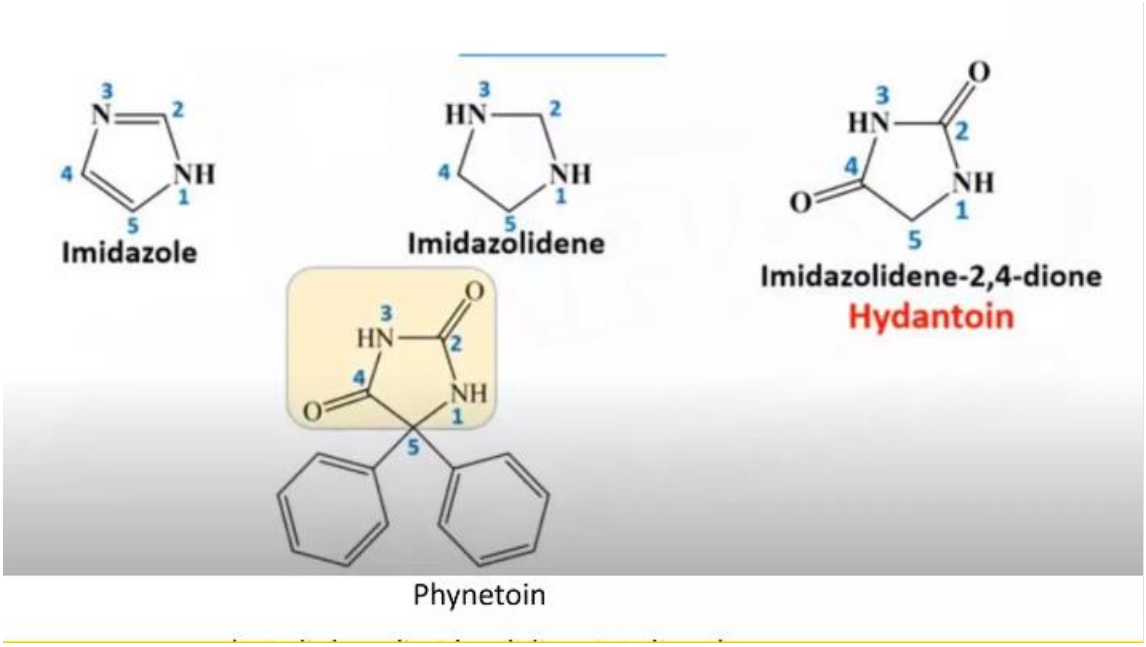
Preparation of (Dilantin) Phenytoin from Benzil by Ultrasound Irradiation

Dilantin is a brand-name drug on the market that is an anti-epileptic drug with the generic name phenytoin.

In 1838, the German chemist, Justus Liebig reported the discovery of Dilantin (Phenytoin) thin was first synthesized by German physician Heinrich Biltz in 1908. In 1938, outside scientists including H. Houston Merritt and Tracy Putnam discovered phenytoin's usefulness for controlling seizures.



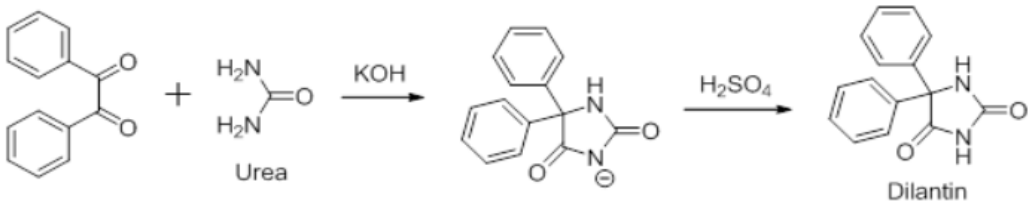
IUPAC Name: 5,5-diphenylhydantoin or 5,5-diphenylimidazolidin-2,4-dione

Phenytoin is synthesized in two different ways:

The first involves a base-catalyzed addition of urea to benzil followed by a benzilic acid rearrangement (1,2 phenyl migration) to form the desired product. This is known as the Biltz Synthesis of phenytoin.

