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# A microwave-assisted, green procedure for the synthesis of *N*-aryl sulfonyl and *N*-aryl pyrroles

ABSTRACT

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A simplified approach to the uncatalyzed Paal-Knorr condensation using microwave irradiation in water is described.

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In recent years, the synthesis of compounds using environmentally friendly solvents with minimal byproduct waste has attracted great interest. The term green as referring to the environment is becoming household vocabulary. 'Green chemistry' implies the *design* of chemical products and processes that reduce or eliminate the *use and/or generation* of hazardous substances.<sup>1</sup>

The use of microwave irradiation to enhance organic reactions in environmentally benign solvents such as water represents a very powerful green chemical technology from both economic and synthetic points of view.<sup>2</sup>

Pyrroles are an important class of heterocyclic compounds, whose structural motifs appear in many biologically active natural products, and serve as building blocks in the total synthesis of these compounds.<sup>3</sup> Current methods use a cyclocondensation reaction, generally employing some type of acid catalyst.<sup>4</sup> Most recently, Abid and colleagues used a microwave-assisted solid phase acid-catalyzed route to synthesize N-substituted pyrroles.<sup>3</sup> Others have used copper iodide catalyzed N-arylation of the pyrrole.<sup>5,6</sup> We wish to report a microwave-assisted route to *N*-aryl and *N*-aryl sulfonyl pyrroles which uses water as solvent and does not require an acid catalysis.

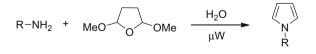
Recently, the need to synthesize a diverse array of *N*-aryl sulfonyl pyrroles arose. An opportunity for improvement presented itself when our initial attempts using a standard literature procedure employing caustic  $P_2O_5$  and dry toluene as solvents resulted in complex reaction mixtures that required difficult purifications.<sup>4</sup> Reaction times were also long and the reaction yields varied.

Microwave reactions have long been viewed as a convenient answer to lengthy reaction times, and have proven themselves amenable to green chemistry conditions.<sup>7</sup> Gratifyingly, the initial conditions that we attempted resulted in satisfactory yields and purity with reaction times and temperature being the only conditions requiring optimization. The initial reactions were performed in water using microwave irradiation without a catalyst. This methodology provided the desired *N*-pyrrole as shown in Scheme 1. Since the initial test reaction worked very well, we decided to carry out a series of reactions to test the scope and limitations of the reaction.

To define the scope of the acid-free condensation reaction we tried a range of nucleophiles. When the nucleophile had a lower  $pK_{a}$ , for example, a sulfonamide, the reaction worked very well, but when the nucleophile had a higher  $pK_{a}$ , for example, a benzyl amine, the reaction failed.

The reaction conditions are very general and can easily be varied for different substrates. The reaction was optimized with phenyl sulfonamide. The reaction works at a range of temperatures (100–180 °C). At temperatures above 150 °C there can be some product decomposition which is generally minor and the precipitated solid tended to be darker in color. Within the 140–150 °C range, the products were white to beige solids. Reactions times can be changed easily too. Reaction times from 10 to 60 min are amenable to this methodology. The optimized reaction time for a wide range of substrates was 30 min at 150 °C, but heating times could always be extended at this temperature without any product decomposition.

The stoichiometry of 2,5-dimethoxytetrahydrofuran was also varied. It was found that the reaction works well with between 1.3 and 5.0 equiv of 2,5-dimethoxytetrahydrofuran. For atom



Scheme 1.

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#### Table 1

A comparison of experimenta	I conditions for the conver	sion of aromatic amir	nes into N-phenyl pyrroles
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Entry	y N-Aryl pyrroles Literature			Acid free		
		Reaction conditions and purification	Yield (%)	Reaction conditions and purification	Yield (%)	
1		$P_2O_5,dry$ toluene, 125 °C, 45 min. $^4$ Evaporation, flash chromatography	87	Water, $\mu W,150$ °C, 30 min. Filtration	90	
2	N-CI	$P_2O_5,dry$ toluene, 125 °C, 45 min. $^4$ Evaporation, flash chromatography	79	Water, $\mu W,150$ °C, 30 min. Filtration	93	
3		$P_2 O_5,  dry \ toluene,  125 \ ^\circ C,  45 \ min.^4 \ Evaporation,  flash chromatography$	89	Water, $\mu W,150$ °C, 30 min. Filtration	95	
4		Cul, <i>n</i> -Bu <sub>4</sub> NBr, NaOH, toluene, reflux, 22 h. <sup>6</sup> Extraction, flash chromatography	84	Water, $\mu W,150$ °C, 30 min. Filtration	99	
5		Cul, N-hydroxysuccinimide, CH <sub>3</sub> ONa, DMSO, 110 °C, 24 $\rm h^5$ Extraction, flash chromatography	96	Water, µW, 150 °C, 30 min. Filtration, flash chromatography	95	
6		Cul, N-hydroxyphthalimide, CH <sub>3</sub> ONa, DMSO, 110 °C, 24 h. $^5$ Extraction, flash chromatography	90	Water, $\mu W,150$ °C, 30 min. Filtration	97	
7		Cul, N-hydroxymaleimide, CH <sub>3</sub> ONa, DMSO, 110 °C, 40 h. $^5$ Extraction, flash chromatography	45	Water, µW, 150 °C, 30 min. Filtration	97	
8		Cul, <i>n</i> -Bu <sub>4</sub> NBr, NaOH, toluene, reflux, 22 h. <sup>6</sup> Extraction, flash chromatography	88	Water, $\mu W,150$ °C, 30 min. Filtration	98	
9		Cul, <i>n</i> -Bu <sub>4</sub> NBr, NaOH, toluene, reflux, 22 h. <sup>6</sup> Extraction, flash chromatography	83	Water, µW, 150 ℃, 30 min. Filtration, flash chromatography	98	
10		Cul, <i>n</i> -Bu <sub>4</sub> NBr, NaOH, toluene, reflux, 22 h. <sup>6</sup> Extraction, flash chromatography	62	Water, µW, 150 °C, 30 min. Filtration, flash chromatography	95	

