Exp 4

Synthesis of Phenytoin from Benzil

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Objective

- The aim of this experiment is to synthesize phenytoin by the condensation of benzil and urea.

Outline

- Introduction to phenytoin
- Synthesis of phenytoin
- Mechanism of the syntheis reaction
- Calcultion
- Procedure

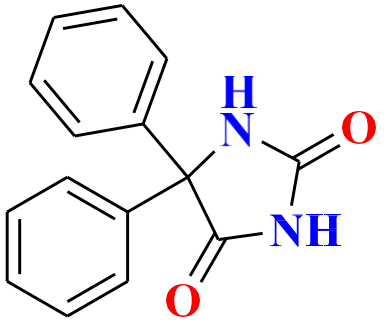
Introduction

- *Phenytoin* blocks **voltage-gated sodium channels** by selectively binding to the channel in the inactive state and slowing its rate of recovery.
- It is effective for treatment of **focal** and generalized **tonic–clonic** seizures and in the treatment of **status epilepticus**.
- The drug may be incompletely or erratically absorbed from sites of administration because of its very low water solubility.
- Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia.
- **Gingival hyperplasia** may cause the gums to grow over the teeth.
- Long-term use may lead to development of peripheral neuropathies and osteoporosis.

Chemistry of phenytoin

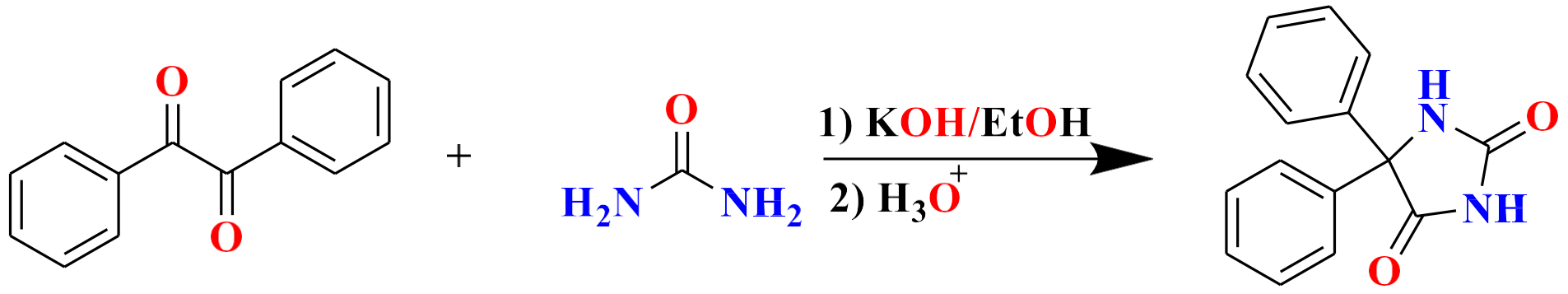
- **IUPAC name**: (5, 5-diphenylimidazolidine-2,4-dione) or 5,5-diphenylhydantoin was also named as dilantin.
- Phenytoin appears as fine white or almost white crystalline odourless powder.
- However, its low solubility in water, both as free acid and sodium salt,

  makes its administration to patients difficult and seldom satisfactory.



Synthesis reaction

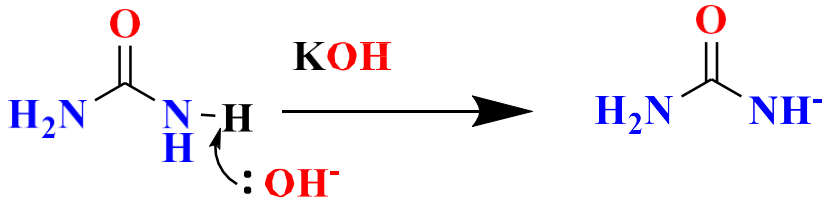
- Generally, according to the reported procedure, phenytoin is synthesized by condensation of **benzil** and **urea** in the presence of a strong base (KOH) and using ethanol as a solvent.



