Article

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An Efficient One-pot Access to Substituted Dihydropyrrol-2-one Derivatives Using Sucrose as Natural, Biodegradable and Inexpensive Catalyst

Nourallah Hazeri,[a]* Seyed Sajad Sajadikhah,[b] Malek Taher Maghsoodlou,[a] Sajad Mohamadian-Souri,[a] Mahmoud Norouzi[a] and Maryam Moein[a]

[a]*Department of Chemistry, University of Sistan and Baluchestan, P.O. Box 98135-674, Zahedan, Iran*

[b]*Department of Chemistry, Payame Noor University, Iran*

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An efficient and simple procedure for the synthesis of highly substituted dihydropyrrol-2-ones has been developed *via* one-pot four-component condensation of amines, dialkyl acetylenedicarboxyaltes and formaldehyde in the presence of sucrose as an organocatalyst. The salient advantages of this method are using a natural, biodegradable and commercial available catalyst, good yields, short reaction times, simple work-up and lack of need for column chromatography.

Keywords: Dihydropyrrol-2-one; Heterocycle; Sucrose; Organocatalyst; Multi-component reaction.

INTRODUCTION

Nitrogen containing heterocycles play key roles in pharmaceutical scenes and exhibit a wide range of biological activities.[1-4] Amongst them, dihydropyrrol-2-ones (dihydro-2-oxopyrroles) are very interesting compounds due to their biological and pharmaceutical activity such as anti-HIV,[5] anti-influenza,[6] anti cancer,[7] antibiotics,[8] nootropic agents,[9] pesticides,[10] and herbicidal.[11] Furthermore, these heterocycles are the core structure of many bioactive natural compounds such as quinolactacins,[12] ypaoamide,[13] oteromycin,[14] jatropham,[15] EBPC,[16] and (*Z*)-pulchellalactam.[17] Recently, Jiang et al. have reported the synthesis of dihydropyrrol-2-ones by means of the reaction between amines, dialkyl acetylenedicarboxylates and aldehydes in the presence of acetic acid,[18] and Khan et al. documented the iodine catalyzed synthesis of dihydropyrrol-2-one derivatives.[19] Additionally, a few efforts have been also paid to the synthesis of highly substituted dihydropyrrol-2-ones using catalysts such as benzoic acid,[20] TiO_2 nanopowder,[21] and $Cu(OAc)_2{\cdot}H_2O$.[22] Therefore, the development of novel methods for the synthesis of dihydropyrrol-2-ones is of great importance because of their potential biological and pharmaceutical activities.

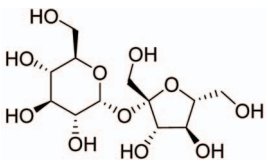
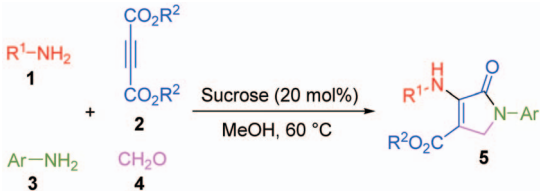


Fig. 1. Chemical structure of sucrose.

In recent years, the use of organocatalysts has received considerable attention in organic chemistry due to their properties such as lack of sensitivity to moisture and oxygen, ready availability, low cost, low toxicity and reduced waste formation.[23-25] Sucrose is a carbohydrate molecule commonly known as table sugar. Chemically, sucrose is a disaccharide composed of the monosaccharides glucose and fructose with molecular formula $C_{12}H_{22}O_{11}$. This small natural molecule contains three primary and five secondary hydroxyl groups and therefore it can acts as mild catalytic system (Fig. 1).

In continuation of our research work on the synthesis of dihydropyrrol-2-ones,[26-29] herein we wish to report commercially available sucrose as bio-resource homogeneous catalyst, for the one-pot synthesis of highly substituted dihydropyrrol-2-ones by means of four-component domino reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde (Scheme I).