economy, we used 1.3 equiv of 2,5-dimethoxytetrahydrofuran for larger scale reactions. To investigate the role of water in this reaction, the reaction was performed neat. The desired product was isolated in good yield, implying that water is acting as solvent and not participating as an acid catalyst under these conditions. This result supports the importance of the  $pK_a$  of the substrate in order for the reaction to work. Nonetheless, the reaction yields and product purity were better when water was used as solvent. The reaction concentration could range from 0.5 M to 2.5 M depending on the scale of the reaction.

With our optimized reaction conditions, we explored the scope of this methodology using several commercially available aryl sulfonamides and anilines. Heating an aniline or an aryl sulfonamide with 2,5-dimethoxytetrahydrofuran in water (0.64 M) in a microwave reactor at 150 °C for 30 min resulted in the formation of the corresponding pyrrole in 81–99% yield. The results are summarized in Tables 1 and 2. There is no noticeable effect of the electronic nature of the aryl nucleophile

on the reaction yield. Additionally, the products were conveniently isolated by filtration to give the desired products with average purities of greater than 90%. If purification was required, a simple filtration through a silica plug eluting with 50% ethyl acetate/hexane was used to purify the product. The reaction was also amenable to scale up using a CEM 80 mL reaction vessel. The reaction was routinely scaled up to 67 mmol in 2.2 M water without any difficulties.

In conclusion, we have demonstrated a simple and efficient synthetic route for the synthesis of *N*-phenyl and *N*-aryl sulfonyl pyrroles. Compared to the classical synthetic method, this approach has the advantage of being inexpensive, simple, and environmentally benign.

A general experimental procedure for the synthesis of N-sulfonyl pyrroles and N-phenyl pyrroles. Aniline (200 mg, 1.27 mmol) and 2,5-dimethoxytetrahydrofuran (425 mg, 3.22 mmol) in water (2.0 mL) were heated to 150 °C for 30 min in a CEM microwave oven. The reaction was allowed to cool and the resulting

## Table 2

A comparison of experimental conditions for the conversion of aryl sulfor	onamides into N-aryl sulfonyl pyrroles
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Entry	/ N-Aryl sulfonyl pyrroles Literature			Acid free		
		Reaction conditions and purification	Yield (%)	Reaction conditions and purification	Yield (%)	
1		Montmorillonite K-10, 3 min $\mu W^3.$ Filtration, flash chromatography	93	Water, μW, 150 °C, 30 min. Filtration	99	
2	$ \boxed[]{N-S} \\ O \\ $	$P_2O_5,dry$ toluene, 125 °C, 20 min. $^4$ Evaporation, flash chromatography	100	Water, µW, 150 °C, 30 min. Filtration	89	
3		$P_2O_5,dry$ toluene, 125 °C, 20 min. $^4$ Evaporation, flash chromatography	85	Water, µW, 150 °C, 30 min. Filtration	92	
4		Montmorillonite K-10, 3 min $\mu W^3.$ Filtration, flash chromatography	95	Water, µW, 150 °C, 30 min. Filtration	95	
5		TfOH, CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h. <sup>8</sup> Extraction, flash chromatography	88	Water, µW, 150 °C, 30 min. Filtration	91	
6		TfOH, $CH_2Cl_2$ , rt, 2 h <sup>8</sup> Extraction, flash chromatography	85	Water, µW, 150 °C, 30 min. Filtration	81	
7	$\underset{O}{\overset{O}{\underset{O}{\overset{H}{\underset{O}{\overset{H}{\underset{O}{\overset{O}{\underset{O}{\overset{O}{\underset{O}{\overset{H}{\underset{O}{\overset{O}{\overset$	TfOH, CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h. <sup>8</sup> Extraction, flash chromatography	80	Water, µW, 150 °C, 30 min. Filtration	98	
8	N-S O O Br	TfOH, CH <sub>2</sub> Cl <sub>2</sub> , rt, 2 h. <sup>8</sup> Extraction, flash chromatography	86	Water, µW, 150 °C, 30 min. Filtration	98	

precipitate was filtered, washed with water, and air dried to give *N*-phenyl pyrrole (295 mg, 96%). The final product was characterized by NMR.

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