Iranian Journal of Organic Chemistry Vol. 5, No. 4 (2013) 1127-1131

Lime juice-ethanol: a natural, green and highly efficient medium for the one-pot synthesis of functionalized dihydropyrrol-2-ones

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Received: September 2013; Revised: September 2013; Accepted: October 2013

Abstract: A mixture of commercial lime juice and ethanol – without any additive - was found to be a natural, biodegradable and highly efficient medium for the extremely facile one-pot synthesis of highly functionalized dihydropyrrol-2-ones from the four-component domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde at ambient temperature. The salient advantages of this method are eco-friendly and mild reaction conditions, green solvent, inexpensive and available material, good to high yields, short reaction times, simple work-up and lack of need for column chromatography.

Keywords: Heterocycle, Dihydro-2-oxypyrrole, Multi-component reaction, Dialkyl acetylenedicarboxylate.

Introduction

The environmental consequence of using volatile organic solvents in the manufacture of chemical products has been an issue of concern for many years. In 1990s Anastas and co-workers have defined concept of *benign by design* on the basis of three factors including efficiency of synthetic methodology, economically viable and environmentally benign [1]. One active area to access the benign by design is multi-component reactions (MCRs). 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 saving, and environmental friendliness by considerable reducing amounts of solvents and waste [2-4]. On the other hand, one approach toward alternatives to volatile organic solvents is the increased use of green solvents such as water and ethanol.

Amongst the nitrogen containing heterocycles, dihydropyrrol-2-ones (dihydro-2-oxopyrroles) are very interesting compounds due to their biological and pharmaceutical activity such as anti-HIV, anti-influenza, anti cancer, antibiotics, nootropic agents, pesticides, and herbicidal [5-11]. Dihydropyrrol-2-one derivatives were also reported as potential inhibitors of *Trypanosoma brucei* leucyl-tRNA synthetase (**A**, **B**) [12], and cardiac cAMP phosphodiesterase (**C**) [13] which represent promising approaches to treatment of Human African trypanosomiasis (sleeping sickness) and congestive heart failure (CHF) disease, respectively (Figure **1**). On the other hand, dihydropyrrol-2-ones are the building blocks in important biological alkaloids such as Jatropham, *Z*-

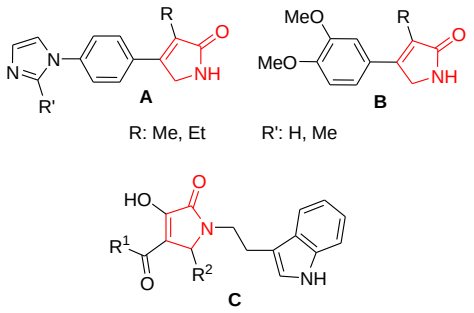

Figure 1: Pharmaceutically active compounds containing dihydropyrrol-2-one unit.

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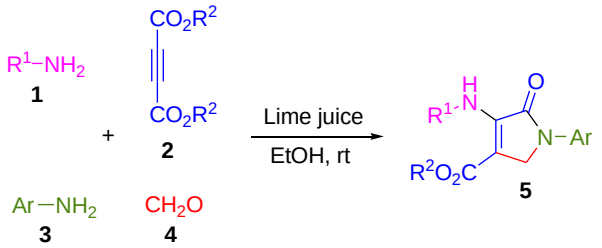
Pulchellalactam, Quinolactacins, holomycin and thiolutin [14-21].

Recently, a few efforts have been paid to the synthesis of highly substituted dihydropyrrol-2-one derivatives from the reaction of amines, dialkyl acetylenedicarboxylates and aldehydes using acetic acid, I_2, benzoic acid, TiO_2 nanopowder and $Cu(OAc)_2{\cdot}H_2O$ as catalyst [22-26]. However, some of these methods suffer from some disadvantages such as use of expensive and excess amount of catalyst, drastic reaction conditions and use of chlorinated solvent under reflux conditions, long reaction times, and need to preparative TLC or column chromatography for products purification. In view of the useful biological and pharmacological applications of dihydropyrrol-2-ones, it is necessary to further develop a facile one-pot synthesis of highly substituted dihydropyrrol-2-ones under mild and green reaction conditions using inexpensive or commercially available reagents.

