



## Green Synthesis of *N*-pyrroles in Water via Using $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ as an Efficient and Eco-Friendly Catalyst

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### Abstract

A simple and efficient protocol for the synthesis of *N*-substituted pyrroles from one-pot condensation reaction of 2, 5-dimethoxytetrahydrofuran with aryl/alkyl, sulfonyl and acyl amines in the presence of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  in water has been developed. This new method has the advantages of simple experimental and work-up procedure, high to excellent yields, easy availability, economical, eco-friendly of the catalyst and high catalytic activity.

**Keywords:** Dimethoxytetrahydrofuran, Amines, *N*-substituted pyrrole, Zirconiumoxychloride, Green synthesis, Water as solvent.

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### Introduction

Pyrrole derivatives are useful intermediates in the synthesis of drugs, pigments that have antibiotic activity, and very structure of natural components is based on pyrrole such as chlorophyll, hemi, porphyrines [1]. Pyrroles can be found in bioactive molecules, including the blockbuster drug, atorvastatin calcium, as well as important anti-inflammations, antitumor agents, and immunosuppressant. These compounds are useful for the development of organic functional materials and also are useful intermediates in the synthesis of natural

product as well as heterocyclic compounds [2-4]. *N*-Substituted pyrroles are one of the most important derivatives of pyrroles which are widely used in the materials science.

These compounds are usually synthesized by Paal-Knorr reaction and other reactions like Aza-Wittig [5]. Paal-Knorr reaction by Clauson-Kaas [6] in 1952 from reaction of primary amines with 2,5-dialkoxytetrahydrofurans in refluxing acetic acid has been reported that recently the reaction is carried out in several methods using different homogeneous or heterogeneous

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catalysts such as  $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$  [7,8],  $\text{I}_2$  [9],  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  [10],  $\text{FeCl}_3 \cdot 5\text{H}_2\text{O}$  [11],  $\text{H}_3\text{PW}_{12}\text{O}_{40}/\text{SiO}_2$  [12],  $\text{Sc}(\text{SO}_3\text{CF}_3)_3$  [13], Ionic liquid (BMIm) [14], Monotmorillonite K-10 [15], p-TSA [16]. However, some of these protocols require long reaction times [17], higher temperatures, using expensive reagents, strictly anhydrous [18-19] and low yields. Therefore, one of the points that should be considered is the use of a suitable catalyst. Among these catalysts, Zr (IV) compounds, specifically  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  has been great attention because of low toxicity, high coordinating ability, low cost and most importantly, their higher activity [20].

Our purpose of research to report a simple and efficient method for the synthesis of N-substituted pyrroles from 2,5-dimethoxytetrahydrofuran and primary amines catalyzed by  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  in water as a green solvent. This reaction is performed under very mild reaction conditions and produces products in excellent yields.

## Experimental

### *Material and methods*

FT-IR spectra were recorded as KBr pellets on a Shimadzu FT-IR-8400 spectrometer. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 on Al-plates. All solvents and chemicals such as

2, 5-dimethoxytetrahydrofuran, amines were purchased from Merck or Aldrich and were used as received, except an aniline which were distilled prior to use.

### *Typical experimental procedure for the preparation of 1H-pyrroles*

To a stirred solution of amines (5 mmol) in 4 mL of water, 2, 5-dimethoxytetrahydrofuran (6 mmol) and 5 mol% of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  were added and the resulting mixture was stirred at 60 °C for 10-240 min. Proceeding of the reaction was monitored by TLC (eluent: n-hexane – ethyl acetate, 3: 1). After completion of the reaction, EtOAc (10 ml) was added. The organic solution was evaporated under reduced pressure and affording the Pyrrole derivative with good analytical purity. All compounds were known and were characterized on the basis of their spectroscopic data (m.p, IR,  $^1\text{H-NMR}$ ).