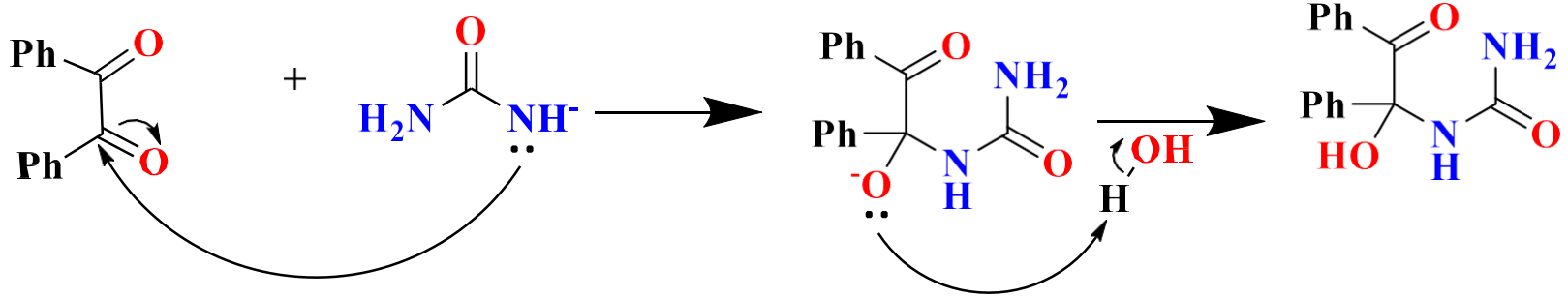
benzil **urea** **phenytoin**

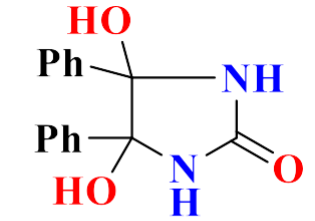
Mechanism of the reaction

Step 1: deprotonation of urea



Step 2: nucleophilic attack on carbonyl carbon

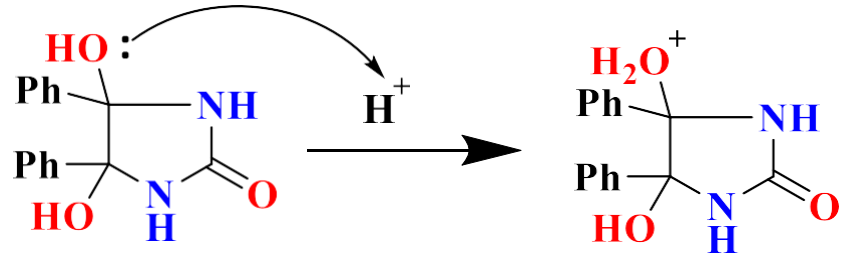




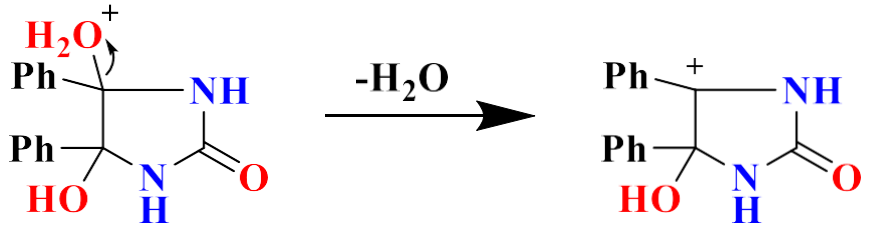
as before

Mechanism of the reaction

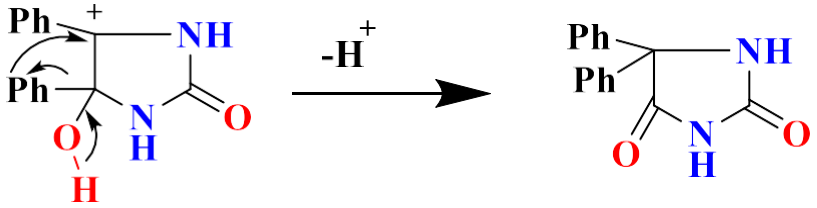
Step 3: Protonation of the OH group



Step 4: Elimination of water

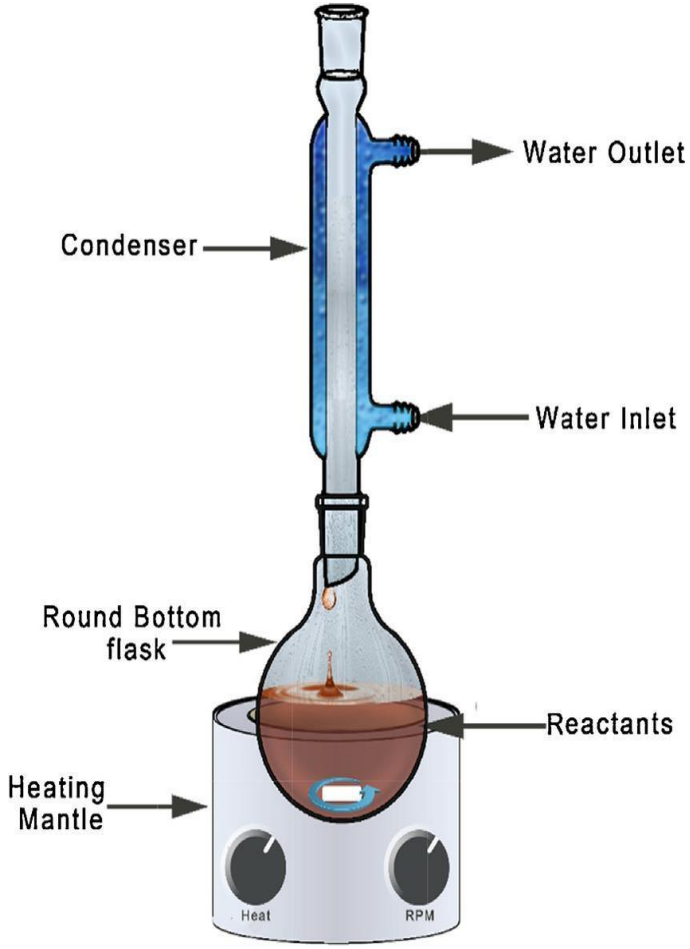


Step 5: Rearrangement and deprotonation



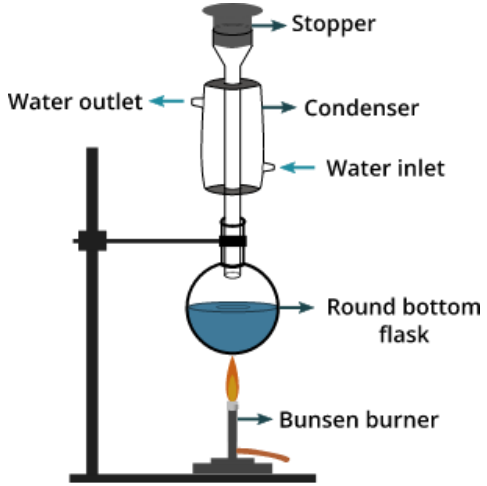
What is reflux?

- Running organic reactions is a lot like cooking.
- Most organic reactions occur slowly at room temperature and require heat to allow them to go to completion in a reasonable time frame.
- However, organic compounds are usually simple molecular structures with low boiling points.
- As such, most organic chemicals are quite volatile, and if heated they will evaporate and be lost.
- Running a reaction under reflux allows the reaction to heat up without losing solvent due to evaporation and without causing an explosion.
- The solution to this problem is to heat the reaction mixture under reflux.



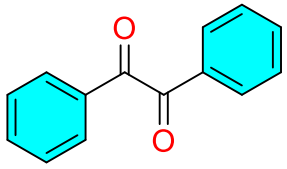
What is reflux?

- A condenser is attached to the boiling flask and is clamped in an upright postion, the "reflux position", and cooling water is circulated to cause the vapours to condense as they rise up the condenser and thus prevent them from escaping.
- The upper level of the vapours in the condenser can often be seen as a reflux line.
- The direction of flow of the water should be such that the condenser will fill with the cooling water; water should enter the condenser at the bottom and leave from the top.