Scheme I Synthesis of dihydropyrrol-2-ones **5**



RESULTS AND DISCUSSION

First, we looked for the optimum reaction conditions. The screening was performed with aniline, dimethyl ace-

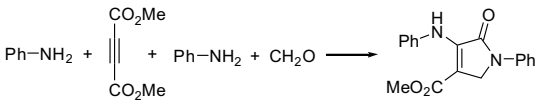
* Corresponding author. Tel: +98-541-2416586; Fax: +98-541-2416586; Email: nhazeri@chem.usb.ac.ir

tylenedicarboxylate (DMAD) and formaldehyde as a model system, and the results are summarized in Table 1. The first experiment was carried out in the presence of sucrose (20 mol%) in methanol at ambient temperature, and the corresponding functionalized dihydropyrrol-2-one **5a** was obtained in 39% yield (Table 1, entry 1). In the absence of catalyst, only a trace yield of product was obtained even after prolonged reaction time. Next, the effect of the catalyst was investigated in various conditions. The best result was obtained in the presence of 20 mol% of the catalyst at 60 °C (Table 1, entry 6).

The scope and limitations of this domino four-component reaction were explored under optimized conditions using a variety of amines and acetylenic esters, as summarized in Table 2. Anilines containing either electron-donating or electron-withdrawing substituents successfully react with dialkyl acetylenedicarboxylates and formaldehyde, affording good yields of products **5a-l**. Next, two different amines were examined to study the generality and scope of the present protocol. Aliphatic amines such as benzyl amine and *n*-butyl amine were treated with varying anilines, dimethyl and/or diethyl acetylenedicarboxylate and formaldehyde under indicated reaction conditions. All reactions underwent smoothly to provide the corresponding dihydropyrrol-2-one derivatives **5m-s** in good to high yields (Table 2, entries 13-19). Satisfactory, the reactions displayed high functional group tolerance and provided the desired products with great efficiency. 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.

A plausible mechanism for the synthesis of highly substituted dihydropyrrol-2-ones **5** is illustrated in Scheme II.

Table 1. Optimization of the reaction conditions



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	20	MeOH	25	5.5	39
2	–	MeOH	25	24	Trace
3	20	EtOH	25	7	31
4	20	MeOH	40	5	50
5	20	MeOH	50	4	78
6	20	MeOH	60	4	89
7	5	MeOH	60	5	63
8	10	MeOH	60	4.5	85
9	15	MeOH	60	4	86
10	25	MeOH	60	4	83
11	30	MeOH	60	5	78

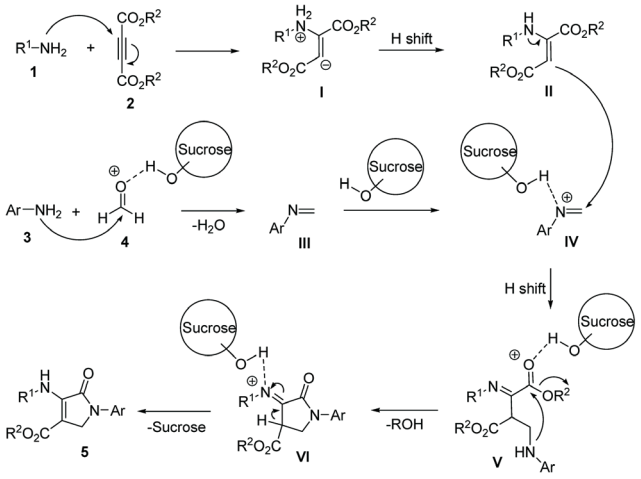
[a] Isolated Yield.

