## Iron-Catalyzed Inexpensive and Practical Synthesis of N-Substituted Pyrroles in Water

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**Abstract:** An operationally simple, practical, and economical protocol for iron(III) chloride catalyzed Paal–Knorr pyrrole synthesis in water in good to excellent yields has been developed. Several Nsubstituted pyrroles are readily prepared from the reaction of 2,5dimethoxytetrahydrofuran and aryl/alkyl, sulfonyl and acyl amines under very mild reaction conditions

Key words: dimethoxytetrahydrofuran, iron, pyrrole, amine, water chemistry

Development of inexpensive and eco-friendly catalysts with a higher activity and selectivity in water as a 'green' medium is an important challenge in organic synthesis.<sup>1</sup>

Pyrrole derivatives are important intermediates not only in the synthesis of drugs, pigments, and pharmaceuticals, but also for the development of organic functional materials.<sup>2</sup> Substituted pyrroles are an important class of compounds displaying remarkable pharmacological properties such as antibacterial, antiviral, anti-inflammatory, antitumoral, and antioxidant activities.<sup>3</sup> Furthermore, they are useful intermediates in the synthesis of natural products and heterocycles<sup>4</sup> and are also widely used in the materials area.<sup>5</sup> Consequently, a wide range of procedures has been developed for the construction of pyrroles.<sup>6</sup> Nevertheless, the Paal-Knorr reaction<sup>7</sup> remains one of the most attractive methods for the synthesis of pyrroles; wherein 1,4-dicarbonyl precursors are converted to pyrroles by the reaction with primary amines or ammonia in the presence of various promoting agents.<sup>8,9</sup>

We have been evaluating the possibility of performing organic transformations using water as the reaction medium or by performing transformations under solvent-free conditions, to develop environmentally benign reactions.<sup>10</sup> In this paper we report a novel, simple procedure for very efficient preparation of *N*-aryl, alkyl, *N*-sulfonyl, and *N*acylpyrroles by the reaction of amines with 2,5-dimethoxytetrahydrofuran (1) in the presence of iron(III) chloride in water (Scheme 1). First, we decided to focus on a catalytic activity screening study of aniline and 2,5dimethoxytetrahydrofuran (1) as a model reaction for optimizing the solvent, reaction temperature, and quantities of reagents. Thus, after studying different reaction conditions, it was found that upon simple mixing of aniline (5 mmol) and 2,5-dimethoxytetrahydrofuran (1, 6 mmol) in water (4 mL) in the presence of FeCl<sub>3</sub>·7H<sub>2</sub>O (2 mol%) at 60 °C, quantitative conversion to *N*-phenyl pyrrole was observed. The reaction was also carried out in organic solvents, such as CH<sub>2</sub>Cl<sub>2</sub>, THF, benzene, MeCN, EtOH, and solvent-free conditions for comparison. Poor yields of product were formed in organic solvents after four hours.



without catalyst: 10%	HCI as catalyst: 88%
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Solvent	CH <sub>2</sub> Cl <sub>2</sub>	THF	$C_6H_6$	EtOH	EtOAc	MeCN	neat	H <sub>2</sub> O
Yield (%)	10	60	20	60	50	45	30	95
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Scheme 1 Optimization of reaction conditions

Encouraged by this result, we further explored the scope and limitation of this simple process by reaction of sterically, electronically, and functionally diverse amines under the same reaction conditions (Scheme 2). In all cases, the reactions proceeded smoothly in water, typically affording a single product in quantitative yield. In the case of anilines having an electron-donating group such as 4-methoxyaniline and 4-butylaniline, the corresponding products were obtained in quantitative yields. Worthy of note, sterically hindered 2,4,6-trimethyl aniline gave the corresponding product in excellent yield. Furthermore, electron-deficient anilines such 4-chloroaniline, 3,4dichloroaniline, and 4-nitroaniline gave the corresponding pyrrole in excellent yields. The conditions are mild enough to perform the reactions in the presence of either acid- or base-sensitive functional groups and aliphatic amines, such as cyclopentylamine and benzylamine gave the corresponding pyrroles in high yield under the same conditions. In addition, the protocol could be easily applied to a large-scale process. The condensation of aniline (100 mmol) with 2,5-dimethoxytetrahydrofuran (130 mmol) catalyzed by FeCl<sub>3</sub>·7H<sub>2</sub>O (2 mol%) in water (40 mL) gave N-phenyl pyrrole in 90% yields.

