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Research Note

Efficient synthesis of highly substituted pyrroles via a multi-component reaction using ZnO nanoparticles as a nanocatalyst

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Abstract. A convenient one-pot multi-component reaction of aromatic aldehydes, 1,3-dicarbonyl compounds, amine and nitromethane in the presence of 10 mol% ZnO nanoparticles for the synthesis of highly substituted pyrroles is described. The products were obtained in moderate to good yields via a one-pot tandem reaction. This method offers several advantages, such as good yields, a simple procedure, non-hazardous reaction conditions and starting from easily accessible substrates.

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1. Introduction

Pyrroles are very important compounds as they exist in a large number of natural products and display a variety of biological and pharmaceutical activities (Figure 1). A diverse range of pharmacological properties, including antibacterial, antitumor, anti-inflammatory, antioxidant, antianginal and antifungal activities of this important class of heterocycles has been reported in the literature [1-6].

There has also been considerable study of pyrrole synthesis in the literature, including Knorr [7], Paale-Knorr [8], Hantzsch synthesis [9], 1,3-dipolar cycloaddition reactions [10], reductive coupling [11] and aza-Wittig reactions [12]. However, some of these methods have some drawbacks, such as harsh reaction conditions, lengthy reaction times, expensive catalysts and low yields. Therefore, it is clearly evident that developing new and flexible methods of synthesis is required.

Over the past few years, nanostructured metal oxides seem to be effective, alternative, and promising transition-metal catalysts and have received much attention due to their low cost, ready availability and nontoxicity [13]. Furthermore, the surface of metal oxides exhibit both Lewis acid and Lewis base characters. They are excellent adsorbents for a wide variety of organic compounds; moreover, they can increase the reactivity of the reactants. On the other hand, multicomponent reactions (MCRs) have emerged as an efficient, time-saving and powerful tool in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner, without isolation of any intermediate. Therefore, the discovery of new MCRs and the improvement of currently-known MCRs are of considerable interest. The development of new strategies for the preparation of complex molecules in neat conditions is a challenging area of organic synthesis. In the last decade, research in academia and industry has increasingly emphasized the use of MCRs, as well as domino reaction sequences, in a broad range

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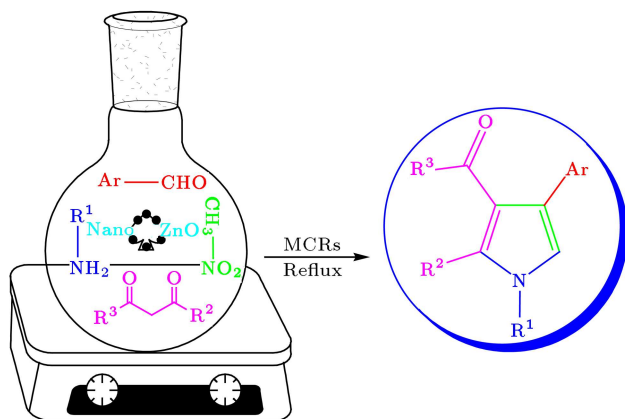
of products [14].

Interest in nano zinc oxide has grown greatly because of its surface properties, which suggest that a large number of chemical reactions occur [15–20]. The high surface area-to-volume ratio of ZnO nanoparticles is mainly responsible for its catalytic properties. During our studies on the preparation of ZnO nanoparticles by controlled microwave heating and its promising application in *O*-acylation of alcohol [21] and synthesis of β -acetamido ketones/esters [22] via a multicomponent reaction, we became interested in the synthesis of highly substituted pyrroles using nano ZnO as the nanocatalyst. Therefore, in continuation of the authors research devoted to the synthesis of heterocycles skeletons [23,24], this paper reports an efficient one-pot four-component reaction of commercially available 1,3-dicarbonyl compounds, aromatic aldehydes, amines, and nitromethane in the presence of ZnO nanoparticles, which leads to highly substituted pyrroles in moderate to good yields (Scheme 1).

2. Experimental investigation

2.1. General information

All chemicals were purchased from Merck and Aldrich and were used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125 MHz for carbon nuclei in CDCl_3 and DMSO. The products were purified by column chromatography



Scheme 1. Synthesis of highly substituted pyrroles via a four-component reaction.

carried out on silica gel using petroleum ether/ethyl acetate. The ZnO nanoparticles were prepared according to our reported procedure [21].

