Experiment 6

The Biginelli Reaction

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1. PURPOSE OF THE EXPERIMENT

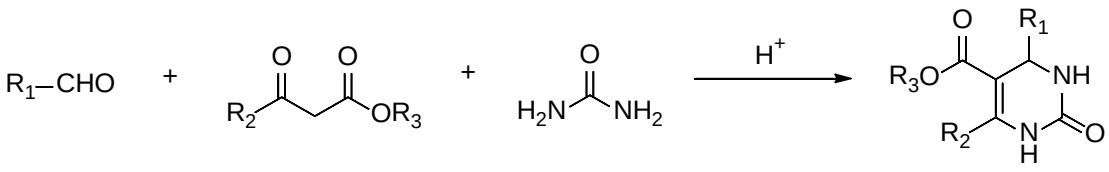
- Perform a Biginelli Reaction with imine formation and β-keto ester formation followed by cyclization.
- Analyze the products by NMR spectroscopy.

2. BACKGROUND INFORMATION

The Biginelli reaction is named after an Italian chemist, Pietro Biginelli. It is also known as Biginelli pyrimidone synthesis since it synthesizes dihydropyrimidones. Most organic reactions require two reagents but the Biginelli reaction is distinct from other organic reactions because it requires three reagents to be performed. The reaction proceeds between a β-keto ester, an aryl aldehyde, and urea under acidic conditions. The products of the Biginelli reaction, dihydropyrimidones, are receiving attention of their various usages in the pharmaceutical fields.

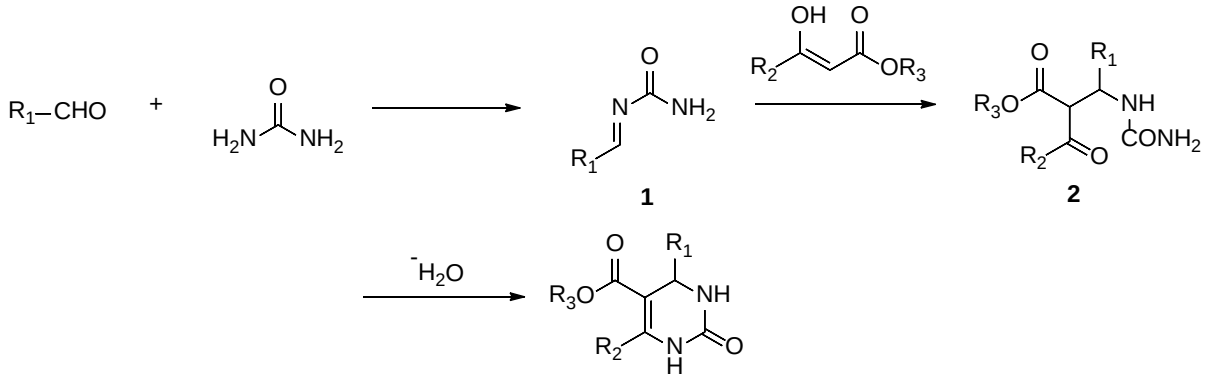
Mechanism of the Biginelli Reaction

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.