## Results and discussion

Herein we reported a green and fast synthesis of N- substituted pyrroles from commercially available 2, 5-dimeth oxytetrahydrofuran and various (aliphatic, aromatic, heteroaromatic, and polyaromatic) amines catalyzed by  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  in water (Scheme1). In order to find the optimized conditions, a systematic study considering different variables affecting the reaction yield was carried out for the reaction of 2,5-dimethoxytetrahydrofuran and aniline (molar ratio:1.2:1) as the model reaction (Table 1).

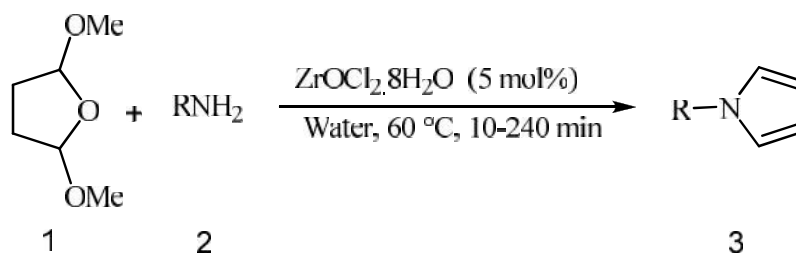
Thus, the best results were obtained by carrying out the model reaction at 60 °C for 30 min in the presence of 5 mol % of  $ZrOCl_2 \cdot 8H_2O$  catalyst in water as a solvent. In addition, the reaction of aniline and 2, 5-dimethoxytetrahydrofuran carried out in various organic solvents such as  $CH_3CH_2OH$ ,  $CH_2Cl_2$ , EtOAc and  $CH_3OH$  subsequently (Table 1). We found that the reaction in water spent shorter time and excellent yields than organic solvents. The use of water as a green solvent for organic reactions would greatly contribute to the development of environmentally friendly processes. Indeed, industry prefers to use water as a solvent rather than toxic organic solvents.

**Table1.** Optimization of conditions for preparation 1-phenyl-1H- pyrrole.

Entry	Catalyst/mol%	Solvent	Temp/°C	Time/min	Yield/%
1	-	H <sub>2</sub> O	Reflux	30	-
2	(1)	H <sub>2</sub> O	Reflux	30	30
3	(5)	H <sub>2</sub> O	Reflux	30	95
4	(5)	H <sub>2</sub> O	60	30	95
5	(10)	H <sub>2</sub> O	60	30	95
6	(5)	MeOH	60	30	50
7	(5)	EtOAc	60	30	55
8	(5)	$CH_2Cl_2$	60	30	60
9	(5)	EtOH	60	30	70
10	(5)	Neat	60	30	75

Reaction conditions: Aniline (5 mmol), 2,5-dimethoxytetrahydrofuran (6 mmol),  $ZrOCl_2 \cdot 8H_2O$  (5 mmol %), 4 cm<sup>3</sup>, water.

Under an optimized reaction condition, to evaluate the scope and diversities of the reaction, various amines, amides and sulfonamides are successfully reacted with 2, 5-dimethoxytetrahydrofuran to high yields in water (Scheme 1 and the results are shown in Table 2).

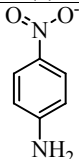
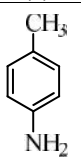
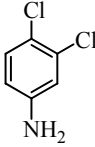
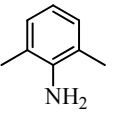
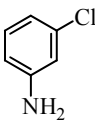
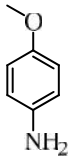
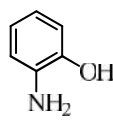
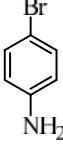
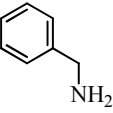
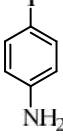
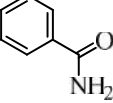
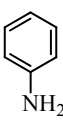
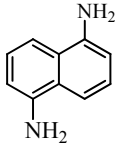
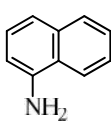
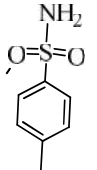
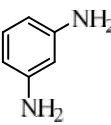
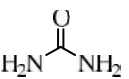


