The Biginelli Reaction

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1. PURPOSE OF THE EXPERIMENT

- Perform a three-component, Biginelli Reaction, which undergoes imine formation and β-keto ester formation followed by cyclization.
- Experience a one-pot reaction, which can actually be applied in synthesizing pharmaceutics.
- Analyze the products by NMR spectroscopy.

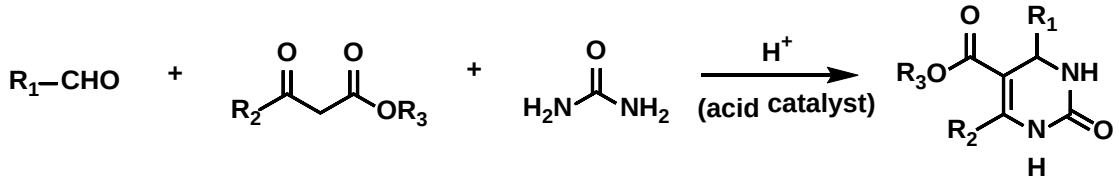
2. BACKGROUND INFORMATION

The Biginelli reaction, which was named after an Italian chemist, Pietro Biginelli, is a multi-component chemical reaction. The reaction is also known as Biginelli pyrimidine synthesis as the product of the reaction is dihydropyrimidone species. Three reagents are required for the Biginelli reaction, whereas most of organic reactions include two reagents generally. The three required are β-keto ester, an aryl aldehyde, and urea, and the reaction proceeds under acidic conditions. Acidic condition may be generated by using catalytic amount of either Brønsted acid or Lewis acid.

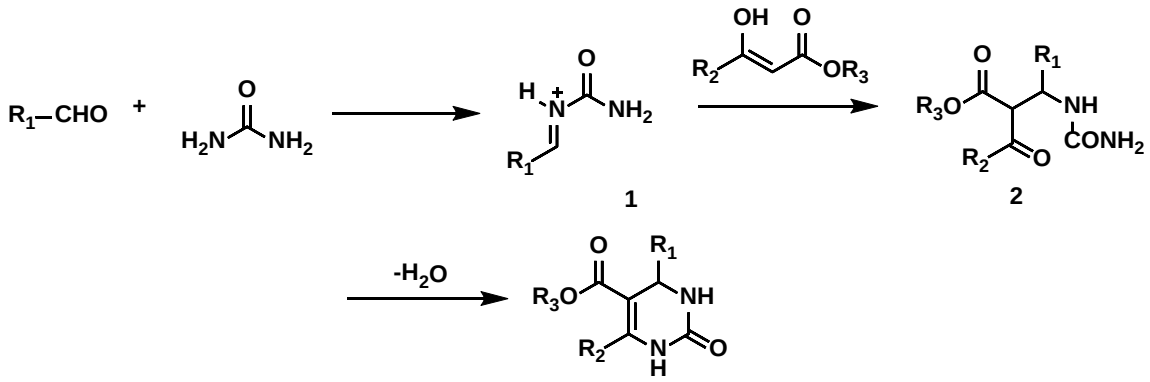
As mentioned earlier, dihydropyrimidones are products of this reaction, and are widely used in the pharmaceutical industry as several usages. Thus, the Biginelli reaction is useful for accessing several desired pharmaceutical samples through simple one-step reaction.

