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Scalability of Heterocyclic Microwave-Assisted Transformations From Batch to Continuous Flow. A Case Study

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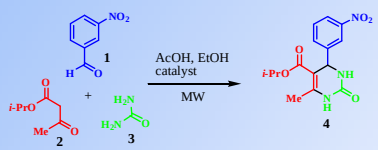
❶ Introduction

The Lewis acid catalyzed condensation of an aldehyde **1**, β-diketoester **2** and urea **3** leads to a 3,4-dihydropyrimidin-2-(*1H*)-one (DHPM) also termed as **THE BIGINELLI SCAFFOLD**.[1]



- Several Biginelli scaffolds have biological value
- Microwave techniques accelerate the synthesis
  - Useful in rapid optimization for drug discovery
- Need to develop these heterocycles in large scale

[1] Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.

Herein we present a case study on the small to large scale microwave-assisted synthesis of the DHPM **4** under **batch** and **continuous flow** conditions in monomode and multimode cavities.

❷ Automated parallel small scale synthesis (4 mmol)

Emrys™ Synthesizer

+ sample robot
+ up to 120 reactions
+ magnetic stirring
+ 12-15 reactions per hour
+ 0-300 W
+ up to 250 °C, 0-20 bar

- Automated dispensing of reaction components
- Single mode microwave irradiation
- Automated sequential synthesis
  4 mmol reaction scale
  Solvent: AcOH/EtOH (3:1) (3mL)
  120 °C 20 min
  52 % yield

❸ Synthesis in multimode cavity (40 mmol)

MicroSYNTH Labstation (Milestone)

REACTOR SPECIFICATIONS:

- Multimode MW cavity (1000W)
- Single (MonoPrep) (**3b**) and multiple vessel (6, 16 & 24 rotor) capability
- Glass/quartz (12-50 mL) or TFM vessels (70-100 mL)
- Max. temperature (180 °C) / Max. Pressure (15 bar)
- Efficient cooling (30 °C/min) in MonoPrep set up (Fig. **3b**)

Reaction conditions for MonoPrep Synthesis of DHPM 4

40 mmol reaction mixture
Solvent: (3:1) AcOH/EtOH (20 mL)
Catalyst: $FeCl_3 . 6H_2O$ (10 mol %)
Microwave conditions: 120 °C, 10 min
Parallel temperature monitoring by IR sensor and internal fiber-optic probe
Isolated yield of DHPM **4** 50-52 %

❹ Parallel synthesis in multimode cavity (8 x 80 mmol)

Anton Paar Synthos 3000™

REACTOR SPECIFICATIONS:

- Continuous MW output power (0-1400 W)
- Multimode cavity with 8 & 16 vessel rotor
- PTFE-TFM (100 mL) / Quartz glass vessels (80 mL)
- Max. Temperature (260-300 °C) / Pressure (60-80 bar)
- Temperature monitoring by IR thermography and an internal gas balloon thermometer

Parallel large scale synthesis of DHPM 4

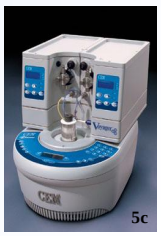
- Scalability examined using 2, 4 and 8 reaction vessels (80 mmol of each component)
- Reaction conditions:
  MW irradiation at 120 °C for 20 minutes
  HCl catalyst (10 mol %)
  EtOH (32 mL) as solvent

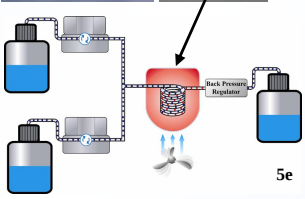
No. of vessels	Reaction volume	Isolated overall yields
2	160 mmol	43 %
4	320 mmol	46 %
8	640 mmol	48 %

❺ Continuous flow synthesis of DHPM 4 (40 mmol)

CEM Discover

CEM Discover / Voyager





Reactor Specifications:

- Continuous MW power (0-300W)
- Circular single-mode cavity (Fig. **5b**)
- Open (1-125 mL) and closed vessels (10 or 80 mL) with 20 bar pressure limit
- Temperature monitoring by IR
- Direct (invasive) or Indirect (non-invasive) pressure monitoring
- Forced cooling feature (PowerMax)
- Magnetic stirring and hot keys to change parameters on fly

- Flow through reactor (Fig. **5c**) built on Discover platform (Fig. **5a**)
- Temperature monitoring by fiber-optic
- Reaction in a Flow cell (Fig. **5d**) placed in the MW cavity
- Reaction mixture injected by HPLC pumps through a heated zone/cavity (Fig. **5e**)

Continuous Flow (CF) synthesis of DHPM 4

- 40 mmol homogeneous reaction mixture
- Total reaction volume 25 mL
- 20 mL EtOH/AcOH (4:1) mixture as solvent
- HCl as catalyst (10 mol %)
- Translation of batch conditions to continuous flow
  - Reaction in a glass flow cell (10 mL)
  - Temperature monitoring with fiber optic
  - Residence time (5 min) in Flow cell translates to time of irradiation in batch
  - 1.59 M building blocks, 2 mL/min flow rate
  - Entire cycle of 25 mL completes in 12.5 min
  - MW irradiation at 120 °C, 5 min (2 min ramp)
  - Approx. 100g DHPM **4** in 16 hours. (52 % yield)

❻ Conclusion

Our scale-up model studies have demonstrated, that

- ❖ Microwave conditions (batch and continuous) are instrumental in accelerating the synthesis and support an easy translation in reaction scale (small to large).
- ❖ Synthesis of DHPM 4 has been afforded in appreciable yields equally in monomode and multimode microwave reactors.
- ❖ An easy translation demonstrated in this case study suggests a possibility of applying microwave techniques in other scale-up syntheses.

No.	Reaction scale		Isolated overall yields
1	4 mmol	(Emrys Synthesizer)	52 %
2	40 mmol	(MicroSYNTH)	52 %
3	640 mmol	(Multiwave 3000)	48 %
4	~ 133 mmol / h	(CEM Voyager)	50 - 52 %

Acknowledgement

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