Table 2. The synthesis of substituted dihydropyrrol-2-ones **5**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	m.p. (lit. reported)[Ref., b]
1	Ph	Me	Ph	**5a**	4	89	153-155 (155-156)[19]
2	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5b**	4	81	173-175 (177-178)[19]
3	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5c**	4.5	77	170-173 (176-177)[19]
4	4-F-C_6H_4	Me	4-F-C_6H_4	**5d**	4	89	163-165 (163-165)[26]
5	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5e**	4.5	84	168-170 (173-174)[19]
6	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5f**	4	90	175-178 (179-180)[19]
7	Ph	Et	Ph	**5g**	4	84	137-139 (138-140)[18]
8	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5h**	5	71	126-128 (131-132)[18]
9	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5i**	4.5	72	152-154 (152-154)[27]
10	4-F-C_6H_4	Et	4-F-C_6H_4	**5j**	4	85	172-174 (172-173)[18]
11	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5k**	4.5	84	167-169 (168-170)[28]
12	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5l**	4	83	170-172 (169-171)[18]
13	$PhCH_2$	Me	Ph	**5m**	4	83	141-143 (140-141)[18]
14	$PhCH_2$	Me	4-Cl-C_6H_4	**5n**	6	83	144-147 (147-148)[19]
15	$PhCH_2$	Me	4-Br-C_6H_4	**5o**	3.5	88	123-125 (120-121)[19]
16	*n*-C_4H_9	Me	Ph	**5p**	5	83	60-62 (60)[19]
17	*n*-C_4H_9	Me	4-F-C_6H_4	**5q**	6	78	81-83 (81-83)[29]
18	*n*-C_4H_9	Me	4-Br-C_6H_4	**5r**	5	88	109-111 (108-109)[19]
19	*n*-C_4H_9	Et	4-Br-C_6H_4	**5s**	5	85	94-96 (94-96)[26]

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

Scheme II Suggested mechanism for the synthesis of dihydropyrrol-2-ones **5**



In conclusion, we have developed a very simple and efficient method for the synthesis substituted dihydropyrrol-2-one derivatives using sucrose as natural, biodegradable and inexpensive catalyst *via* condensation of amines, dialkyl acetylenedicarboxylates and formaldehyde in methanol. This method offers several advantages such as easy purification and lack of need for column chromatography, high yields, short reaction times, simple and readily available precursors.

EXPERIMENTAL

General: All the chemicals were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification. Melting points were determined on an Electrothermal 9100 apparatus. IR spectra were obtained on a JASCO FT/IR-460 plus spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avanve instrument with $CDCl_3$ as solvent at 400 and 100 MHz, respectively; chemical shifts are given in δ ppm, relative to TMS as internal standard.

General procedure for the synthesis of dihydropyrrol-2-one 5: A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in methanol (3 mL) was stirred for 30 min. Next, amine **3** (1 mmol), formaldehyde **4** (1.5 mmol) and sucrose (20 mol %) were added successively. The reaction mixture was allowed to stir at 60 °C for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the solid precipitate was obtained through simple filtering, and washed with methanol to give the pure product **5**. Physical and spectral data for selected products are represented below.

Methyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate (5a): White solid, IR (KBr) (ν_{max}, cm^{-1}): 3266 (NH), 1676 (C=O), 1645 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (3H, s, OCH_3), 4.57 (2H, s, CH_2), 7.16-7.23 (4H, m, ArH), 7.35 (2H, t, *J* = 7.8 Hz, ArH), 7.42 (2H, t, *J* = 8.0 Hz, ArH), 7.81 (2H, d, *J* = 8.0 Hz, ArH), 8.05 (1H, br s, NH).

Methyl 3-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5d): White solid, IR (KBr) (ν_{max}, cm^{-1}): 3286 (NH), 1676 (C=O), 1646 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 4.53 (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 48.3, 51.4, 115.1 (d, J_{CF} = 23.0 Hz), 115.9 (d, J_{CF} = 22.1 Hz), 121.0 (d, J_{CF} = 7.0 Hz), 125.1 (d, J_{CF} = 8.1 Hz), 134.4 (d, J_{CF} = 3.0 Hz), 134.7 (d, J_{CF} = 2.0 Hz), 143.4, 159.8 (d, J_{CF} = 243.0 Hz), 160.1 (d, J_{CF} = 242.0 Hz), 163.5 (C=O), 164.8 (C=O).

Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5k): White solid, IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1696 (C=O), 1640 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$), 4.27 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.52 (2H, s, CH_2), 7.09 (2H, d, *J* = 8.4 Hz, ArH), 7.28 (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, br s, NH).

Ethyl 1-(4-bromophenyl)-3-(butylamino)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5s): White solid, IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1698 (C=O), 1646 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.2 Hz, CH_3), 1.35 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.44 (2H, sextet, *J* = 7.4 Hz, CH_2), 1.62 (2H, quintet, *J* = 7.4 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 (100 MHz, $CDCl_3$): δ 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 (C=O), 165.5 (C=O).

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