Mechanism of the Biginelli Reaction

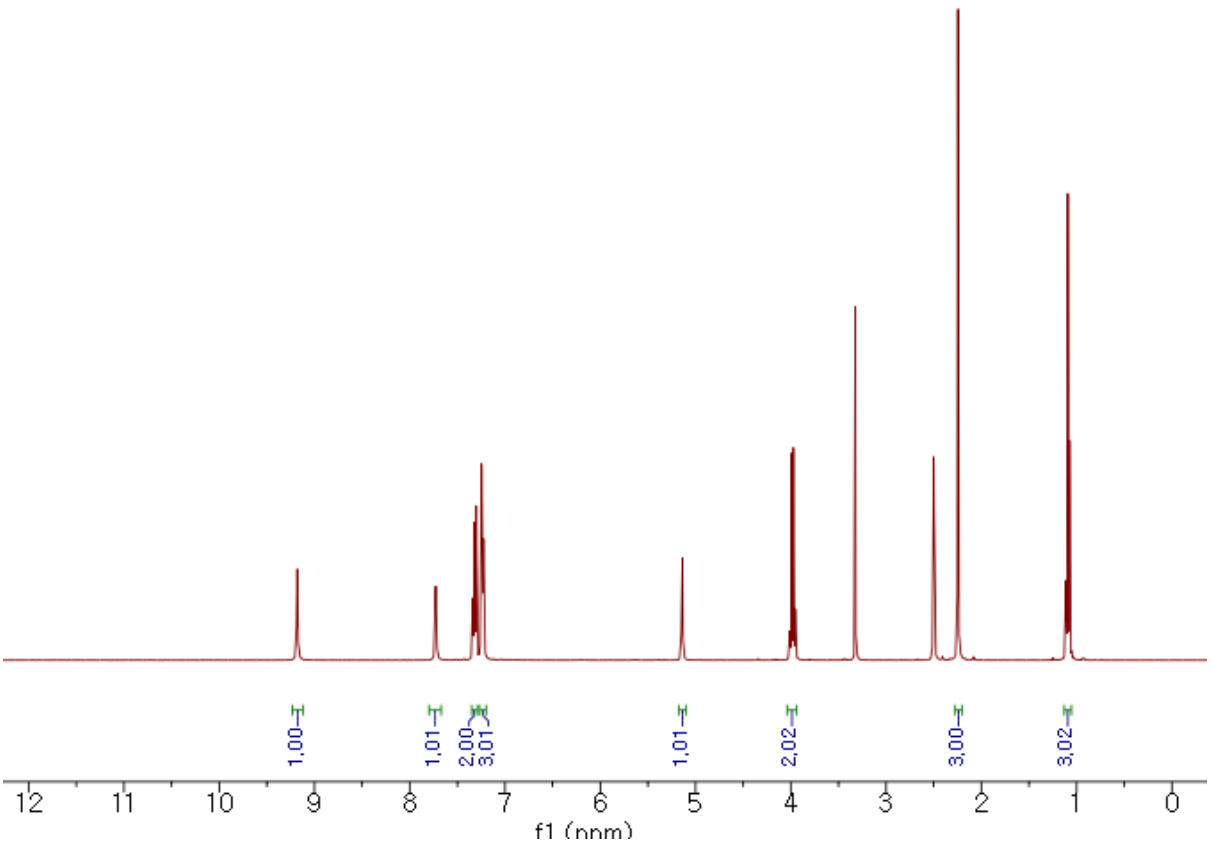
The following figure is the scheme of the Biginelli reaction. Biginelli reaction can be catalyzed by Brønsted acids and by Lewis acids. The copper(II) trifluoroacetate hydrate and boron trifluoride are the examples of catalysts. In our case, we will use concentrated HCl will be used as acid catalyst.



As you can see in the figure above, Biginellli reaction is a multicomponent reaction. The first step in the mechanism is condensation between the aldehyde and urea forming an imine species. During this step, the proton transfer step happens and an N-acyliminium ion intermediate is formed. This is attacked by the enol form of the β-keto ester. Cyclic intermediate is generated and the pyrimidone product is the synthesized at the final step. The first step is the rate determining step. Intermediate steps of the first step are shown in the below figure.



The following NMR spectrum is that of the product of our experiment. DMSO was used as the NMR solvent. Use this to compare with your own results.



3. MATERIALS USED

25mL round-bottom flask

Reflux condenser

Buchner funnel (Hirsch funnel can be replaced)

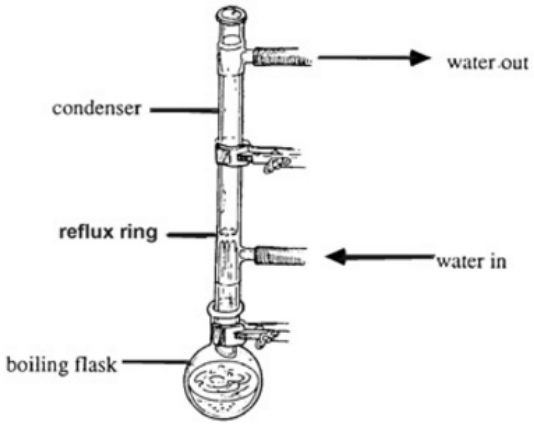
4. REAGENTS AND PROPERTIES

Reagents	Molecular weight	Density	mmol	equivalent
Benzaldehyde	106.12	1.044		
Ethyl acetoacetate	130.14	1.021		
Urea	60.06	-		
Ethanol	46.07	-	-	-
3M HCl	36.46	-	-	-