2.2. General procedure for synthesis of highly substituted pyrroles

Aryl aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol) and an amine (1.3 mmol) were added to a stirred suspension of ZnO nanoparticles (10 mol %) in nitromethane (3 mL). The reaction mixture was stirred at 100–105°C for 15 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture concentrated under vacuum. The residue was purified by preparative TLC (petroleum ether/ethyl acetate 5:1) to afford the desired compound. The structure of the products was confirmed by NMR spectroscopic data (^1H -NMR, ^{13}C -NMR), and a comparison of authentic samples was performed by the reported methods [25–28].

3. Results and discussion

Initially, a model reaction was conducted at room temperature to examine the feasibility of the reaction (Table 1). Therefore, we examined the four-component reaction of 4-chlorobenzaldehyde (1 mmol), methyl acetoacetate (1 mmol), benzyl amine (1.3 mmol) and nitromethane (3 mL) as a reagent and reaction medium, using nano zinc oxide as a catalyst. At room temperature, only a trace amount of the desired pyrrole was observed. However, the reaction finally gave rise to the desired product in good overall yield when conducted at 100°C. During optimization of the reaction conditions, we found that 10 mol% of ZnO nanoparticles could effectively catalyze the reaction for synthesis of the desired product. Commercially available ZnO bulk was also evaluated for the synthesis of the desired compounds. Using ZnO nanoparticles as a catalyst, the reaction time was clearly reduced by 3 times, with higher yield than bulk ZnO (71% versus 47%). The reaction did not occur in the absence of the catalyst.

The characteristic signals for **1a** in the ^1H NMR spectra were a singlet for the protons of the methoxy group at 3.70 ppm, a singlet for methyl protons of the pyrrole ring at 2.50 ppm, a resonance for the deshielded

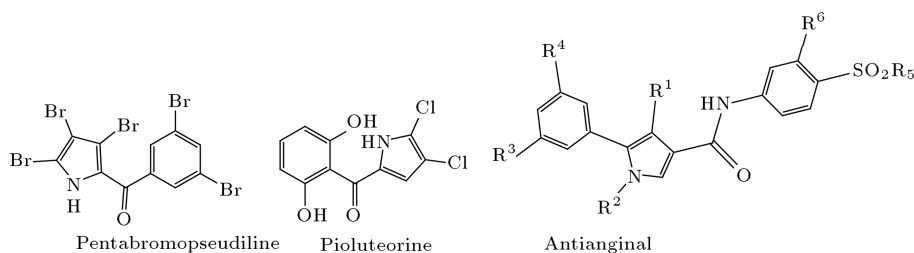
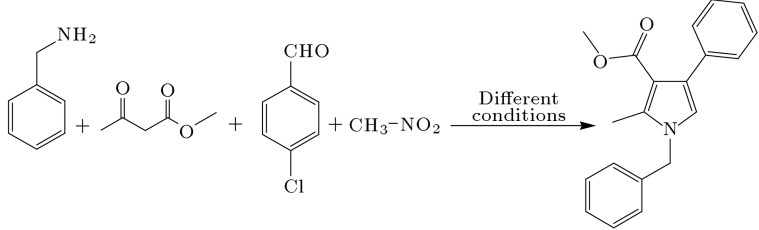
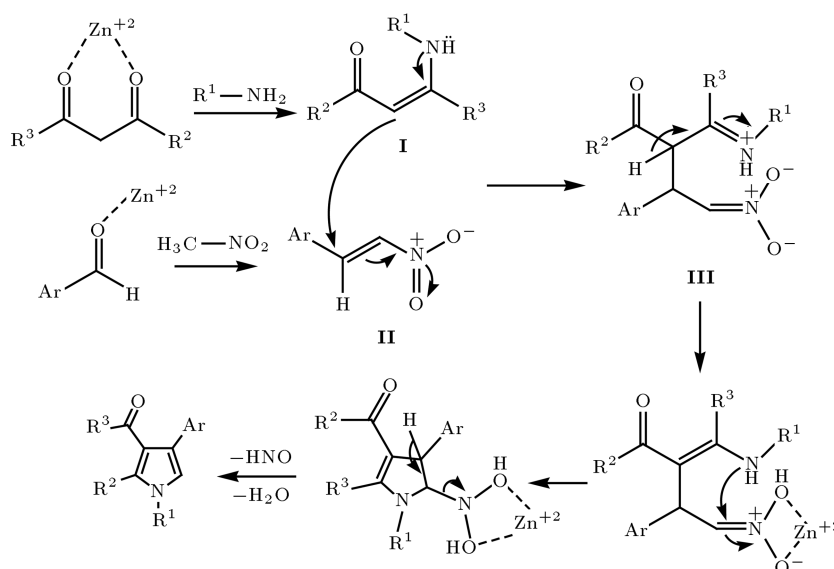