**Scheme 1.** Synthesis of 1-phenyl-1H-pyrrole catalyzed by  $ZrOCl_2 \cdot 8H_2O$  at 60 °C in water.

Both electron-rich as well as electron-deficient amines reacted remarkably with 2, 5-dimethoxytetrahydrofuran in water and provided the desired products in good to

excellent yields. In general, substituted amines with electron-withdrawing groups (4-NO<sub>2</sub>, 4-Cl) require shorter reaction time compared to those with electron-donating groups (4-OCH<sub>3</sub>). Resonance of lone pair nitrogen with the carbonyl or sulfonyl decreased nucleophilicity of the nitrogen reagent and increased the reaction time (entry 17, 18).

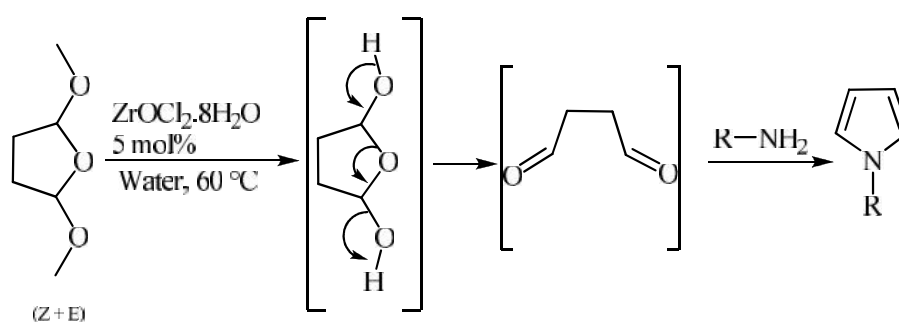
**Table 2.** Synthesis of N-Substituted Pyrroles derivatives under optimized conditions.

Entry	R-NH <sub>2</sub> (2)	Product (3)	Time (min)	Yield (%)	Ref	Entry	R-NH <sub>2</sub> (2)	Product (3)	Time (min)	Yield (%)	Ref
1		3a	10	95	[11]	10		3j	60	92	[24]
2		3b	10	98	[11]	11		3k	75	85	[25]
3		3c	20	98	[21]	12		3l	120	90	[26]
4		3d	20	98	[11]	13		3m	180	70	[27]
5		3e	60	90	[22]	14		3n	180	86	[28]
6		3f	90	92	[23]	15		3o	180	82	[29]
7		3g	30	95	[11]	16		3p	180	82	[11]
8		3h	60	85	[23]	17		3q	220	80	[11]
9		3i	60	85	[11]	18		3r	240	80	[24]

Reaction conditions: amine (5 mmol), 2,5-dimethoxytetrahydrofuran (6 mmol), ZrOCl<sub>2</sub>·8H<sub>2</sub>O (5 mmol %), 4 cm<sup>3</sup>, water.

McMullan has shown  $ZrOCl_2 \cdot 8H_2O$  in water is hydrolyzed and  $ZrO_2$  and HCl are produced [30]. A possible mechanism of the reaction is as follows according to the type of catalyst used and the nature of the substrate and experimental conditions. In this progress, the methoxy group can be opened by the deprotection reaction

under the influence of acid catalyst in solvent and to form an unstable intermediate that can be easily formed and activated dialdehyde. The activated dialdehyde condensed with amines in a nucleophilic addition reaction and finally results corresponding pyrroles by elimination of two water molecules (Scheme 2).



**Scheme 2.** Suggested mechanism for the preparation of N-Substituted Pyrroles derivatives.

## Conclusions

We have obtained that  $ZrOCl_2 \cdot 8H_2O$  is a highly effective acidic catalyst for the condensation of various primary amines, amide and sulfonamide with 2,5-dimethoxytetrahydrofuran in aqueous solution and pyrroles can be synthesized in high purity. The prominent properties of this research are high yield of the products, short reaction times and using green solvent.

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