BIGINELLI DIHYDROPYRIMIDINE SYNTHESIS

Reflux and Thin Layer Chromatography (TLC)

EXPERIMENTAL OBJECTIVES

To synthesize an organic compound and examine its purity using thin layer chromatography (TLC)

LEARNING OBJECTIVES

- To learn how to carry a reaction from start to finish, including reaction setup, monitoring, workup, purification, and product verification
- To learn how to setup and why to use a reflux reaction
- To learn how to use TLC to monitor a reaction and determine sample purity

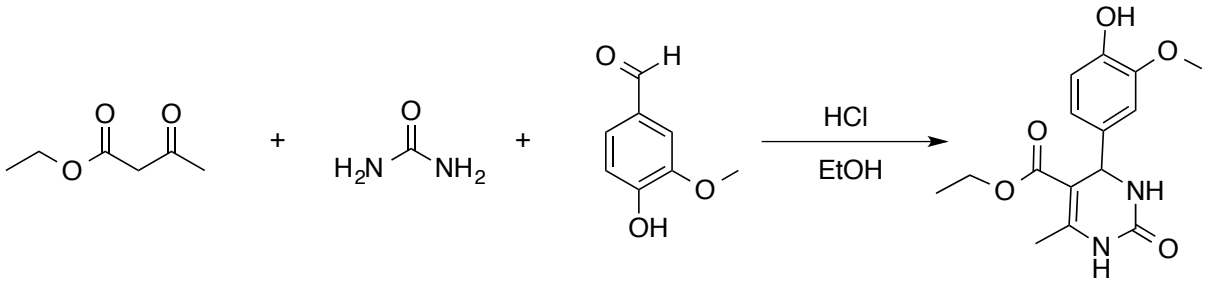
PRE-LAB EXERCISES

Please read:

See links on Blackboard for **Reflux,** and **Thin-layer Chromatography**
Calculate amounts of starting materials by converting from millimoles (mmol) to grams.

BACKGROUND

The Biginelli pyrimidone synthesis is a reaction named after the scientist who first published its use in 1891, Pietro Biginelli.[1]



The multicomponent reaction involves the combining of a β-dicarbonyl compound (also known as a 1,3-dicarbonyl), an aldehyde, and a urea to form a dihydropyrimidine heterocycle. The reaction mechanism is quite complex, involving an aldol condensation (Carey Chpt. 20), a 1,4-addition (Carey Chpt. 20), and subsequent ring closure with elimination (Carey Chpt 5). The dihydropyrimidine heterocycle product is a common pharmacophore and is found in molecules with antiviral, antitumor, antibacterial, anti-inflammatory, and antihypertensive activity.[2] For

[1] Biginelli, P. Aldehyde–Urea Derivatives of Aceto- and Oxaloacetic Acids. *Gazz. Chim. Ital.* **1893**, 23, 360–413
[2] Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. *Accounts of Chemical Research*. **2000**, *33*, 879-888.

our purposes though, it is a very efficient reaction, which can be monitored by TLC, and it produces an easily isolatable product. Specifically, we will react 4-methoxybenzaldehyde, urea, and ethylacetoacetate (ethyl 3-oxobutanoate) under acid catalysis to form ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

PROCEDURE – WEEK 1

1. Place 10 mmol vanillin, 15 mmol ethyl acetoacetate, 10 mmol urea, and 5 mL of 95% ethanol into a 25 mL round bottom flask equipped with a reflux condenser
2. Add 0.2 mL of concentrated HCl to the reaction solution
3. Heat the reaction mixture at reflux for 1.5 hours
4. Cool the flask to 0°C, a precipitate should form
5. Collect the solid product by vacuum filtration, wash with cold 95% ethanol (~5 mL)
6. Once dry, be sure to record the mass of your solid product and save for the next lab period
7. Discard all waste into the appropriate waste container

PROCEDURE – WEEK 2

1. Analyze your product using Thin Layer Chromatography (TLC).
    a. Set up a co-spot TLC plate using vanillin and your crude reaction product
    b. Run the TLC in a closed chamber using your chosen mobile phase
    c. When the solvent line nears the top of the plate, remove the plate from the chamber, mark the solvent line, and then allow it to dry
    d. Visualize your spots using a UV-light (be sure to outline the spots in pencil on the TLC plate)
    e. Determine R_f values for each spot, and the purity of your crude product
    f. Copy the TLC plate into your lab notebook and discard the TLC plate into the broken glass container
2. After TLC analysis, make a determination of how pure your product is..
3. Also verify the purity and identity of your compound by melting point analysis (your need to report a range - expected melting point ~220°C).
4. Discard your product in the appropriate waste container when you are certain you have acquired all necessary data.