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Scale-Up of the Green Synthesis of Azacycloalkanes and Isoindolines under Microwave Irradiation

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Abstract:

A green approach to *N*-heterocyclization reactions ranging in scale from 20 mmol to 1 mol performed under microwave irradiation in open vessels has been investigated. By using water as the solvent and no transition metal catalysts, *N*-heterocycles are formed in a fraction of the time needed for conventional synthesis of these compounds. The obtained yields indicate that reactions can be performed at atmospheric pressure using the same reaction conditions as the corresponding sealed-vessel reactions. Single-mode and multimode microwave cavities have been used for open-vessel synthesis without changing reaction times producing similar yields.

Introduction

Chemicals used in the production of goods have, over the years, damaged the environment through pollution and waste. Increased environmental awareness along with the high costs associated with environmental pollution control[1] are challenging chemists to find alternative ways to harness the benefits chemistry has to offer. Some of these alternatives include the use of more environmentally friendly solvents, microwave reactors, and alternative reaction conditions.[2]

In the search for green chemistries, aqueous media is one of the greenist for reactions next to neat. Water as a solvent has the advantage of being readily available, inexpensive, and nontoxic,[3] though it is rarely looked at due to the need for additives such as phase transfer catalysts[4] due to the limited aqueous solubility of organic compounds. However, as water increases in temperature, it becomes more nonpolar, more acidic, and less dense, and its dielectric constant decreases, allowing organic compounds to become more soluble eliminating the need for phase transfer catalysts.[5,6] Demko and Sharpless[7] found that 1 *H*-tetrazoles can be synthesized in water despite the relative insolubility of the starting materials. Sharpless[8] later found that water increases the rate of reactivity for a variety of "on water" chemistries and is continuing to research this phenomenon. The use of water as a reaction solvent also allows for the easy separation of the product from the solvent due to the limited solubility of organic compounds in water at room temperature.

Over the past two decades, the use of microwaves for chemical syntheses has drastically increased as can be implied by the increasing number of publications in the field of microwave chemistry.[9,10] Microwave-assisted organic synthesis has been shown to enhance the rate of reactions and improve product yields, as well as be energy efficient.[11] A growing area of interest in microwave-promoted synthesis is the scaling-up of reactions.[12] This can be achieved in two possible ways: continuous flow[13] or a batch process.[14−16] Continuous flow microwave reactors can be problematic when processing solids, heterogeneous reaction mixtures, and high viscosity liquids.[10,16] Batch processes can involve parallel batch reactors,[9d,16] where multiple reaction vessels are placed in the microwave at one time, or use one large vessel.[14−16]

Microwave synthesis can be performed either under sealed-vessel or open-vessel conditions. Reactions performed in sealed vessels can reach temperatures much higher than the boiling point of the solvent used at elevated pressure. In open-vessel microwave assisted reactions, reactions are carried out at atmospheric pressure; yet solvents can still

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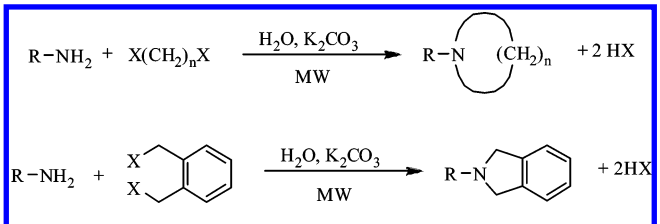
Scheme 1*N*-**Heterocyclizations performed by Varma and Ju**[23,24]



R = H, alkyl, aryl. X = Cl or Br. Performed on 1 mmole scale.

n = 3,4,5,6. Yields between 54 and 96%.

reach temperatures that are 10−20 °C above their boiling points,[6,10,17,18] which may be explained by the occurrence of instantaneous hot spots.[17,19] Open-vessel synthesis allows for any gases that may be generated in a reaction to evolve from the reaction environment possibly causing reactions to progress further to completion than when performed in a sealed vessel. Also, open-vessel reactions can be performed using standard laboratory glassware, such as round-bottom flasks and reflux condensers, in the microwave cavity allowing reactions to be carried out on a larger scale.