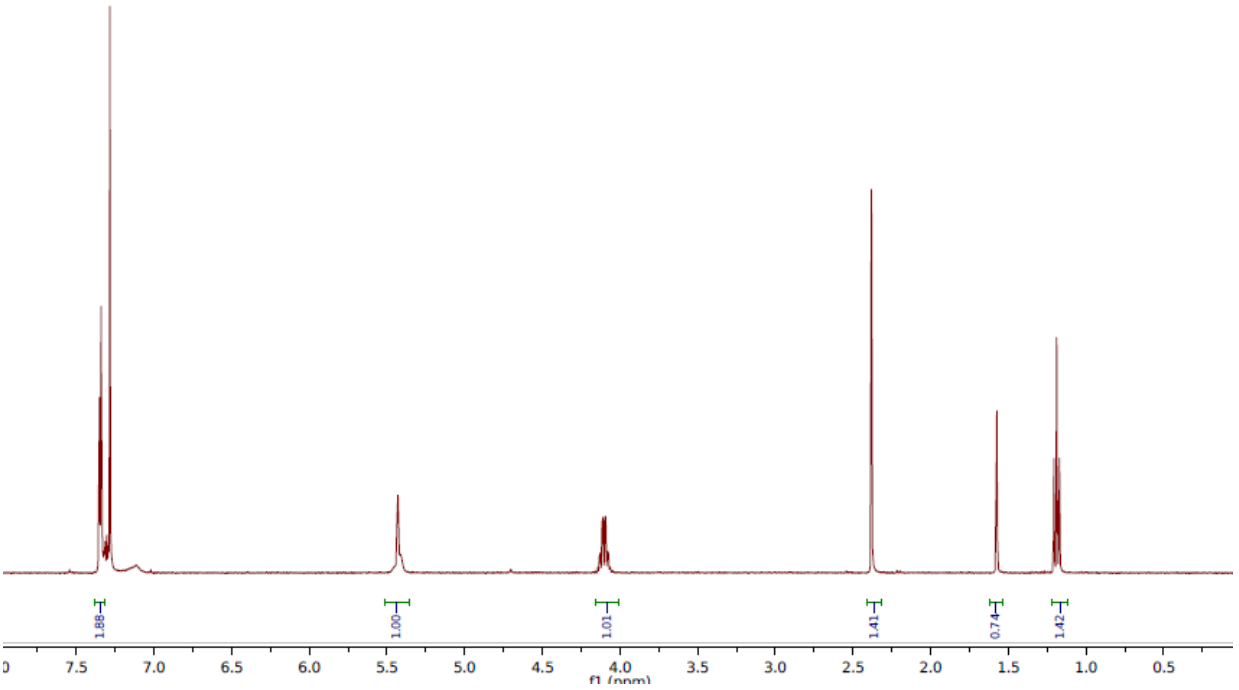


As you can see in the figure above, Biginellli reaction is a multicomponent reaction. The first step in the mechanism is condensation between the aldehyde and urea. Among this step, the proton transfer step happens and an N-acyliminium ion intermediate is made as a result. This is attacked by the enol for of the β-keto ester.

Cyclic intermediate forms and the pyrimidone product is the final product. The first step is the rate determining step. Intermediate steps of the first step are well explained in the next figure.



Atul Kumar has reported a yeast catalyzed Biginelli reaction in high yields. According to the reference paper, the percent yield of the product was up to 58%. However, this experiment demonstrated a percent yield 0f 66%. This is because the amount of chemicals used in this experiment was 4 times greater than the amount used in the reference experiment. The loss during the filtration could give less effect on the percent yield in this experiment. The following NMR data is obtained in this experiment. Other experimenters could use this data to compare with their NMR data.



3. MATERIALS USED

5mL round-bottom flask

Reflux condenser

Buchner funnel (Hirsch funnel can be replaced)

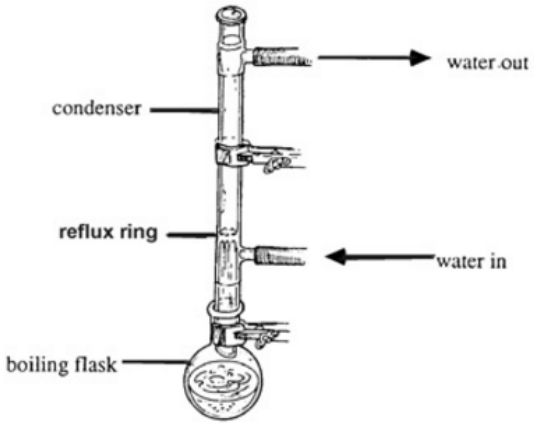
4. REAGENTS AND PROPERTIES

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.

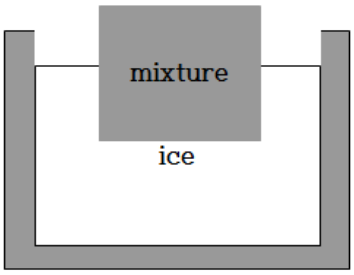


b. Add one drop of concentrated HCl to the reaction flask.

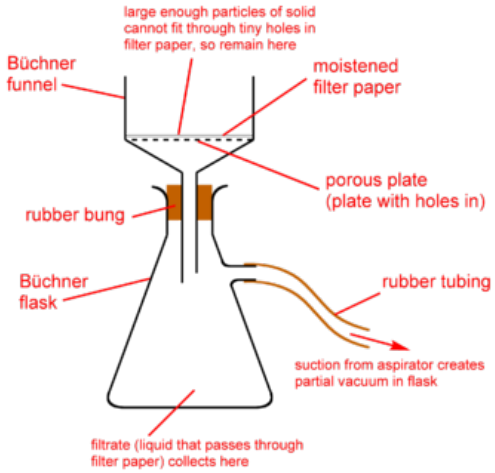
c. Heat the mixture at reflux, stirring with stir bar for 1.5 h.

d. Cool the flask to 0 °C.

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 excess ethanol. The yield may be decreased. Do not pour in one time. If you put a lot of ethanol at once, the filter paper can be torn and the crystals can flow out of the filter paper. This makes your yield lower.

g. Record the mass of your product.

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 the peaks in the ^{1}H NMR and explain it.
3. Explain the role of HCl.
4. List at least 2 ways to improve the reaction yield.

7. PRE-LABORATORY QUESTIONS

1. Summarize all the MSDS of chemicals used in the experiment
2. Provide an overall mechanism with the movements of electrons in an arrow for the Biginelli reaction.
3. Explain the reactions between amines and carbonyls, namely, imine formation and enamine formation.
4. Compare the characteristics of alkyl amine, aniline and amide in terms of its nucleophilicity and basicity (pK_a). Which one is the poorly reactive functional group toward imine formation?