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Automated Generation of a Dihydropyrimidine Library Using Sequential Microwave-Assisted Synthesis

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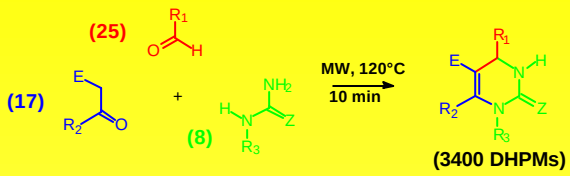
❶ Introduction: The Biginelli MCR (1893)



For reviews see C.O. Kappe, *Acc. Chem. Res.*, **2000**, *33*, 879-888
C.O. Kappe, *Eur. J. Med. Chem.*, **2000**, *35*, 1042-1053

Aim: **Generate a Library of Dihydropyrimidines Utilizing Rapid Automated Sequential Microwave-Assisted Chemistry**

❷ Microwave Equipment

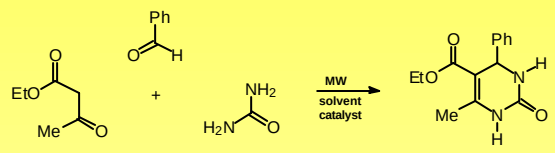
SmithSynthesizer

- **Single-mode microwave cavity, 2.45 GHz**
- **Continuous MW irradiation power 0-300W**
- **Automated liquid handling & vial transfer**
- **Temperature measurement by IR sensor**
- **Built-in magnetic stirring**
- **Teflon-sealed reaction vials**
- **Reactions up to 20 bar and 250°C**
- **Rapid gas jet cooling**

http://www.personalchemistry.com

❸ Optimization of Reaction Conditions using Microwaves

Model Reaction:

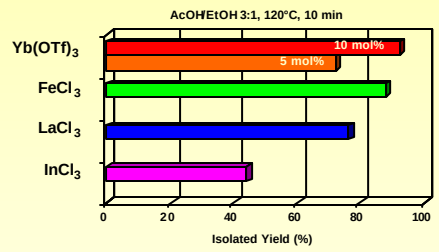


Conventional Conditions: EtOH, cat. HCl, reflux, 3h, 78% yield
K. Folkers et al., *J. Am. Chem. Soc.*, **1932**, *54*, 3751-3758

Step 1: Choose Solvent

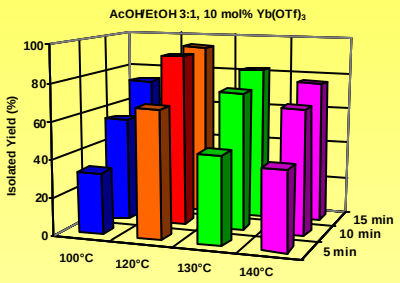
- **best solvent: AcOH/EtOH 3:1**
- **• effectively couples with microwaves**
- **• dissolves building blocks under reaction conditions**
- **• DHPM products sparingly soluble at rt**

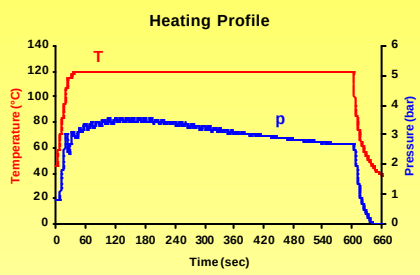
Step 2: Select Catalyst



- **HCl causes decomposition of urea and leads to unwanted byproducts at higher temperatures**
- **Lewis acids are more tolerable and have been reported to be effective catalysts**

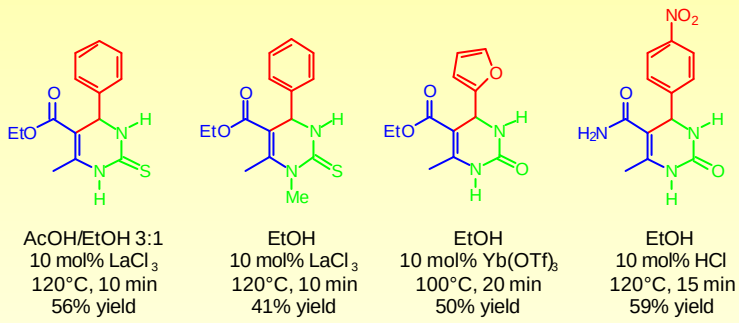
Step 3: Optimize Temperature & Time





➪ **General MW Protocol: 4 mmol building blocks, 2 ml AcOH/EtOH 3:1 10mol% $Yb(OTf)_3$, 10 min, 120°C**

Step 4: Reoptimization for Troublesome Building Block Combinations



AcOH/EtOH 3:1
10 mol% $LaCl_3$
120°C, 10 min
56% yield

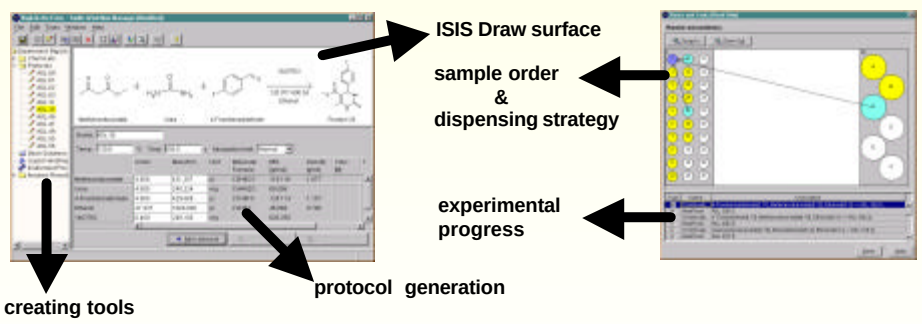
EtOH
10 mol% $LaCl_3$
120°C, 10 min
41% yield

EtOH
10 mol% $Yb(OTf)_3$
100°C, 20 min
50% yield

EtOH
10 mol% HCl
120°C, 15 min
59% yield

❹ Software Aided Library Generation

Smith Workflow Manager



- **Prepare stock solutions of aldehydes (AcOH) and CH-acidic carbonyls (EtOH)**
- **Enter building blocks & reaction conditions into the software**
- **Generate dispensing strategy**
- **Run the automated protocol (unattended)**
- **Work up (filter products directly or add H_2O)**

❺ Results and Conclusions

- **48 member DHPM library generated within 12h (52% average yield)**
- **DHPMs produced in 200-1000 mg quantities**
- **Reaction times reduced from hours to minutes**
- **Reaction optimization within hours**
- **Establishing of library production protocol within days**
- **Sequential treatment allows for individuality optimized conditions**

Stadler A., Kappe C.O., *J. Comb. Chem.*, **2001**, *3*, 624-630

Acknowledgements

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