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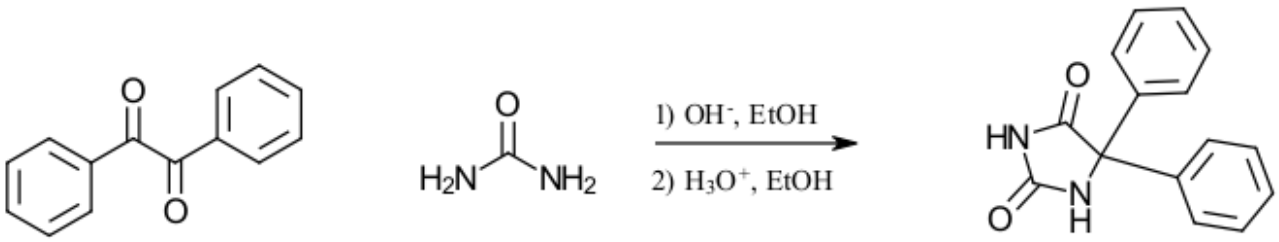
Synthesis of Phenytoin

Abstract

The purpose of this experiment was to synthesize the anticonvulsant phenytoin from benzil and urea. The reaction was done in basic conditions attained using 6 M sodium hydroxide and the product was assessed by IR spectroscopy. The benzil and urea were put in 85% ethanol and heated under reflux for thirty minutes to complete the reaction. The solution was neutralized to a pH of five using hydrochloric acid and the solid product was collected on a Hirsch funnel. An IR spectrum of the product was obtained, and the melting point was determined. The mass of product obtained was 0.5441 g for a percent yield of 85%. However, by comparison to a literature IR spectrum, it was determined that the product contained some water which invalidates the percent yield. The expected yield is 44%[13] and our yield is likely closer to that value. Comparison of experimental and literature melting points (297 – 298 °C and 295 °C[11] respectively) suggested the isolated phenytoin was highly pure disregarding the water content.

Proposed Reaction



Benzil

$C_{14}H_{10}O_2$

210.23 g/mol[9]

Urea

CH_4N_2O

60.056 g/mol[10]

Phenytoin

$C_{15}H_{12}N_2O_2$

252.27 g/mol[11]

MP: 295 °C[11]

List of reagents

Compound	Formula	Mol. Weight (g/mol)	Quantity used	SDS Information
Benzil	$C_{14}H_{10}O_2$	210.23[9]	0.5342 g	Warning; eye/skin irritant, wear PPE[3]
Urea	CH_4N_2O	60.056[10]	0.3031 g	None; Not considered hazardous[1]
Ethanol	C_2H_6O	46.068[8]	6 mL	Danger; irritant, flammable liquid, wear PPE[2]
6 M Sodium Hydroxide	$NaOH_{(aq)}$	-	1.2 mL	Danger; Corrosive, severe skin burns and eye damage[4]
3 M Hydrochloric acid	$HCl_{(aq)}$	-	~2.5 mL	Danger; Corrosive, severe skin burns and eye damage[5]