There are two types of microwave cavities, single-mode and multimode. Single-mode cavities are much smaller than multimode cavities and have only one mode present. The microwave energy in a single-mode cavity is directed into the reaction vessel, whereas in a multimode cavity the microwave energy not being absorbed by the reaction solution is being reflected by the walls of the cavity. A more detailed explanation of single-mode and multimode cavities can be found elsewhere.[20]

Results and Discussion

Nitrogen containing heterocycles are present in many natural products and show great biological activity in pharmaceuticals.[21] Conventional syntheses of these compounds require long reaction times, expensive catalysts, and hazardous solvents.[22−25] Microwave assisted syntheses of *N*-heterocycles has led to a decrease in reaction time, improved yields, and the use of more benign solvents and has eliminated the need for transition metal catalysts.[23,24,26] This research uses water as the solvent and no metal catalyst for the synthesis of *N*-azacycloalkanes and *N*-isoindolines. Reaction times are minimal with greatly improved yields compared to those of conventional syntheses of these compounds.[24]

This research is based on the work of Varma and Ju[23,24] (Scheme 1) where reactions were performed in a single-mode microwave cavity using sealed vessels at moderate temperatures. The reactions were heated to and maintained at a temperature of 120 °C with pressures of 50 psi for 20 min. Our first step in scaling-up the reactions was transitioning from sealed-vessel to open-vessel reactions. Previous work has shown open-vessel reactions give yields equal to, if not greater than, those performed in sealed vessels with reaction temperatures still going above the solvent boiling point.[9d,10,18,27] We performed open-vessel reactions on a 20 mmol scale, in a single-mode microwave cavity, using a standard 100 mL round-bottom flask fitted with a reflux condenser. These open-vessel reactions were heated to reflux, where the temperature limit was set to 120 °C allowing for maximum power input, and allowed to reflux for 20 min. Actual temperatures reached varied between 103 °C and 115 °C, thus demonstrating that water can reach temperatures above the boiling point while remaining at atmospheric pressure.

Comparisons for the different reactions performed in sealed and open vessels can be found in Table 1. We have confirmed that the yields for open-vessel synthesis in a single-mode microwave cavity are equal to, and in some cases much greater than, those obtained in sealed vessels. Reactions producing higher yields (entries 2 and 3) could possibly be attributed to the release of the volatile gas HBr, shifting the reaction equilibrium to the product side.

To scale-up further, we moved to a multimode system where we are able to use round-bottom flasks up to 5 L. Previous research has shown that transitioning from single-mode to multimode microwave systems has produced similar yields with no significant change in reaction times.[16,27] Our research confirmed these results (Tables 2 and 3). Open-vessel reactions carried out in the multimode cavity were heated and allowed to reflux for 20 min. The temperature limit was set at 110 °C, and actual temperatures reached varied between 100 °C and 106 °C.

Reactions performed on the 0.2, 0.6, and 1.0 mol scales were irradiated with 300, 600, and 1200 W, respectively. Each reaction was rapidly heated by selecting a power input to allow reactions to reach reflux in approximately 10 min making the overall reaction time from heating to reaction completion 30 min. A considerable time savings can be seen for microwave synthesis compared to conventional synthesis when comparing the 30 min needed for reactions in a microwave to the time needed for conventional synthesis where 30 min are needed to heat the reaction solution to temperature and then maintaining this temperature for an additional 5 h in order to reach reaction completion.[28]

Isolation of the synthesized compounds consisted of simple washing steps. No time-consuming column chromatography was needed, eliminating the need for large quantities of solvent use. Liquid products (**1** and **3**) were extracted into a minimal amount of ethyl acetate and washed with deionized water and then the solvent was removed in vacuo, whereas the solid products were filtered and washed with deionized water followed by chilled hexanes. These isolation

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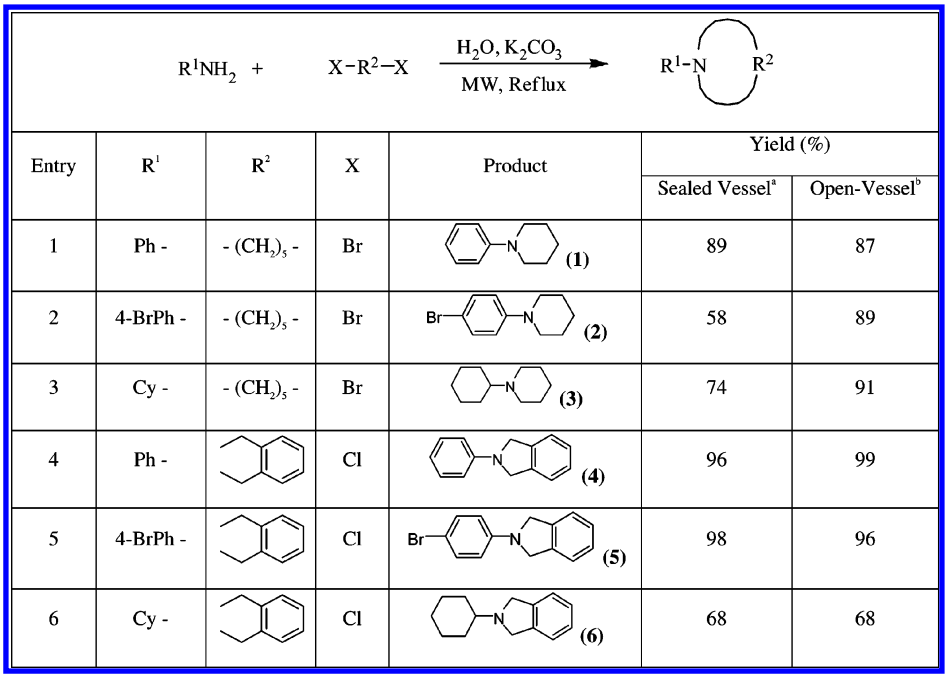
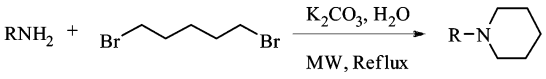
Table 1. ***N*-Heterocyclization reactions in water performed in a monomode microwave apparatus using sealed and open vessels**



