6**) in MeOH (3 mL) was stirred for 25 min. Next, amine **3** (1 mmol for product **5**, 2 mmol for product **6**), formaldehyde **4** (37% solution, 1.5 mmol for product **5**, 3 mmol for product **6**) and $InCl_3$ (20 mol%) were added successively. The reaction mixture was allowed to stir at ambient temperature for appropriate time. 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** or **6**. The structures of the synthesized compounds were characterized by their IR, ^1H NMR and ^{13}C NMR spectra and were found to be identical with data described in the literature [21,22,28–31]. The physical and spectral data of the products are given as Supporting information.

3. Results and discussion

To find the optimal conditions, the reaction between aniline, dimethyl acetylendicarboxylate (DMAD) and formaldehyde was chosen as a model. This reaction was performed under different conditions and the results are summarized in Table 1. The best result was obtained in the presence of 20 mol% of $InCl_3$ in MeOH (Table 1, entry 6). Notably, when the reaction was examined in the absence of the catalyst only a trace amount of the target product was obtained.

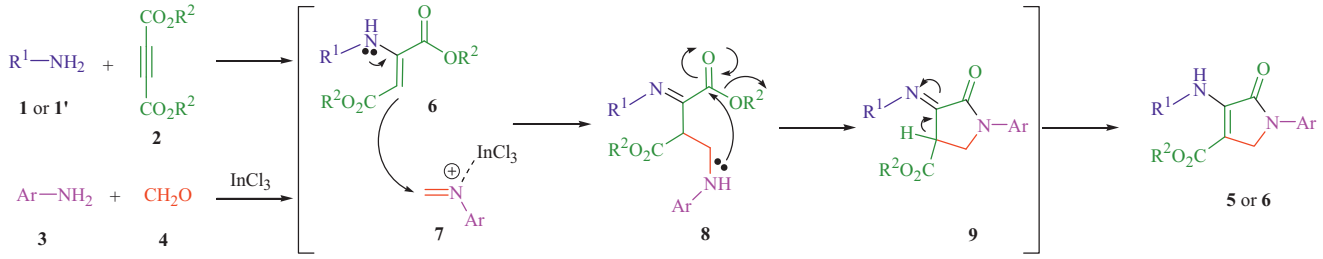
To demonstrate the utility and generality of this method, the various substituted anilines, dimethyl and/or diethyl acetylenedicarboxylates and formaldehyde were employed successfully to generate the desired *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5a–h** (Table 2). Encouraged by these results, different polyfunctionalized dihydropyrrol-2-ones **5i–q** were synthesized using two different amines. Aliphatic amines, such as benzyl amine, 1-(pyridin-2-yl)methanamine and *n*-butyl amine, were reacted with dialkyl acetylenedicarboxylates, anilines and formaldehyde to produce the corresponding products in good to high yields. We next explored the scope of this procedure in the four-component (pseudo seven-component) synthesis of bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **6**, *via* the condensation of ethane-1,2-diamine **1′** (1 equiv.), dialkyl acetylenedicarboxylates **2** (2 equiv.), aromatic amine **3** (2 equiv.) and formaldehyde **4** (2 equiv.). In all cases, the reaction proceeded smoothly and the desired products were obtained in good yields.

On the basis of the above experimental results, together with the related reports, a plausible reaction mechanism for this one-pot, four-component heteroannulation is illustrated in Scheme 2.

Table 2
Synthesis of mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5** and **6**.

Product	R^1	R^2	Ar	Time (h)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref.][b]
5a	Ph	Me	Ph	3	85	154–155	155–156 [22]
5b	Ph	Et	Ph	3	85	136–138	138–140 [21]
5c	4-Me-C_6H_4	Me	4-Me-C_6H_4	3.5	86	177–179	177–178 [22]
5d	4-Me-C_6H_4	Et	4-Me-C_6H_4	3	81	128–130	131–132 [21]
5e	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	5	73	152–154	152–154 [28]
5f	4-F-C_6H_4	Me	4-F-C_6H_4	3.5	81	163–165	163–165 [31]
5g	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	3	79	167–170	168–170 [29]
5h	4-Br-C_6H_4	Et	4-Br-C_6H_4	3	84	167–169	169–171 [21]
5i	$PhCH_2$	Me	Ph	3	80	136–138	140–141 [21]
5j	$PhCH_2$	Et	Ph	3.5	81	127–129	130–132 [21]
5k	$PhCH_2$	Me	4-F-C_6H_4	3	84	166–168	166–168 [28]
5l	$PhCH_2$	Me	4-Br-C_6H_4	3.5	86	119–121	120–121 [22]
5m	$PhCH_2$	Me	4-Me-C_6H_4	3.5	80	144–146	144–146 [30]
5n	C_5H_4N-2-CH_2	Me	4-Me-C_6H_4	5	68	104–106	106–108 [29]
5o	*n*-C_4H_9	Me	Ph	3.5	79	60–62	60 [22]
5p	*n*-C_4H_9	Et	4-Br-C_6H_4	3	83	94–97	94–96 [31]
5q	*n*-C_4H_9	Me	3,4-Cl_2-C_6H_3	4.5	76	97–99	97–99 [28]
6a	$H_2NCH_2CH_2$	Me	Ph	5	79	148–150	149–151 [29]
6b	$H_2NCH_2CH_2$	Me	4-F-C_6H_4	5	82	200–202	199–201 [29]
6c	$H_2NCH_2CH_2$	Et	4-Me-C_6H_4	4.5	80	210–212	210–212 [29]
6d	$H_2NCH_2CH_2$	Et	3,4-Cl_2-C_6H_3	6	78	204–207	206–208 [29]

[a] Isolated yield.
[b] References refer to known products as mentioned in the literature.



Scheme 2. Proposed mechanism for the synthesis of *N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates **5** and **6**.

4. Conclusion

In summary, we have developed an efficient one-pot, four-component synthesis of highly substituted mono- and bis-*N*-aryl-3-aminodihydropyrrol-2-one-4-carboxylates using $InCl_3$ as a Lewis acid catalyst. This methodology has advantages including mild reaction conditions, available starting materials, easy operation and simple work-up by avoiding column chromatography, short reaction times, and good to high yields.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2013.10.010.

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