Special equipment

Cotton fitted Pasteur pipet

Mel-Temp apparatus

Hirsch funnel

IR spectrometer

Transfer Syringe

pH Paper

Procedure and Observations

This procedure was based on that found in the TRU Organic Chemistry II Winter 2024 Laboratory Manual.[7] Before beginning, all the proper PPE was put on including a lab coat, goggles and gloves. First, 0.5342 g of benzil (98% purity), a solid with fluffy, light-yellow crystals, was weighed on an analytical balance and placed into a 25 mL round bottom flask. Next, 0.3031 g of solid urea, which resembled small white beads, was also weighed out and placed into the flask. As the reaction solvent, 6 mL of 85% ethanol solution was added to the flask and it was swirled around to promote dissolution of the solids. As some dissolved, the solution turned yellow and five small boiling stones were also added. The final reagent was 6 M sodium hydroxide solution and 1.2 mL was carefully added using a syringe. It was necessary to do this with extreme care and wear gloves since this concentration of base can cause serious skin damage. Upon addition of the base, the clear, yellow solution turned a cloudy off-white. The flask was then clamped to the bottom of a vertical condenser column and a heating mantle was placed on a lab jack underneath. The heat was turned on and the heating mantle was jacked up close to the flask. Once the heat was on, the water through the condenser column was turned on and after four minutes, the reaction solution began boiling smoothly. Once heated, the solution cleared up again to a transparent yellow liquid. The reaction was left to proceed under reflux for half an hour. During this time, the benzil and the urea were reacting to form the desired product, phenytoin. One step of the mechanism requires a deprotonation, facilitated by the high pH attained by including the sodium hydroxide. After being under reflux for thirty minutes, the heating mantle was removed from the flask. The reaction solution was now a transparent orange and some solid had settled to the bottom of the flask. The flask was removed from the condenser as soon as possible since the glass joint can fuse in the basic conditions. The orange liquid in the flask was filtered through a cotton plugged Pasteur pipet to remove any precipitate and the

filtrate was collected in a 50 mL Erlenmeyer flask. The filtrate was chilled in an ice bath for a few minutes. Using a total of 2.5 mL 3 M hydrochloric acid, the filtrate solution was neutralized to a pH of about 5. The acid was added small amounts at a time and some pH paper strips were used to estimate when the solution reached neutral. The protons produced by the hydrochloric acid were necessary to neutralize the basic reaction conditions and protonate the product which remains an anion under basic conditions. Once the acid was added, a large amount of precipitate immediately came out of solution. The contents of the Erlenmeyer were transferred to a Hirsch funnel and the vacuum was turned on. Once dry, the product was collected into a pre-weighed weigh boat and the mass was determined. The melting point was then determined using a Mel-Temp apparatus set initially to 280 ℃ and set to increase 1 ℃ per minute. An IR spectrum of the product was also obtained by grinding a small portion with two drops of nujol oil using a mortar and pestle and placing a small amount between two salt plates.

Purification and Results

Table 1. Measured and calculated results from the synthesis of phenytoin.

Mass of weigh boat	0.7026 g
Mass of weigh boat and product	1.2467 g
Mass of product	0.5441 g
Theoretical yield	0.6410 g
Percent yield	85%
Experimental Melting Point	297 – 298 °C

Mass of product = 1.2467 g – 0.7026 g = 0.5441 g

Theoretical yield:

$$mol\ benzil = 0.5342\ g \times \frac{1\ mol}{210.23\ g} = 0.002541\ mol$$

$$mol\ urea = 0.3031\ g \times \frac{1\ mol}{60.056\ g} = 0.005047\ mol$$

Benzil is the limiting reagent.

$$mass\ phenytoin = 0.002541\ mol \times \frac{1}{1}\ stoich \times \frac{252.27\ g}{1\ mol} = 0.6410\ g$$

$$percent\ yield = \frac{0.5441\ g}{0.6410\ g} \times 100\% = 85\%$$

Table 2. Reference table for an IR spectrum (Figure 1) of phenytoin synthesis product.

Functional Group	Suggested molecule	Wave Number (cm^{-1})	Amplitude	Peak Width
O-H	H_2O	3430	Strong	Broad
C=O	Phenytoin	1740, 1777	Strong	Narrow
N-H	Phenytoin	3273	Strong	Medium
C=C	Phenytoin	1660	Medium	Narrow
C-H	Nujol Oil	2917	Strong	Medium