Figure 1. Some bioactive pyrrole derivatives.

Table 1. Optimization conditions of the model reaction for the synthesis of highly substituted pyrroles.


Entry	Catalyst	T (°C)	Yield (%)
1	–	r.t	–
2	Nano ZnO (10 mol%)	r.t	Trace
3	Nano ZnO (10 mol%)	60	53
4	Nano ZnO (10 mol%)	100	71
5	Nano ZnO (5 mol%)	100	59
6	Nano ZnO (20 mol%)	100	73
7	Bulk ZnO (10 mol%)	100	47

**Scheme 2.** Suggested reaction mechanism for formation of highly substituted pyrroles.

benzylic proton at 5.09 ppm, and another singlet for the aromatic proton of the pyrrole ring at 6.58 ppm. The presence of this signal in ^1H NMR spectra of synthesized compounds is a good indication of the formation of the desired compounds. ^{13}C NMR spectrum of **1a** showed 16 distinct resonances in agreement with the proposed structure. A resonance at δ 11.2 ppm was readily recognized as methyl carbon, a resonance at δ 50.5 ppm as methoxy carbon, a resonance at δ 50.6 ppm as benzylic carbon, a resonance at δ 165.7 ppm as carbonyl carbon and 12 distinct resonances for aromatic carbons.

According to this procedure, the reaction of substituted benzaldehydes, primary amines and 1,3-dicarbonyl compounds with nitromethane proceeded

smoothly at 100°C in the presence of 10 mol% of ZnO to afford highly substituted pyrroles in moderate to good yields via one-pot tandem reaction (Table 2).

A plausible mechanism for the reaction is shown in Scheme 2. In the first step, ZnO nanoparticles are coordinated to the oxygen of carbonyl groups and activated for nucleophilic attack. So, ZnO nanoparticles facilitate the Knoevenagel-type coupling, as well as enamine formation, through Lewis acid sites (Zn^{2+}) with the release of H_2O . The enamine **I** reacts with nitrostyrene **II** to provide Michael adduct **III**. Subsequently, the ring closures proceed through an intramolecular attack of amine, followed by the loss of HNO_2 , to give pyrroles.

Table 2. ZnO nanoparticles catalyzed formation of highly substituted pyrroles.

Entry	R ¹	R ²	R ³	Ar	Products [25-28]	Yield (%)
1	C ₆ H ₄ CH ₂	Me	OMe	<i>p</i> -ClC ₆ H ₄	1a	71
2	C ₆ H ₄ CH ₂	Me	OMe	<i>p</i> -MeC ₆ H ₄	1b	82
3	C ₆ H ₄ CH ₂	Me	OMe	<i>p</i> -NO ₂ C ₆ H ₄	1c	41
4	C ₆ H ₄ CH ₂	Me	OMe	Ph	1d	61
5	C ₆ H ₄ CH ₂	Me	OMe	<i>p</i> -MeOC ₆ H ₄	1e	67
6	C ₆ H ₄ CH ₂	Me	OMe	2-furyl	1f	37
7	C ₆ H ₄ CH ₂	Me	Me	<i>m</i> -NO ₂ C ₆ H ₄	1g	56
8	C ₆ H ₄ CH ₂	Me	OEt	<i>p</i> -ClC ₆ H ₄	1h	63
9	C ₆ H ₄ CH ₂	Me	OEt	<i>p</i> -MeOC ₆ H ₄	1i	69
10	C ₆ H ₄ CH ₂	Me	OEt	<i>p</i> -MeC ₆ H ₄	1j	75
11	<i>p</i> -MeOC ₆ H ₄	Me	OMe	<i>p</i> -ClC ₆ H ₄	1k	47
12	<i>p</i> -MeOC ₆ H ₄	Me	OMe	<i>p</i> -NO ₂ C ₆ H ₄	1l	38
13	<i>p</i> -BrC ₆ H ₄	Me	OMe	Ph	1m	58
14	<i>p</i> -BrC ₆ H ₄	Me	OEt	<i>p</i> -ClC ₆ H ₄	1n	61
15	<i>p</i> -MeOC ₆ H ₄	Me	OEt	<i>p</i> -ClC ₆ H ₄	1o	67