In continuation of our ongoing research to develop mild and efficient catalyst system for the synthesis of dihydropyrrol-2-ones [27-31], herein we wish to report a mixture of commercially available lime juice and ethanol - without any additive - as natural medium for the one-pot synthesis of highly substituted dihydropyrrol-2-ones **5** *via* four-component domino reaction of amines (**1** and **3**), dialkyl acetylenedicarboxylates **2** and formaldehyde **4** at ambient temperature (Scheme **1**).

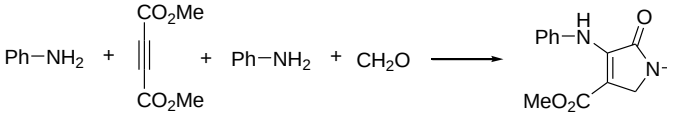


Scheme 1: Synthesis of highly substituted dihydropyrrol-2-ones **5**.

Results and discussion

At the outset, a test reaction using aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was performed in ethanol at room temperature. It was observed which only a trace amount of the desired product **5a** was obtained even after 12 h. To optimize the reaction conditions, the above reaction was chosen as a model and performed under different conditions. The results are summarized in Table **1**. Mixtures of ethanol and different fruits juice (volume ratio 3:1) such as lime, chino, orange, tangerine, kiwi, and grapefruit were investigated as a reaction medium. Lime juice proved to be superior and produced better yield of compound **5a** (73%). To determine the appropriate amount of lime juice, the model reaction was carried out at different quantities of lime juice, such as 0.5, 2, 3 and 4 mL. The best result was obtained in the presence of 3 mL of lime juice (Table **1**, entry 10), with no improvement upon increasing the amount of juice. When the reaction performed in water medium, the product **5a** was obtained in low yield.

Table 1: Optimization of reaction conditions for the synthesis of dihydropyrrol-2-one **5a**[a].



Entry	Solvent	Juice (mL)	Time (h)	Yield (%)[b]
1	EtOH	—	12	Trace
2	EtOH	Lime (1)	6	73
3	EtOH	Chino (1)	8	52
4	EtOH	Orange (1)	10	65
5	EtOH	Tangerine (1)	9	63
6	EtOH	Kiwi (1)	8	54
7	EtOH	Grapefruit (1)	9	60
8	EtOH	Lime (0.5)	7	61
9	EtOH	Lime (2)	5	81
10	EtOH	Lime (3)	3	88
11	EtOH	Lime (4)	3	85
12	H_2O	Lime (3)	12	15

[a] Reaction was run with the following steps: a mixture of aniline (1 mmol) DMAD (1 mmol) in solvent (3 mL) at room temperature was stirred for 30 min. Next, another aniline (1 mmol), formaldehyde (1.5 mmol) and juice were added successively.
[b] Isolated yields.

Therefore, we investigated several reactions between variety of anilines, dimethyl and/or diethylacetylenedicarboxylate and formaldehyde under optimized reaction conditions. The results are summarized in Table **2**. Anilines with substituents F, Cl, Br, Me and OMe were reacted efficiently to generate the expected polyfunctionalized dihdropyrrol-2ones **5a-i** in good to high yields (Table **2**, entries 1-9). Encouraged by these results and, to evaluate the generality and versatility of this method, the optimized

conditions were used for the synthesis of different substituted dihdropyrrol-2ones **5j-r**. Four-component domino reactions of aliphatic amines such as benzyl amine, *n*-butylamine and *n*-propylamine with dialkyl acetylenedicarboxylates, formaldehyde and aromatic amines were proceeded smoothly to afford the corresponding products (Table **2**, entries 10-18). Satisfactory, the reactions display high functional group tolerance and provided the desired dihydropyrrol-2-one derivatives in good yields. In all reactions, at the commencing, the reactants were completely dissolved in reaction medium to form a homogeneous mixture. But near the completion of the reaction, the system became a suspension, and the products precipitated at the end of the reaction. The crud products were obtained by simple filtration and washed with ethanol to afford pure products.

