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http://heteroletters.org
ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
Vol. 1, special issue, July (2011), 103-106

MICROWAVE-INDUCED N-BROMOSUCCINIMIDE-MEDIATED NOVEL SYNTHESIS OF PYRROLES

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Abstract:
Extremely rapid synthesis of N-substituted pyrroles using microwave-induced N-bromosuccinimide-mediated conditions has been accomplished with an excellent yield.

Keywords: Microwave, N-Bromosuccinimide, Pyrrole

Introduction:

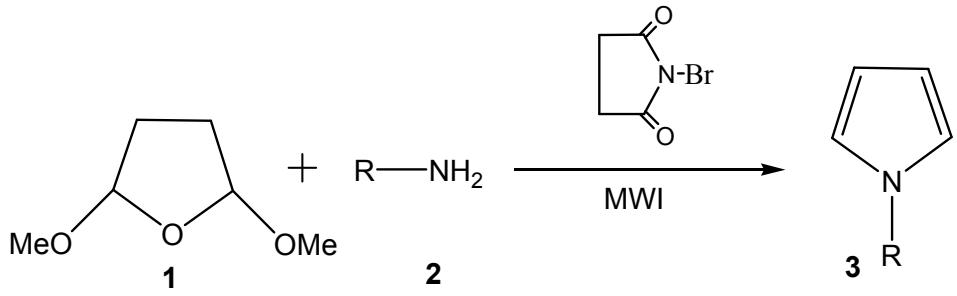
Pyrroles are important class of heterocyclic compounds with different medicinal activities.[1] Therefore, many methods for the synthesis of substituted pyrroles are developed.[2] For example, conjugate addition reactions, transition metal-mediated reactions, reductive couplings, aza-Wittig reactions, and other multistep operations have been performed for the synthesis of pyrroles. Despite these huge developments, the Paal-Knorr reaction is considered to be the most attractive methods for the synthesis of pyrroles. Clay-mediated organic reaction has been used for the preparation of pyrroles following Paal-Knorr conditions. In this paper, we describe a simple and extremely rapid method of synthesis of N-substituted pyrroles starting from 2,5-dimethoxytetrhydrofuran and amines by N-bromosuccinimide-catalyzed reaction in a microwave oven.

Results and Discussions:

We[3] have synthesized various polyaromatic compounds toward the development of novel anticancer agents and found that modification of the heterocyclic ring is crucial in determining the biological activity of these compounds. Because of the biological activities of these derivatives, we became interested in the synthesis of pyrroles bound to the amines of different structures. Paal-Knorr method requires a 1, 4-dicarbonyl compound and Lewis acids. Previously, we have investigated N-bromosuccinimide-induced samarium metal-mediated reductive dimerization reactions of carbonyl compounds. From our previous results, we envision that N-bromosuccinimide may prove useful as a catalyst for the facile synthesis of pyrroles under mild conditions if we select 2, 5-dimethoxytetrahydrofuran (**1**) and amines as the starting materials. Our hypothesis has been proved to be successful since different types of amines (**2**) and 2, 5-dimethoxytetrahydrofuran produced pyrroles in a microwave oven in the presence of N-bromosuccinimide as a catalyst. Most of the reactions are completed within 3-8 minutes of

irradiation at 100°C and 300 watts power level. The yields of the products and solvents are shown in the Table 1 (**Scheme 1 and Table 1**).

Scheme 1:



N-Bromosuccinimide is considered as a brominating reagent and this has been used as a catalyst in various chemical reactions. Importantly, there are no examples of the use of NBS as a catalyst for the synthesis of pyrroles.

NBS at high temperature and under microwave irradiation can generate trace amounts of hydrobromic acid. The methoxy groups can be easily deprotected under acidic conditions and microwave irradiation to form the reactive dialdehyde. The dialdehyde on reaction with amines leads to pyrroles following a nucleophilic addition and subsequent dehydration-aromatization pathways.

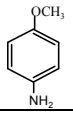
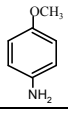
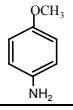
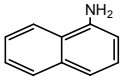
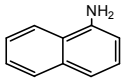
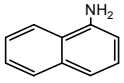
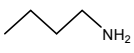
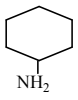
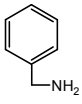
The reaction between **1** and **2** produces pyrrole (about 60%) in the absence of NBS by irradiating the reaction mixture for a long time. But, in the presence of NBS, the reaction gives products within 3-8 minutes.

The NBS-catalyzed microwave-induced environmentally benign method is superior over the Lewis acid-mediated synthesis of N-substituted pyrroles in terms of various factors, such as simplicity, yield of the products and time of the reaction. [4]

Experimental:
General procedure for the synthesis of pyrroles (3): Amine **1** (1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol) and NBS (20-50 mg) was irradiated in a CEM automated microwave oven as specified in Table 1. Pure product was isolated from the reaction mixture using ether as solvent.

Acknowledgements:
We gratefully acknowledge the financial support for this research project from National Institutes of Health-SCORE (2SO6GM008038-37) and (NCIP20CA138022).

Table 1. NBS-catalyzed microwave assisted synthesis of Pyrroles from the reaction between Amines (1 mmol) and 2,5-Dimethoxytetrahydrofuran (1 mmol)

RNH_2	**Solvent**	**NBS**	**MWI temp/time/pressure**	**Yield (%)[a]**
	Neat	20 mg	300 watts 90°C 5 min.	100
	THF	50 mg	300 watts 75°C 15 min.	90
	H_2O	20 mg	300 watts 90°C 5 min.	95
	Neat	30mg	300 watts 90°C 10 min.	95
	THF	40 mg	300 watts 90°C 10 min.	80
	H_2O	30mg	300 watts 90°C 10 min.	85
	Neat	20 mg	300 watts 75°C 5 min.	100
	THF	20mg	300 watts 90°C 10 min.	90
	H_2O	20mg	300 watts 90°C 10 min.	95
	Neat	20 mg	300 watts 75°C 5 min.	100
	Neat	20mg	300 watts 75°C 5 min.	95
	Neat	20mg	300 watts 75°C 5 min.	100

[a]**NMR-** indicated the formation of the product without any side reactions. Starting materials were consumed completely.

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