Entry	R^1	R^2	X	Product	Yield (%)	
					Sealed Vessel[a]	Open-Vessel[b]
1	Ph -	- $(CH_2)_5$ -	Br	**(1)**	89	87
2	4-BrPh -	- $(CH_2)_5$ -	Br	**(2)**	58	89
3	Cy -	- $(CH_2)_5$ -	Br	**(3)**	74	91
4	Ph -		Cl	**(4)**	96	99
5	4-BrPh -		Cl	**(5)**	98	96
6	Cy -		Cl	**(6)**	68	68

[a] 1 mmol of amine, 1.1 mmol of dihalide, 1.1 mmol of K_2CO_3, 2 mL of H_2O. [b] 20 mmol of amine, 22 mmol of dihalide, 22 mmol of K_2CO_3, 40 mL of H_2O.

Table 2. **Scale-up of open-vessel microwave promoted azacycloalkane synthesis in water**



Entry	R	Product	Yield (%)			
			20.0 mmole [a]	0.2 mole [b]	0.6 mole [b]	1.0 mole [b]
1	Ph -	**(1)**	87	83	91	89
2	4-BrPh -	**(2)**	89	89	92	86
3	Cy -	**(3)**	91	87	85	77

[a] Reactions carried out in a single-mode microwave cavity. [b] Reactions carried out in a multimode microwave cavity.

procedures held true for all compounds synthesized from the 1 mmol scale (**5** affording 0.305 g) to the 1 mol scale (**5** affording 267 g). The ease of isolation comes from the fact that no byproducts were detected after the reactions. The only impurities found in the products were unreacted starting material that could be easily washed away in the case of the isoindolines.

Conclusion

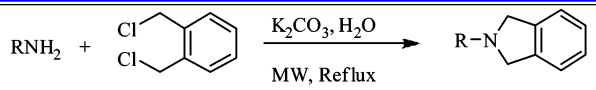
N-Heterocyclization reactions performed under microwave irradiation can easily be scaled 1000-fold from mmole to mole quantities in approximately 30 min with no decrease in yield. We have shown the ease in translating reaction conditions from sealed vessels to open vessels and the simplicity of switching between single-mode and multimode microwave cavities.

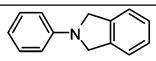
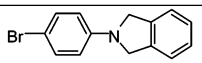
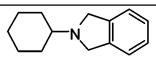
The green synthesis and purification of *N*-heterocycles is shown using water as the solvent with no transition metal catalysts and eliminating the need for large quantities of solvent for purification. Reactions are completed in 30 min with minimal time needed for purification affording hundreds of grams of product.

Experimental Section

General. All reagents were obtained from commercial suppliers and were used without further purification. GC−MS analysis was run using a Perkin-Elmer AutoSystemXL Gas Chromatograph/TurboMass mass spectrometer equipped

Table 3. **Scale-up of open-vessel microwave promoted isoindoline synthesis in water**



Entry	R	Product	Yield (%)			
			20.0 mmole [a]	0.2 mole [b]	0.6 mole [b]	1.0 mole [b]
1	Ph -	 (4)	99	98	97	98
2	4-BrPh -	 (5)	96	96	93	97
3	Cy -	 (6)	68	68	66	61

[a] Reactions carried out in a single-mode microwave cavity. [b] Reactions carried out in a multimode microwave cavity.

with a column Elite-5MS (30 m × 0.25 mm × 0.25 μm). All samples were examined under the following temperature gradient: Temp 1, 50 °C (1 min); Temp 2, 210 °C (5.17 min); rate 32.0 °C/min; Temp 3, 300 °C (5.50 min); rate 27.0 °C/min. ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a BRUKER AVANCE-400 spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz).