Table 2: Synthesis of highly substituted dihydropyrrol-2-ones **5**.

Entry	R^1	R^2	Ar	Compound	Time (h)	Yield (%)[a]	Mp (°C)	Lit. mp (°C)[Ref.][b]
1	Ph	Me	Ph	**5a**	3	88	153-155	155-156 [23]
2	4-F-C_6H_5	Me	4-F-C_6H_5	**5b**	3	92	163-165	163-165 [28]
3	4-Cl-C_6H_5	Me	4-Cl-C_6H_5	**5c**	2.5	80	175-177	173-174 [23]
4	4-Br-C_6H_5	Me	4-Br-C_6H_5	**5d**	3	92	177-179	179-180 [23]
5	4-Me-C_6H_5	Me	4-Me-C_6H_5	**5e**	3.5	88	173-175	177-178 [23]
6	Ph	Et	Ph	**5f**	3.5	78	139-141	138-140 [22]
7	4-F-C_6H_5	Et	4-F-C_6H_5	**5g**	3	84	173-176	172-173 [22]
8	4-Br-C_6H_5	Et	4-Br-C_6H_5	**5h**	3.5	90	164-166	169-171 [22]
9	4-OMe-C_6H_5	Et	4-OMe-C_6H_5	**5i**	4	79	152-154	152-154 [28]
10	$PhCH_2$	Me	Ph	**5j**	2.5	86	135-137	139-140 [23]
11	$PhCH_2$	Me	4-F-C_6H_5	**5k**	4	82	166-168	166-168 [28]
12	$PhCH_2$	Et	Ph	**5l**	3	87	133-135	130-132 [22]
13	$PhCH_2$	Me	4-Me-C_6H_5	**5m**	3.5	85	144-146	144-146 [30]
14	*n*-C_4H_9	Me	Ph	**5n**	3	85	58-60	60 [23]
15	*n*-C_4H_9	Me	4-F-C_6H_5	**5o**	3	83	80-82	81-83 [30]
16	*n*-C_4H_9	Me	4-Br-C_6H_5	**5p**	4	82	105-107	108-109 [23]
17	*n*-C_4H_9	Et	4-Br-C_6H_5	**5q**	3	80	94-96	94-96 [27]
18	*n*-C_3H_7	Et	Ph	**5r**	3	78	74-76	78-79 [22]

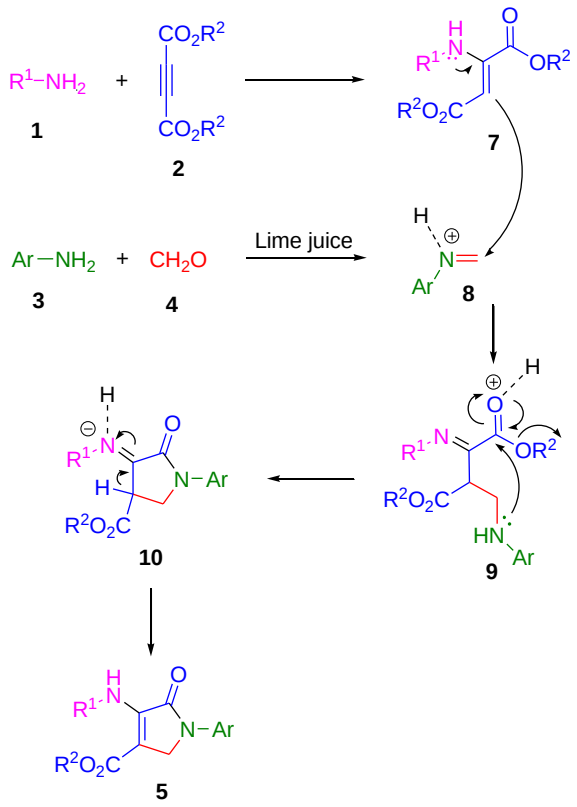
[a] Isolated yields.
[b] The references of known products in the literature.

