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Application of Phase Transfer Catalyst for Synthesizing of 5, 5-diphenylimidazolidine-2,4-dione as a Famous Anticonvulsant Drug

Abbas Ahmadi*, Babak Nahri-Niknafs, Mohammad Hadi Riahi

Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj Branch, Karaj, Iran.

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Abstract

Epilepsy is a major neurological disorder in the world and most epileptics are currently controlled by a variety of drugs. 5, 5-diphenylimidazolidine-2,4-dione (Phenytoin, **I**) is a widely used antiepileptic drug. It has been synthesized previously by different methods in some solvents. In this work, **I** was synthesized from the condensation of benzil and urea in ethanol and water by application of phase transfer catalyst and without it. Results indicated that higher yield was obtained when the catalyst used.

Keywords: *Phenytoin, 5,5-diphenyl-2,4-imidazolidinedione, Benzil, antiepileptic.*

Introduction

Epilepsy is a medical condition that produces a variety of mental and physical functions. It is also called a seizure disorder. It happens when clusters of nerve cells in the brain signal abnormally, which may briefly alter a person's consciousness movements or actions [1]. Antiepileptic drugs (AEDs) are those which decrease the frequency and/or severity of seizures in people with epilepsy. The older term, anticonvulsant drug, is still sometimes used as a synonym for AED but is less accurate because many seizures do not involve convulsive movements [2, 3].

Phenytoin (5,5-diphenylhydantoin, Dilantin, I) is a three-ringed molecule with a reactive urea component that has been an essential pharmacological tool since 1938, when discovered its anti-epileptic properties. The discovery of phenytoin revolutionized the treatment of epilepsy due to its anti-sedative effects, which offered patients an alternative to the previously used phenobarbitols, which yield sedation and other behavioral side

***Corresponding author:** Dr. Abbas Ahmadi, Associate Professor, Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj branch, P.O. Box: 31485-313, Karaj, Iran. E-mail: a-ahmadi@kiau.ac.ir. Tel/Fax: +98-26-34403575.*

effects [4, 5]. Although the exact mechanism by which phenytoin combats epileptic seizures is unknown, leading theories suggest that the molecule lowers the efficacy of sodium, potassium adenosine triphosphatase pumps in the brain which thus counters electrical hyperexcitability of neurons [6].

Phenytoin has served as a pillar of neurological treatment since 1938, and is still widely used today. It was first synthesized by German chemist in 1908 [7] and involves the reflux of urea and benzil in an alkaline solvent which allows a condensation reaction and phenyl shift to occur [8-12].

In this research, condensation reaction of urea and benzil in ethanol and water (as solvents) were investigated for synthesizing of phenytoin by using of phase transfer catalyst and without it and the results compared together concerning to yield and rate of reaction.

Experimental

Materials and Instruments

All chemicals and solvents were obtained from E-Merck and used without further purification. All melting points are uncorrected and taken with an Electrothermal melting point apparatus (Electrothermal Eng. Ltd, Essex, UK). IR spectra were determined in KBr on a Shimadzu Dr-8031 instrument. The ^{1}H and ^{13}C-NMR spectrums of the synthesized compounds were measured in DMSO and TMS as the internal standard using a Varian Mercury 400, 400MHz instrument. All Chemical shifts were reported as δ (ppm) values. The Mass Spectra were recorded on a LCQ ion trap mass spectrometer (Thermo Fisher. San Jose.CA, USA), equipped with an EI source.

Synthesis of phenytoin by using of ethanol as solvent

a) *Without catalyst [13]*

Benzil (500 mg), urea (0.25 g), 90% ethanol (7.5 mL) and 30% (wt./wt.) aqueous solution of NaOH (1.3 mL) were added to a round bottom flask and refluxed for 48 hour. Reaction was monitored by TLC (standard was benzil diluted with dichloromethane). Upon reaching completion reaction was quenched by pouring solution into 12 mL cold distilled water and acidification slowly by concentrated HCl dropwise until the pH of the filtrate is 2-3. Reaction was put on ice and cooling yielded a precipitate. Product was collected by vacuum filtration and rinsed with cold distilled water. Product was then re-crystallized (95% ethanol) to yield a powdery whitish-yellow solid and was collected by vacuum filtration (m.p 297-299.5 oC, Yield 51%).