Description of the Microwave Apparatus. Reactions in sealed vessels on the 1 mmol scale along with the open-vessel reactions on the 20 mmol scale were performed in a commercially available single-mode microwave system (CEM Discover), with a power output ranging from 0 to 300 W. Reactions were performed in a 100 mL round-bottom flask fitted with a reflux condenser. The temperature was monitored via an IR sensor located directly below the vessel. The vessel contents were stirred by means of an adjustable speed electromagnet located below the microwave cavity and a Teflon-coated magnetic stir bar inside the vessel. Temperature and power profiles were recorded using computer controlled software. Subsequent reactions were scaled up to 1 mole and performed in a multimode microwave apparatus (CEM MARS, Microwave Accelerated Reaction System), with the power output ranging from 0 to 1200 W. Reactions were performed on a 0.2 mol, 0.6 mol, and 1.0 mol scale in a 1, 3, and 5 L round-bottom flask, respectively. The temperature was monitored via a fiber optic probe inserted directly in the reaction mixture. Stirring was achieved by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the reaction vessel.

Representative Example of the Synthesis of Azacycloalkanes on a 20 mmol Scale: Single-Mode Microwave Cavity. To a 100 mL round-bottom flask was added aniline (1.9 g, 20 mmole), 1,5-dibromopentane (5.6 g, 22 mmole), and potassium carbonate (3.2 g, 23 mmole) in 40 mL of distilled water. The reaction vessel was placed in a single-mode focused microwave reactor and fitted with a reflux condenser. The reaction was irradiated with 150 W to a temperature of 115 °C (reflux) where it was held for 20 min. Upon cooling, the reaction mixture is extracted with ethyl acetate, the organic layer was washed with distilled water, and the solvent was removed in vacuo giving 2.94 g (87% isolated yield, 94% purity) of *N*-phenylpiperidine. ^{1}H and ^{13}C NMR data are consistent with those found in the literature.[22,26,28,29]

Representative Example of the Synthesis of Isoindolines on a 20 mmol Scale: Single-Mode Microwave Cavity. To a 100 mL round-bottom flask was added aniline (1.9 g, 20 mmol), 1,2-bis(chloromethyl)benzene (3.9 g, 22 mmol), and potassium carbonate (3.2 g, 23 mmole) in 40 mL of distilled water. The reaction vessel was placed in a single-mode focused microwave reactor and fitted with a reflux condenser. The reaction was irradiated with 150 W to a temperature of 105 °C (reflux) where it was held for 20 min. Upon cooling, the solid product is filtered, washed with distilled water followed by chilled hexanes, and dried in vacuo giving 3.86 g (99% isolated yield, 99% purity) *N*-phenylisoindoline. ^{1}H and ^{13}C NMR data are consistent with those found in the literature.[30]

Representative Example of the Scale-Up of Azacycloalkanes on a 0.2 mol Scale: Multimode Microwave Cavity.[31] To a 1 L round-bottom flask was added aniline (18.9 g, 0.2 mol), 1,5-dibromopentane (56.0 g, 0.22 mol), and potassium carbonate (32.5 g, 0.23 mol) in 400 mL of distilled water. The reaction vessel was placed in a multimode microwave reactor and fitted with a reflux condenser. The reaction was irradiated with 300 W of power to a temperature of 110 °C (reflux) where it was held for 20 min. Upon cooling, the reaction mixture is extracted with ethyl acetate, the organic layer was washed with distilled water, and the solvent was removed in vacuo giving 26.8 g (83%

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(31) Reagent quantities are representative of the 0.2 mol scale. Subsequent reaction quantities were scaled accordingly.

isolated yield, 96% purity) of *N*-phenylpiperidine. ^{1}H and ^{13}C NMR data are consistent with those found in the literature.[22,26,28,29]

Representative Example of the Scale-Up of Isoindolines on a 0.2 mol Scale: Multimode Microwave Cavity.[31] To a 1 L round-bottom flask were added aniline (18.6 g, 0.2 mol), 1,2-bis(chloromethyl)benzene (38.6 g, 0.22 mol), and potassium carbonate (32.5 g, 0.23 mol) in 400 mL of distilled water. The reaction vessel was placed in a multimode microwave reactor and fitted with a reflux condenser. The reaction was irradiated with 300 W of power to a temperature of 110 °C (reflux) where it was held for 20 min. Upon cooling, the solid product is filtered, washed with distilled water followed by chilled hexanes, and dried in vacuo giving 38.3 g (98% isolated yield, 98% purity) of *N*-phenylisoindoline. ^{1}H and ^{13}C NMR data are consistent with those found in the literature.[30]

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