Microwave-Assisted Biginelli Reaction

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The Microwave-Assisted Biginelli Reaction

Introduction:

Multicomponents reactions (MCRs) involve the combination of different starting materials in the same reaction flask to provide one distinct product upon completion. This class of reactions is useful in generating large libraries of compounds with variable structure in a short amount of time. They are used extensively in the pharmaceutical industry in the search for compounds with promising biological activity, and have spawned the development of robotic techniques and microwave-compatible procedures to facilitate large numbers of products.

The Biginelli reaction, which is just one example of the many MCRs used industrially, can be used to prepare 3,4-dihydropyrimidinones in a one-pot procedure. Examples of 3,4-dihydropyrimidinones useful in a clinical setting include the antihypertensive drug SQ32926 and the mitotic inhibitor monastrol, among many others.

The classic Biginelli reaction involves the reaction between an aldehyde, a β-dicarbonyl, and urea under acidic conditions, which proceeds through a sequence of reactions (Kappe, O. C. *Tetrahedron* 1993, 49, 6937). First, urea condenses with the aldehyde to produce an imine intermediate upon elimination of water. This intermediate then reacts with the enol form of the β-dicarbonyl compound to give an intermediate ureide, which cyclizes intramolecularly with loss of water to give 3,4-dihydropyrimidinones.

A number of modifications to the reaction conditions have been reported since the Biginelli reaction was first discovered (Biginelli, P. *Gazz. Chim. Ital.* 1893, 23, 360). Many of these modifications include variability in the acid catalyst, solvent, and temperature, as well as a development of the substrate scope. In this laboratory, you will be assigned an aryl aldehyde and a β-dicarbonyl compound which you will use to
perform a microwave-assisted and Lewis-acid catalyzed version of the Biginelli reaction. You will generate new 3,4-dihydropyrimidinones which will be used at Boston University’s Center for Chemical Methodology and Library Development for screening against a variety of biological targets.

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![Chemical structure of the Biginelli reaction](image)

**Equipment:**
- Microscale glassware kit
- NMR tubes
- $d_6$-DMSO
- Microwave tubes
- HPLC vials
- 1 mL syringes and needles
- Crystallization dish (for ice bath)
- Melting tubes
- MeltTemp

**Chemicals:**
- Benzaldehyde
- 4-Chlorobenzaldehyde
- $m$-Tolualdehyde
- 3,4,5-trimethoxybenzaldehyde
- 2-Thiophene carboxaldehyde
- 2,4-pentanedione
- Ethyl acetoacetate
- Acetoacetamide
- Methyl acetoacetate
- Urea
- Ytterbium triflate
- 95% Ethanol
- Acetic acid
**Procedure:**

**Biginelli Reaction:** Sign out a microwave tube from your TF, making sure to write down the position of your tube. To the tube equipped with stir bar, add 600 mg of urea and 624 mg of Yb(OTf)₃. Then add 1.0 mL 95% ethanol and then 10 mmol of your assigned aryl aldehyde. Finally, add 3.0 mL glacial acetic acid and 10 mmol of your assigned β-dicarbonyl compound and cap tightly. Be sure that you have a stir bar in your tube and that the Teflon wedge is positioned correctly. Microwave the reaction for 10 minutes at 120 ºC.

**Work-up:** Cool the product mixture to room temperature and then place in an ice bath. The dihydropyrimidinone should precipitate out of solution after approximately 20 minutes. Scratching or agitation at the surface of the solution may help this process. Filter the solid using a Hirsch funnel and wash with ice-cold 95% ethanol. Transfer your crude product to an Erlenmeyer flask or beaker and dissolve your product in a minimal amount of warm ethanol (1 mL at a time until almost completely soluble). Allow the solution to cool to room temperature fully before placing in an ice bath. Filter and collect the recrystallized solid on a Hirsch funnel and wash with ice cold 95% ethanol.

**Analysis:** Tare your purified compound to obtain a percent yield. Measure the melting point of your solid and obtain both a ¹H NMR and IR of your solid. Submit your NMR tube to your TF who will run an overnight ¹³C NMR spectrum for you (instrument time pending).

**Pre-lab Questions:**

1) Provide a mechanism for the Biginelli product you will synthesize in this experiment.

2) Draw a reaction scheme for another multicomponent reaction that is of importance to the pharmaceutical industry (a mechanism is not necessary).

3) What role does Yb(OTf)₃ play in the reaction?

4) Is the product you will synthesize aromatic, anti-aromatic, or neither?

5) How can monastrol be prepared using the Biginelli reaction? Draw the structures of the three components.

**Post-Lab Questions:**

1) Multicomponent reactions are used extensively in the pharmaceutical industry to develop new drugs. Conduct a literature search on the medicinal chemistry of 3,4-
dihydropyrimidinones and select an interesting (and relevant) primary reference. Write a brief 2-3 sentence summary of the authors’ findings. Be sure to include the reference in your lab report (you do not need to attach a paper copy of the reference itself).

2) How would you synthesize the following dihydropyrimidinones using the Biginelli reaction?

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\begin{array}{c}
\text{N} & \text{N} & \text{N} & \text{N} \\
\text{O} & \text{O} & \text{O} & \text{O} \\
\end{array}
\begin{array}{c}
\text{CM}_3 \text{O}_3 \\
\text{I} & \text{I} \\
\text{F} & \text{F} \\
\text{O} & \text{O} \\
\text{H} & \text{N} & \text{H} & \text{O} \\
\end{array}
\]