b) *With catalyst*

Benzil (500 mg), urea (0.25 g), tetrabutyl ammonium bromide (phase transfer catalyst, 20 mg), 90% ethanol (7.5 mL) and 30% (wt./wt.) aqueous solution of NaOH (1.3

mL) were added to a round bottom flask and refluxed for 1 hour. Reaction was monitored by TLC (standard was benzil diluted with dichloromethane). Upon reaching completion reaction was quenched by pouring solution into 12 mL cold distilled water and acidification slowly by concentrated HCl dropwise until the pH of the filtrate is 2-3. Reaction was put on ice and cooling yielded a precipitate. Product was collected by vacuum filtration and rinsed with cold distilled water. Product was then re-crystallized (95% ethanol) to yield a powdery whitish-yellow solid and was collected by vacuum filtration (m.p 298-299 oC, Yield 68.4 %).

Synthesis of phenytoin by using of water as solvent

a) *Without catalyst [14]*

Benzil (395 mg), urea (214 mg), 30% (wt./wt.) sodium hydroxide solution (1.5 mL) and distilled water (6 mL) were placed in a 25 mL round bottom flask and refluxed for 72 hours. After cooling to room temperature, the reaction mixture was poured into 10 mL of cooled distilled water with stirring. It was allowed to stand for 15 minutes and filtered under vacuum to remove the insoluble by-product. The filtrate thus obtained was cooled and acidified by using concentrate hydrochloric acid until the pH of 2-3. The precipitates obtained was collected by vacuum filtration and rinsed with cold distilled water (m.p 296-300 oC, Yield 41%).

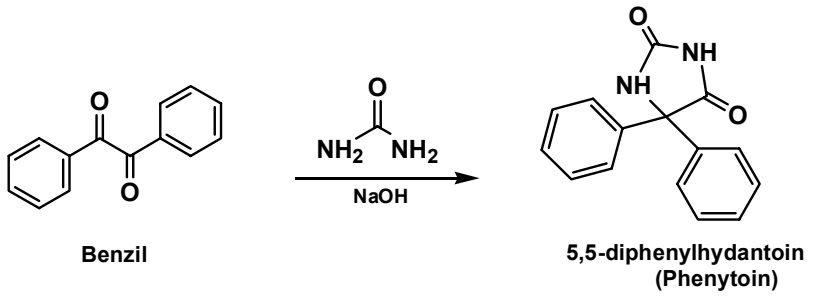
a) *With catalyst*

Benzil (395 mg), urea (214 mg), tetrabutyl ammonium bromide (phase transfer catalyst, 20 mg), 30% (wt./wt.) sodium hydroxide solution (1.5 mL) and distilled water (6 mL) were placed in a 25 mL round bottom flask and refluxed for 2 hours. After cooling to room temperature, the reaction mixture was poured into 10 mL of cooled distilled water with stirring. It was allowed to stand for 15 minutes and filtered under vacuum to remove the insoluble by-product. The filtrate thus obtained was cooled and acidified by using concentrate hydrochloric acid until the pH of 2-3. The precipitates obtained was collected by vacuum filtration and rinsed with cold distilled water (m.p 296-299 oC, Yield 55%).

