Back to Basics: Open Vessel Microwave Reactions and Their Ability to Increase in Scale

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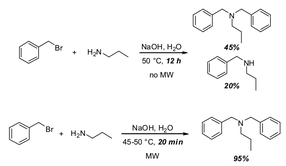
The breadth of microwave reactions has expanded in an ever-increasing fashion over the last 20 years. After Giguere/Majetich and Gedye[1] performed the first documented organic transformation in 1986, the number and range of applications began to rapidly expand, forcing the technology to evolve. While the first transformation occurred in a beaker in a domestic microwave system, without any of the safeguards associated with today's industrially designed systems, the advent of more robust systems designed for laboratory use enabled chemists to easily perform transformations at high temperatures and high pressures. These conditions were not only very easy to attain using microwave irradiation, but, due to the design of the systems, the vessel was contained within the cavity, rendering the reaction much safer than those performed on a hot plate.

The large amount of focus on high temperature, high pressure reactions did not extend to all areas of organic chemistry; several different groups continued to focus on open vessel-type applications, sometimes using solid supported reagents or neat reactions to make the transformation more environmentally-friendly.[2] As more chemists become focused on the ability to increase the scale of reactions and generate several hundred grams or kilograms using microwave irradiation, the utility of performing reactions in an open vessel, or at atmospheric pressure, has come back under scrutiny.

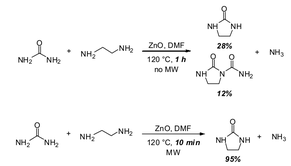
Herein we report the use of round-bottom flasks to perform reactions in a microwave and the linear scale up of those reactions.

Examples of Open Vessel Reactions In Microwave

N-Alkylation of amines[4]



Synthesis of cyclic ureas[5]



OPEN VS. SEALED REACTIONS

BOTH

- Rate enhancements, compared to conventional heating
- Cleaner, faster transformation to product
- Quick, easy answer

OPEN

- No concern for pressure
- Can use conventional glassware
- Can use conventional scale
- In general, larger scale reactions can be performed
- Will release unnecessary gas generated

SEALED

- Can use lower boiling solvent
- Will retain all reagents necessary for reaction
- Can produce gas in-situ

N-Heterocyclizations: A comparison to Sealed-Vessel Conditions

N-Aryl Azacycloalkanes[3]

Favorable product transition to upper layer

Literature:

[1] Gedye, R.; Smith, F.; Westaways, K.; Ali, J.; Baldisera, L.; Laberge, L.; Rousel, J.; Tetrahedron Lett., 1986, 27, 279. Giguere, R.J.; Bray, T.L.; Ducan, S.M.; Majetich, G.; Tetrahedron Lett., 1986, 27, 4945.

[2] Representative publications include: (a) Varma, R.S. Organic Synthesis Using Microwaves and Solid Supported Reagents. in Microwaves in Organic Synthesis; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; 181-218. (b) Loupy, A.; Hamelin, P.J.; Texier-Boullet, F.; Mathe, J.D. Synthesis, 1998, 1213. (c) Varma, R.S., Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation, Kavitha Printers, Bangalore, 2002.

[3] Ju, Y.; Varma, R. S. Org. Lett. 2005, 7, 2409 – 2411.

[4] Ju, Y.; Varma, R. S. Green Chem. 2004, 6, 219-221.

[5] Kim, Y. J.; Varma, R. S. Tetrahedron Lett. 2004, 45, 7205-7208.

Work also published in: Barnard, T.M., Vanier, G.S., Collins, M.J., OPRD, 2006, 10, 1233.

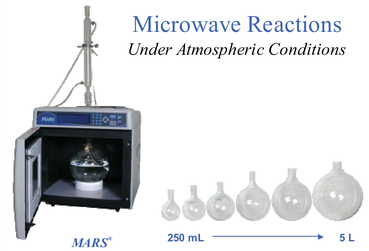
CEM

Microwave Reactions
Under Atmospheric Conditions

100 ml flask

Discover® 1 Monomode System

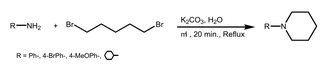
Microwave Reactions
Under Atmospheric Conditions



MARS® Multimode System

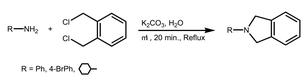
250 mL → 5 L

Piperidine Formations



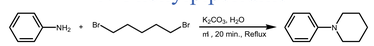
	Sealed (120°C)	Open (100°C)
Ph-	89%	86%
4-BrPh-	57%	78%
4-MeOPh-	71%	86%
◯—	74%	91%

Isoindoline Formations



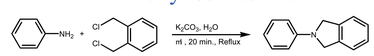
	Sealed (120°C)	Open (100°C)
Ph-	96%	99%
4-BrPh-	98%	96%
◯—	68%	84%

N-Phenylpiperidine



Scale (mole)	Mode	Vessel Size	Yield (Isolated)
0.001	Mono	10 mL (sealed)	0.1485 g (89%)
0.02	Mono	100 mL	2.94 g (87%)
0.2	Multi	1 L	26.81 g (83%)
0.6	Multi	3 L	91.35 g (91%)
1.0	Multi	5 L	145.58 g (89%)

N-Phenylisoindoline



Scale (mole)	Mode	Vessel Size	Yield (Isolated)
0.001	Mono	10 mL (sealed)	0.204 g (96%)
0.02	Mono	100 mL	3.863 g (99%)
0.2	Multi	1 L	38.346 g (98%)
0.6	Multi	3 L	114.01 g (97%)
1.0	Multi	5 L	196.55 g (98%)

- C – N bond formation at reflux with no catalyst
- Wide variety of substrates
- Green Chemistry
- Easy work up
- Easy translation from sealed tube to open vessel

- 1000x increase in scale with same yield
- Synthesis time comparable between microwave systems
- Up to 5 L reaction vessel in microwave
- Straight forward translation from monomode to multi-mode