The second is prepared by condensation of benzil and urea under reflex condensation to give the heterocyclic compound Pinnacol. When the pinacol is treated with sodium hydroxide it's rearrangement to produce phenytoin as sodium salt thin add acid to give phenytoin as a crude product.

Phenytoin can be produced with ease from benzil and urea under basic conditions, as shown in the reaction below.



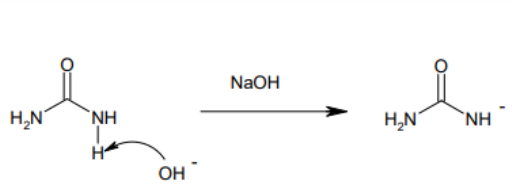
Using ultrasound irradiation technique

Ultrasonic irradiation, as a new technology, has been widely used in chemical synthesis. When an ultrasonic wave passes through a liquid medium, a large number of microbubbles form, grow, and collapse in a very short time of about a few microseconds, an effect that is called ultrasonic cavitation.

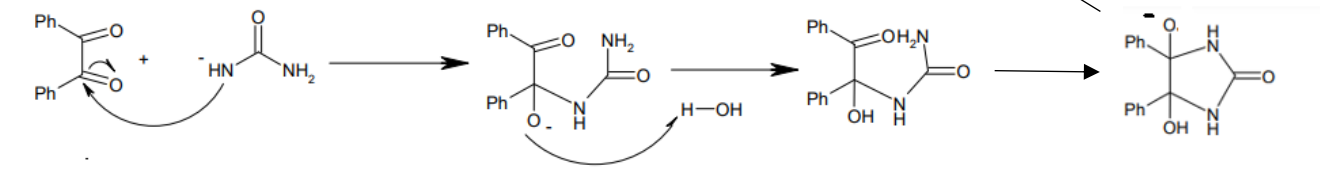
Ultrasonic irradiation has been considered a clean and useful protocol in organic synthesis during the last three decades, compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time, or milder conditions under ultrasonic irradiation.

Reaction Mechanism

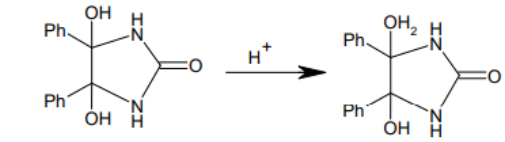
Step1 urea + OH^-



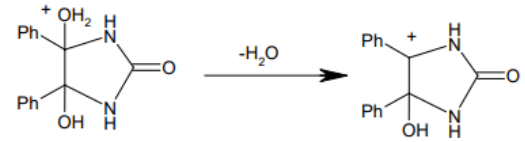
Step 2: Nucleophilic attack on carbonyl carbon



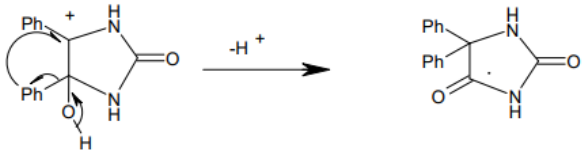
Step 3: Protonation of the OH group



Step 4: Elimination of water



Step 5: Rearrangement and deprotonation



Procedure:

Place the 0.005mol sample of crude benzil in a round-bottomed flask with 0.009mol of urea, 15mL of absolute ethanol, and 0.0025mol sodium hydroxide, and the reaction mixture was exposed to ultrasonic irradiation at room temperature for 15min. Cool the reaction mixture before adding 10 mL of water. (If the solution is not clear, remove the suspended solids by filtration.) Then, cautiously acidify the clear solution with concentrated hydrochloric acid. Collect the product by vacuum filtration and wash thoroughly with water. Recrystallize the product from ethanol, weigh it dry, and calculate the yield.