Results and discussion

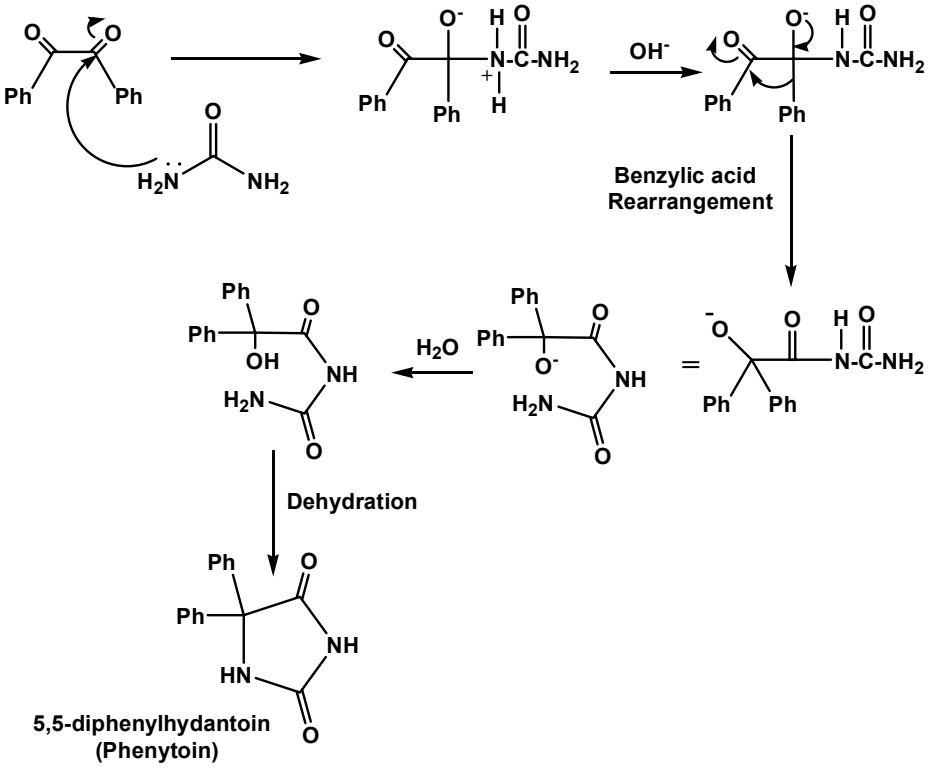
Epilepsy is one of the most common neurological disorders in the world's population and characterized by recurrent seizure attacks [15]. Many drugs have been synthesized for control it but because existing significant side-effects and narrow therapeutic properties, they have shown some difficulties to formulate. For example, to exert its anticonvulsant therapeutic effect, the drug must reach its receptors in the central nervous system (CNS). Yet, many of the drugs exhibit physicochemical and protein-binding properties that would not permit crossing of the blood-brain barrier (BBB) [16].

Phenytoin is one of the most widely used drugs in the therapy of epilepsy. It was synthesized by condensation of benzil and urea in presence of 30% NaOH solution by using 90% ethanol and water as solvents (Scheme 1) [13].



Scheme 1. Schematic synthesis of phenytoin by condensation of benzil and urea**.**

The mechanism of this reaction begins with the nucleophilic attack of a urea nitrogen atom on one of the carbonyls of benzyl (Scheme 2) [17].



Scheme 2. Reaction mechanism of phenytoin synthesis.

The loss of a proton from the quaternary nitrogen atom produces an intermediate containing a ketone and an oxyanion. Then, this intermediate undergoes the classic benzilic acid rearrangement. In this reaction, the benzilic acid rearrangement precedes through a 1,2-phenyl migration to produce an amide and a tertiary alkoxide in the resulting

intermediate. Finally, dehydration produces the 5,5-diphenylhydantoin product. The progression of the reaction was monitored by TLC, where the more polar phenytoin eluted earlier than the less polar benzil starting product [17]. Although the obtained yield and rate of this reaction is 51% (with ethanol as solvent) and 41 % (with water as solvent), literature suggests that typical yields for this reaction (with both of solvents) rarely exceed 64% [14, 18, 19] due to the creation of multiple produces (diphenylhydantoin and diphenylthiohydantoin) [20]. Considering these alternative yields, our work can be considered more successful for increasing the yield of reaction by using a phase transfer catalyst (tetrabutyl ammonium bromide).

The results indicated that application of this catalyst could modify rate and yield of reaction with both of solvents which probably concern to increasing the solubility of starting materials in the solvents.

Conclusion

It can be concluded that application of phase transfer catalyst enhance the rate and yield of reaction for synthesizing of phenytoin which considered as two major parameters for economically beneficial production of this drug in large scale.

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