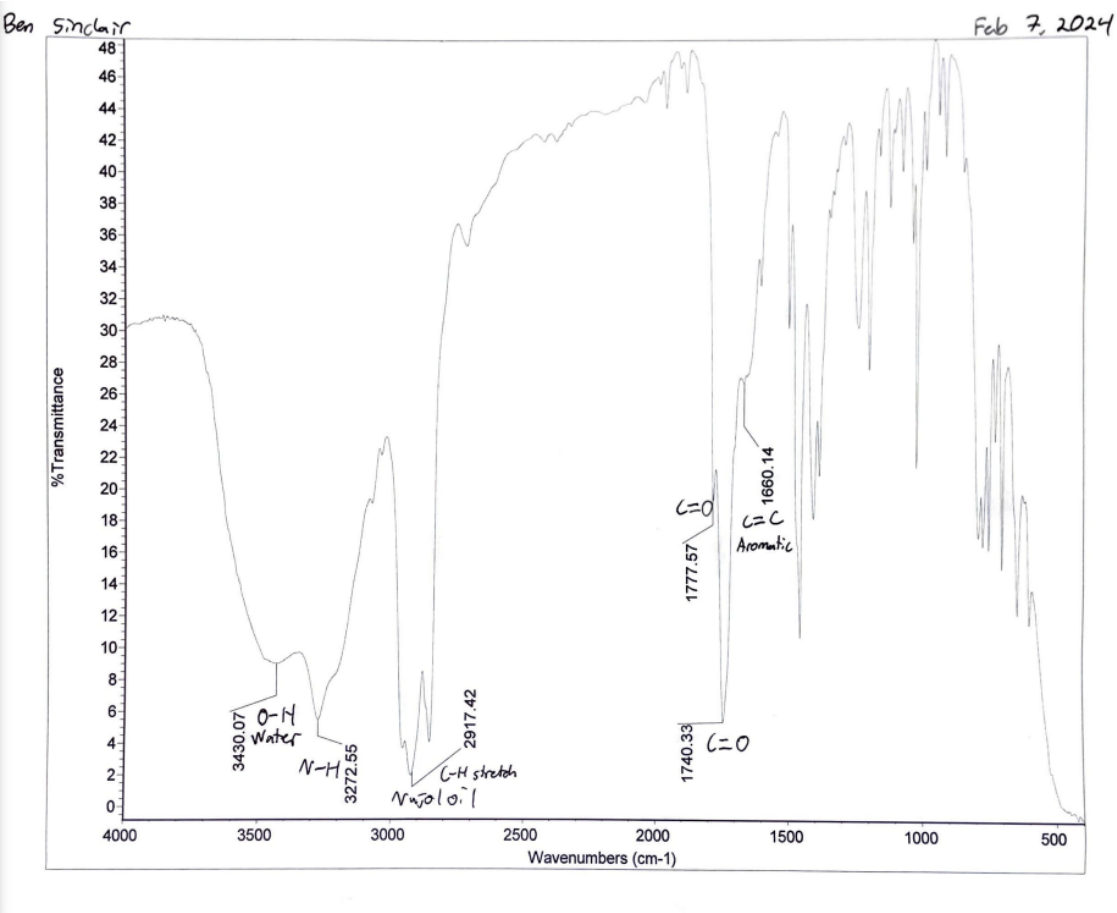


Figure 1. IR spectrum of phenytoin synthesis product.

This IR spectrum was taken of the phenytoin product after it was isolated. Beyond the fingerprint region, the first small peak at 1660 cm^{-1} is indicative of the C=C bonds found in the aromatic rings of the phenytoin. At 1740 cm^{-1}, we see the C=O peak which is found in the heterocyclic portion of phenytoin. The N-H peak at about 3270 cm^{-1} is further evidence that phenytoin is present, but a tall and broad hydroxyl peak is also present. This indicates that a large amount of water was present in the product.