5. PROCEDURE

a. Put 5 mmol benzaldehyde, 7.6 mmol ethyl acetoacetate, 5 mmol urea and 2mL ethanol into a 25mL round-bottomed flask equipped with a reflux condenser.

Caution: Allow water to flow from bottom to top during reflux.

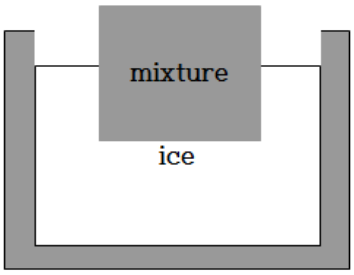


b. Add one drop of concentrated HCl to the reaction flask.

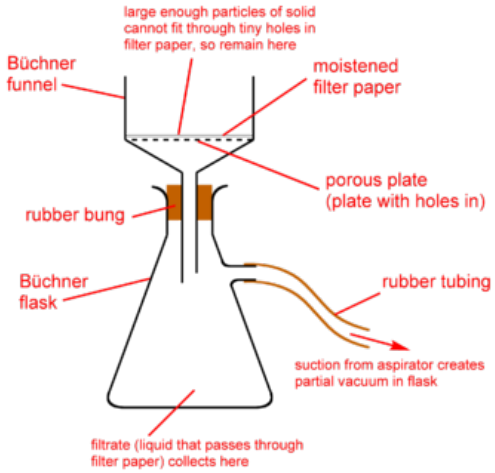
c. Heat the mixture at reflux, stirring with stir bar for 1.5 h. (*Make sure the reaction temperature doesn't go too high, watch carefully and keep the temperature to be in between 80°C - 90°C.*)

d. Cool the flask to 0 °C. (*Make sure you cool it to room temperature first!)*

Using ice bath is recommended but ice-based tap water can also be used.



e. Collect the product by filtration, using a Buchner funnel.



f. Wash with 30mL 95% cold ethanol.

Caution: Do not use too much ethanol. The yield may decrease. Do not pour ethanol at once. If you put a large amount of ethanol at once, the filter paper might get torn, and the crystals can flow out of the filter paper. This lowers your yield.

g. Record the mass of your product. (*measure the mass of empty vial, collect your white crystals from filter paper)*

Caution: Make sure that you should dry your product as much as possible before weighing.

h. Calculate your percent yield.

i. Obtain the NMR spectrum.

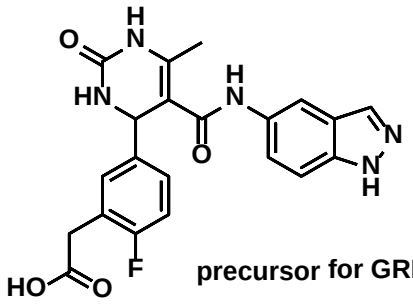
6. POST-LABORATORY QUESTIONS

1. Calculate the percent yield of your product.
2. Assign peaks in the ^{1}H NMR and explain why.
3. Explain the role of HCl.
4. Why do you think we used DMSO as the NMR solvent, not generally used $CDCl_3$?

5. List at least 2 ways to improve the reaction yield.

7. PRE-LABORATORY QUESTIONS

1. Summarize all the MSDS's of chemicals used in this experiment
2. Provide an overall mechanism of the Biginelli reaction, including the movements of electrons using arrows.
3. When the reaction is completed, there is no suspension remaining in the mixture, and the mixture becomes transparent. What does this physical property change indicate?
4. Explain the reactions between amines and carbonyls, namely, imine formation and enamine formation. (*you may draw the reaction mechanism.)*
5. Below compound is a precursor for GRK 2 inhibitors developed by medicinal chemists using biginelli reaction. Draw the three components of Biginelli reaction to synthesize the below compound.



precursor for GRK2 inhibitors