On the basis of above experimental results together with the related reports [23-24], a plausible mechanism for this four-component domino reaction is proposed as shown in Scheme **2**. The first two steps involve the reaction of amine **1** with dialkyl acetylenedicarboxylate **2** to form dialkyl 2-(aryl or alkylamino) fumarate **7**, and the condensation of aromatic amine **3** with formaldehyde **4** to generate imine **8**. The next step is reaction of intermediate **7** with activated imine **8** to form intermediate **9**, followed by intramolecular cyclization to afford intermediate **10**. In final step, cyclic intermediate **10** undergoes proton transfer to obtain the substituted dihydropyrrol-2-one **5.**

Conclusion

In summary, a simple, efficient and environmentally benign method has been described for the synthesis of highly substituted dihydropyrrol-2-ones by use of lime

juice-ethanol mixture as reaction medium without any post-modification. The promising points for the presented methodology are extremely mild and green reaction conditions, good to high yields, short reaction times, cheap, easy purification and lack of need for column chromatography, which makes it a useful and attractive process for the synthesis of these important heterocycles.



Scheme 2: Proposed mechanism for the synthesis of highly substituted dihydropyrrol-2-ones 5.

Experimental

General:

Melting points were taken 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 Avanve instrument with $CDCl_3$ as solvent and using TMS as internal reference at 400 and 100 MHz, respectively. Chemicals were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

Preparation of lime juice:

Lime fruits were collected from Jahrom, Fars province, Iran and their juice were extracted by simple filtration. Next, for the further purification, the lime juice was several times filtered. The obtained clear lime juice was used for the preparation of dihydropyrrol-2-one derivatives.

General procedure for the synthesis of dihydropyrrol-2-one **5**:

A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in ethanol (3 mL) was stirred for 30 min. Next, amine **3** (1 mmol), formaldehyde **4** (37% solution, 1.5 mmol) and lime juice (3 mL) 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**. The structure of the products was characterized by IR, ^{1}H and ^{13}C NMR spectral data and comparison of their melting points with those of authentic samples [22, 23, 27-30].

Methyl 1-phenyl-3-(phenylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5a**):

IR (KBr) (ν_{max}, cm^{-1}): 3264 (NH), 1692 (C=O), 1641 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.76 (s, 3H, OCH_3), 4.57 (s, 2H, CH_2), 7.16-7.23 (m, 4H, ArH), 7.34 (t, *J* = 8.0 Hz, 2H, ArH), 7.42 (t, *J* = 8.0 Hz, 2H, ArH), 7.81 (d, *J* = 8.0 Hz, 2H, ArH), 8.05 (br s, 1H, NH).

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

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.35 (s, 6H, $2CH_3$), 3.79 (s, 3H, OCH_3), 4.41 (s, 2H, CH_2), 7.08 (d, *J* = 8.0 Hz, 2H, ArH), 7.15 (d, *J* = 8.2 Hz, 2H, ArH), 7.22 (d, *J* = 8.4 Hz, 2H, ArH), 7.63 (d, *J* = 8.4 Hz, 2H, ArH), 8.04 (br s, 1H, NH).

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

IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1698 (C=O), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), 1.35 (t, *J* = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.43 (sextet, *J* = 7.6 Hz, 2H, CH_2), 1.61 (quintet, *J* = 7.6 Hz, 2H, CH_2), 3.87 (t, *J* = 7.2 Hz, 2H, $C\underline{H}_2$-NH), 4.28 (t, *J* = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.40 (s, 2H, $C\underline{H}_2$-N), 6.72 (br s, 1H, NH), 7.52 (d, *J* = 8.8 Hz, 2H, ArH), 7.71 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.8, 14.5, 19.8, 33.4, 42.5, 47.8, 59.8, 98.1, 117.7, 120.5, 132.1, 137.9, 164.5 (C=O), 165.5 (C=O).

Acknowledgments

We gratefully acknowledge financial support from the Research Council of the University of Sistan and Baluchestan.

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