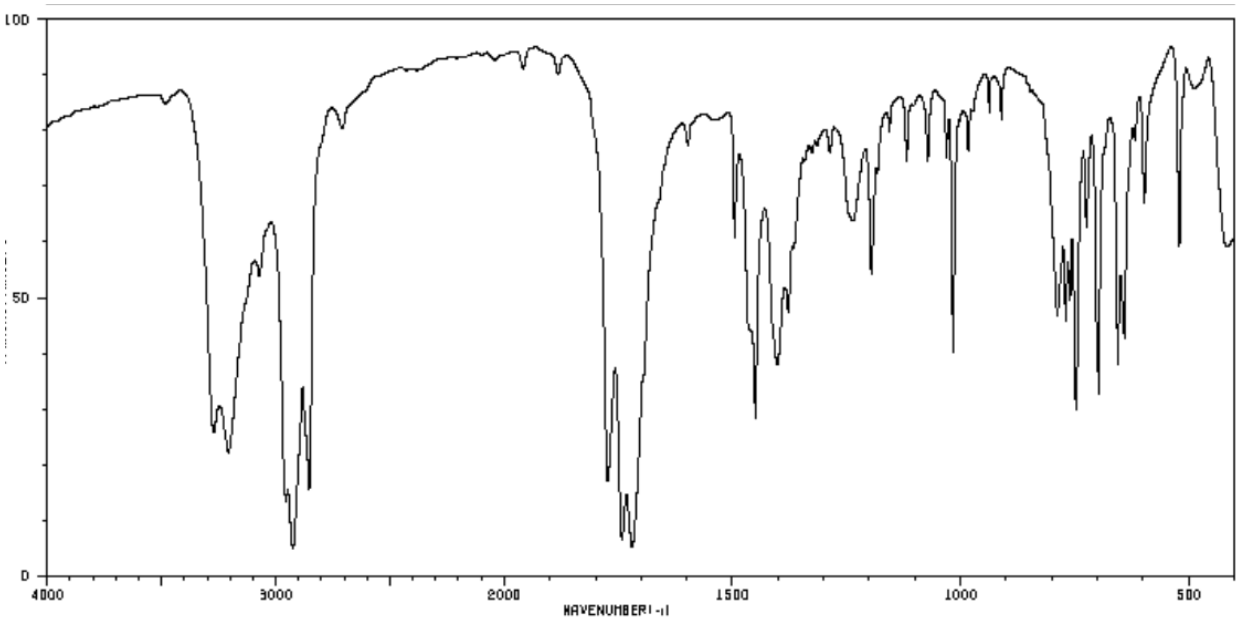


Figure 2. Literature IR spectrum of phenytoin. Obtained from Spectral Database for Organic Compounds.[12]

Discussion and Conclusion

The synthesis of phenytoin was successfully completed from benzil and urea in basic conditions. The theoretical yield for this experiment was 0.6410 g and 0.5441 g (Table 1) of product was obtained to attain a percent yield of 85%. This yield is quite high for this experiment which suggests that an inflated number was obtained when weighing the product. The most likely explanation, which was proposed during the experiment, is that the crystals were not completely dry, and the water was contributing to the mass of product. To assess the purity of the product as phenytoin, the melting point was determined and an IR spectrum was obtained for comparison to literature. The IR spectrum obtained of the product (Figure 1), shows peaks indicative of multiple functional groups which are present in phenytoin. Comparing to the literature spectrum[12] seen in figure 2, all of the major functional group peaks including the N-H at about 3250 cm^{-1} and the C=O at about 1750 cm^{-1} are seen in both spectra. The C-H stretch from use of nujol oil is also seen in both spectra. The only exception is a large, broad peak at about 3340 cm^{-1} on the synthesis product spectrum which indicates an O-H group. This indicates that there was a large amount of water present in our sample which invalidates the percent yield value of 85%. One literature procedure gives an expected yield of 44%[13], which is likely closer to what our yield actually is. This same procedure listed phenytoin's melting point as 297 – 298 °C[13] and another source listed its melting point as 295 °C[11]. Our experimental melting point was measured as 297 – 298 °C. This suggests that our phenytoin was highly pure except for the water content since there was no melting point depression observed and the range is accurate and narrow. To fix the problem of wet product, the crystals could have been dried more thoroughly once collected by leaving them under suction on the Hirsch funnel for longer or even using an oven to dry them completely. To improve the yield of the experiment, stirring the reaction mixture may have helped to get a completely homogenous solution and prevent some solids from sticking to the flask and not reacting.

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