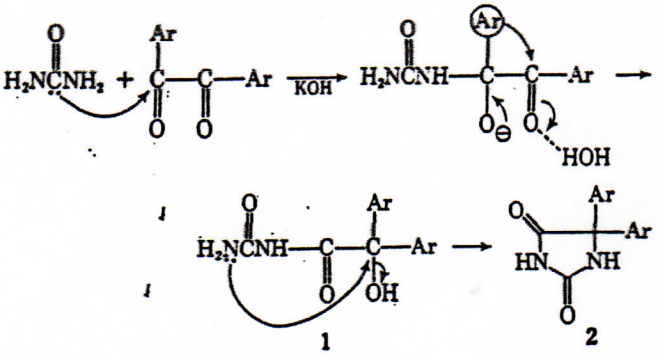
Reference : JCE Vol 63 N°7 Juillet 86 p 650

The Synthesis of 5, 5′-Diphenylhydantoin

A Novel Benzil-Benzilic Acid Rearrangement

Marvin C. Pankaskie and LaVerne Small
College of Pharmacy, University of Nebraska Medical Center, Omaha, NE 68105

The application of organic chemistry to the large-scale commercial production of biologically active, medicinal agents has in many cases resulted in the discovery of new and potentially useful reactions or reaction products, using simple and easily obtainable starting materials. The synthesis of hydantoins, such as 5,5′-diphenylhydantoin (phenytoin), from their corresponding 1,2-diketones illustrates one such novel reaction that avoids the use of sodium cyanide characteristic of more classical methods of hydantoin synthesis. The mechanism of this transformation closely resembles that of the benzil-benzilic acid rearrangement, except that instead of using hydroxide or alkoxide anion as the nucleophile, urea is used to generate the ureide intermediate **1**, which then undergoes cyclization to the hydantoin **2**.



[1] Blitz, H.; Seydel, K. *Ber.* **1911**, *44*, 411.

[2] The small amount of alkali insoluble material is likely the diureide of diphenylacetylene, while the hydantoin (pK_a 8.3) remains in solution as its potassium salt.

[3] Philip, J.; Holcomb, I.; Fusari, S. "Analytical Profiles of Drug Substances"; Florey, K., Ed.; American Pharmaceutical Association: Washington, 1984; pp 417–438.

Although usually applied to the synthesis of aryl-substituted diphenylhydantoins, it can also be carried out using aliphatic diketones or keto acids.

Experimental

Materials

benzil, reagent grade
ethanol, 95%
potassium hydroxide
sulfuric acid, 6*N*
urea

Apparatus

round-bottom flask, 250 ml
reflux condenser
heating mantle + voltage regulator
vacuum filtration apparatus
melting point apparatus

Procedure[1]

Dissolve 10.1 g (0.05 mol) of benzil, and 6.0 g (0.1 mol) of urea in 100 ml of ethanol in a 250-ml round-bottom flask, and add to this a solution of 16.5 g (0.3 mol) of potassium hydroxide in 20 ml of water. After refluxing the mixture for 2.5 h, the flask is cooled and the solids[2] filtered off. The alkaline filtrate is cooled in an ice-water bath and slowly acidified with 6*N* sulfuric acid to pH 3, during which the hydantoin precipitates out of solution. The product is filtered and air dried to yield 5,5′-diphenylhydantoin (phenytoin), mp 295–298°C with decomposition.[3] Recrystallization can be accomplished from 95% ethanol, although the product isolated by acidificaton of the filtered reaction mixture is usually better than 95% pure. If time and instrument availability permits, the final product can be subjected to tests for identification (IR, UV, and NMR spectroscopy) and purity (colorometric, titrimetric, or chromatographic analysis) and compared to authenic material obtained commercially.[3]