*N*-Sulfonyl pyrroles are very useful compounds providing the possibility to manipulate these functional groups for the synthesis of heterocyclic compounds containing sulfur

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Scheme 2 Synthesis of pyrrole derivatives in water. a) Isolated yields; b) 15 mmol of 1 were used; b) HCl as catalyst (2 drops HCl, 4 mL  $H_2O$ ); c) AcOH as catalyst (0.1 mL AcOH, 4 mL  $H_2O$ ).

and nitrogen building blocks, or introduction of other functional groups.

General methods for their synthesis involve the introduction of a sulfonyl group on the nitrogen of pyrrole by

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reaction of pyrrolyl anion with the corresponding sulfonyl halide, but this approach often suffers from low yields and selectivites.<sup>11</sup> The counterion, solvent, and the electrophile are all important for avoiding electrophilic substitution at the 2-position. In this context, a simple synthesis of *N*-sulfonyl pyrrole has been reported in the presence of triflic acid.<sup>12</sup>

Thus, we also focused our attention on the use of aromatic sulfonamides as the source of the amines for the synthesis of *N*-sulfonyl pyrroles. When *p*-toluenesulfonamide (5 mmol) and 2,5-dimethoxy-tetrahydrofuran (1, 6 mmol) were mixed in water at 60 °C in the presence of iron(III) chloride, the corresponding *N*-sulfonyl pyrrole was produced in high yield (Scheme 3). In a similar manner, several arylsulfonamides reacted with 2,5-dimethoxy-tetrahydrofuran (1) to afford the corresponding products in excellent yields (Scheme 3).



**Scheme 3** Synthesis of *N*-sulfonylpyrrole in water. *Reagents and conditions*: sulfonamide (5 mmol), 2,5-dimethoxytetrahydrofuran (6 mmol), H<sub>2</sub>O (4 mL).

To expand the scope of this reaction a further, one-step preparation of N-acylpyrrole using iron(III) chloride was carried out with primary aryl amides and 2,5-dimethoxytetrahydrofuran (Scheme 4). The results clearly show that aryl amides are also good substrates in this reaction, and the corresponding acyl pyrroles are formed in good to excellent yields. N-Acylpyrroles can be regarded as activated carboxylic acid equivalents<sup>13</sup> and are usually obtained by the reaction of pyrrolyl anion with the appropriate acylating agents.<sup>14</sup> Preparation using primary amides in refluxing acetic acid has been reported,<sup>15</sup> however; the harsh reaction conditions and relatively long reaction times limit this method. In an attempt to overcome these problems, recently, it was reported that the reaction of amides with 2,5-dimethoxytetrahydrofuran in the presence of  $P_2O_5$  and SOCl<sub>2</sub> gave good yields of *N*-acylpyrroles. However, moisture must be avoided during the reaction and conditions precluded large-scale use.<sup>16</sup>

We therefore examined the scope and generality of our methodology using different substituted amides and 2,5-dimethoxytetrahydrofuran. The results are summarized in

Scheme 4. Primary aromatic amide with electron-rich functionality as well as electron-poor functionality undergo condensation with 2,5-dimethoxytetrahydrofuran equally well to afford the corresponding acylpyrroles in excellent isolated yields. In all cases, a mixture of amide and 2,5-dimethoxytetrahydrofuran was vigorously stirred in water at 60 °C in the presence of iron(III) chloride until completion of the reaction.<sup>17</sup> The probable pathway for this transformation involves hydrolysis of FeCl<sub>3</sub> in water and in situ generation of HCl as active catalyst.

Scheme 4 Synthesis of *N*-acylpyrroles in water. *Reagents and conditions*: arylamide (5 mmol), 2,5-dimethoxytetrahydrofuran (6 mmol),  $H_2O$  (4 mL).

In summary, we described a single step, environmentally friendly, and simple procedure for the synthesis of *N*-aryl, alkyl, sulfonyl, and acyl pyrroles in the presence of iron(III) chloride catalyst. Exploitation of this strategy for the generation of novel multicyclic structures and their biological evaluation is currently under way.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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- (17) General Procedure for the Synthesis of Pyrroles in Water

To a mixture of the amine (5 mmol) and 2,5 dimethoxytetrahydrofuran (6 mmol) in  $H_2O$  (4 mL) at 60 °C FeCl<sub>3</sub>·7H<sub>2</sub>O (2 mol%) was added. The mixture was stirred at this temperature for 1–4 h and was diluted with EtOAc and filtered. The organic solution was evaporated under vacuum affording the pyrrole derivative with good analytical purity. In the few cases, the crude product was purified by flash chromatography.