Representative spectroscopic data

Methyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**1a**): IR (KBr) 3018, 1687, 1526, 1284, 1125, 765 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 2.50 (s, 3H), 3.70 (s, 3H), 5.09 (s, 2H), 6.58 (s, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 7.30-7.33 (m, 5H), 7.37 (d, *J* = 7.2 Hz, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ 11.2, 50.5, 50.6, 110.9, 120.6, 125.1, 127.6, 127.7, 127.9, 129.0, 129.1, 129.3, 130.7, 132.0, 134.5, 165.7. Methyl 1-benzyl-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate (**1d**): IR (KBr) 3400, 3017, 1687, 1525, 1454, 1284, 1215 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 2.50 (s, 3H), 3.70 (s, 3H), 5.09 (s, 2H), 6.62 (s, 1H), 7.10-7.49 (m, 10H); ¹³C-NMR (125 MHz, CDCl₃): δ 11.1, 50.6, 50.7, 111.1, 120.4, 126.1, 126.3, 126.6, 127.6, 127.9, 129.0, 129.4, 135.9, 136.5, 136.8, 165.9. Methyl 1-benzyl-4-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (**1f**): IR (KBr) 2917, 1700, 1595, 1489, 1280, 1207 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 2.44 (s, 3H), 3.87 (s, 3H), 5.09 (s, 2H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.76 (d, *J* = 3.3 Hz, 1H), 6.96 (s, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 7.30-7.39 (m, 5H); ¹³C-NMR (125 MHz, CDCl₃): δ 11.2, 29.8, 50.7, 107.1, 109.9, 111.1, 115.7, 120.5, 126.8, 127.5, 127.9, 129.0, 136.7, 140.1, 149.3, 165.7. Ethyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**1h**): IR (KBr) 3018, 1686, 1528, 1454, 1284, 1065 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): δ 1.21 (t, *J* = 7.1 Hz, 3H), 2.50

(s, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 5.10 (s, 2H), 6.61 (s, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 7.32-7.35 (m, 5H), 7.39 (d, *J* = 7.1 Hz, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ 11.6, 14.2, 50.6, 59.5, 110.9, 120.6, 125.1, 127.6, 127.7, 127.9, 128.9, 129.0, 129.4, 130.6, 131.9, 134.4, 165.8. Ethyl 1-(4-bromophenyl)-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**1n**): ¹H-NMR (500 MHz, CDCl₃): δ 1.20 (t, *J* = 7.1 Hz, 3H), 2.48 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.65 (s, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.28-7.35 (m, 4H), 7.65 (d, *J* = 8.6 Hz, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ 11.6, 14.3, 59.5, 126.9, 127.6, 127.7, 127.9, 129.0, 129.1, 129.4, 130.7, 131.9, 132.1, 133.6, 134.5, 165.8.

4. Conclusions

In conclusion, ZnO nanoparticles were found to be a non-toxic, inexpensive and efficient heterogeneous nanocatalyst for the synthesis of highly substituted pyrroles, starting from easily accessible substrates. The procedure is simple, general and efficient, and affords the products in moderate to good yields via a one-pot tandem reaction.

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Firouz Matloubi Moghaddam was born in Maragheh, Iran. He obtained BS and MS degrees in Chemistry and Organic Chemistry from Tabriz University, Iran, respectively, and a ‘Doctorat d’Etat’ (Habilitation) in 1982 from the University of Louis Pasteur, Strasbourg, France, from where he also obtained an MS degree in Medicinal Chemistry. He spent three years of postdoctoral appointments at the University of Zurich, and is currently Professor of Organic Chemistry at Sharif University of Technology, Tehran, Iran. His research interests include total synthesis of bioactive compounds, isolation, structure elucidation and synthesis of bioactive natural products, heterocyclic chemistry, and catalysis.

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