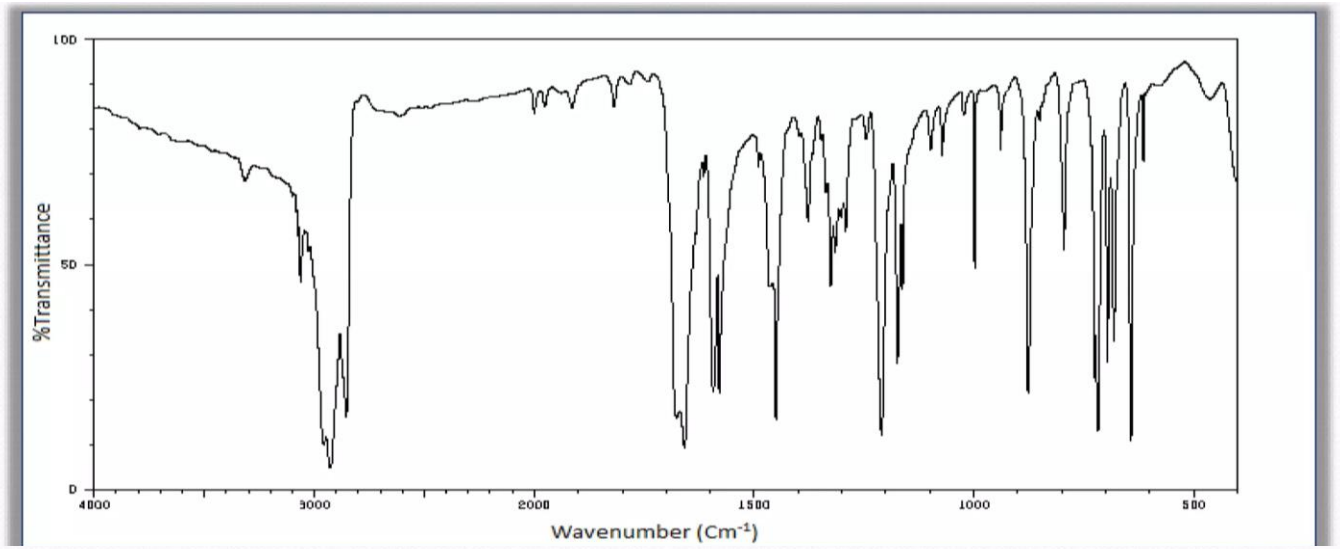


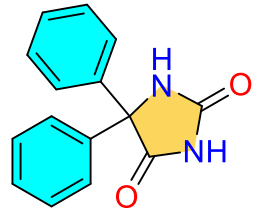
Heating under Reflux

IR Spectrum of Benzil vs Phenytoin

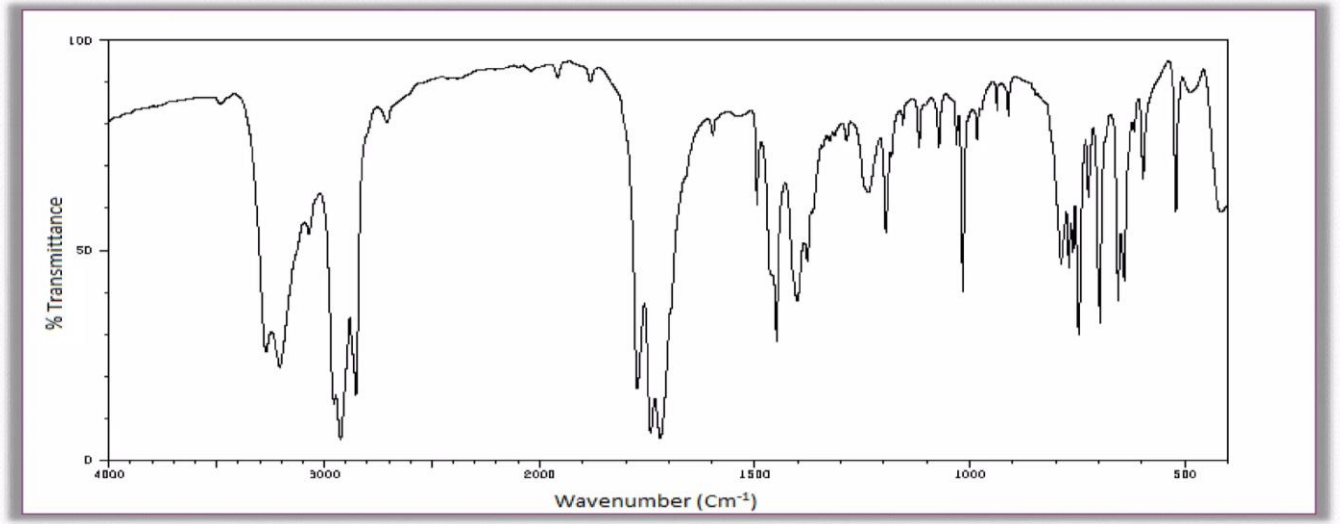


Benzil

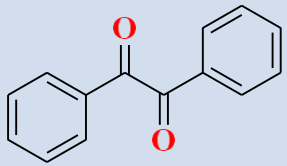
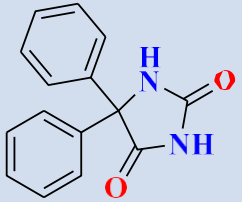




Phenytoin



Calculation

Feature	Benzil	Phenytoin
Chemical structure		
Chemical formula	(C6 H5 CO)2 or (PhCO)2	C15H12N2O2
Molecular weight	210.23 Da	252.09 Da

%Yield = (actual wt/th.wt)*100

Requirements

Materials

Benzil
Urea
KOH
EtOH
H_2SO_4 (conc.)

Glassware

Round Bottom Flask (100ml)
Heating mantle
Reflux condenser
Magnetic stirrer bar

Procedure

1. Prepare a **KOH** solution by dissolving 2.5 g of KOH flakes in 3 ml DW.
2. Weigh 0.36 g of **Urea** crystal on the balance.
3. Weigh 0.6 g of **Benzil**.
4. Mix all the three components in a round bottom flask, add 6ml of 95% ethanol and then start refluxing with continous stirring for 2 hrs.
5. Cool the reaction mixture and perform filtration to remove insoluble impurities.
6. The remaining red solution is acidified by dropwise addition of 6M H_2SO_4 (2-3 ml) to precipitate the product as a white solid, which is removed by filtration, washed with cold water, and dried to give the product that is recrystallized by ethanol.
7. **Dry** the pure product and **weigh**, then **calculate** the %yield.