



Influence study of catalysts and solvents on the synthesis of 5,5-diphenyl-2-thiohydantoin

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Abstract : Heterocyclic nitrogen compounds such as phenytoins or hydantoins and thiohydantoins are bioactive molecules which have often aroused research infatuation both in terms of synthesis and in terms of the study of their properties and applications in various fields such as pharmacy, biology, organic synthesis or industry. In the aim to enhance the Blitz's reaction, 5,5-diphenyl-2-thiohydantoin (DPTH) was synthesized by condensation of benzil with thio-urea, in alkaline solution. Benzil was synthesized from benzaldehyde through benzoin condensation. A variety of catalysts and solvents have been explored in the synthesis of DPTH. The structures of compounds obtained have been elucidated using spectral data (¹H NMR and ¹³C NMR) and their melting point. The best reaction yields (83 to 93%) were obtained for DPTH in absolute alcohol in the presence of strongly basic media but with the glycol-thioureid. The mixtures of NaOH/aniline and aniline/H₂SO₄ produced only the DPTH (79 and 67% respectively) without other product. Syntheses with mixtures of catalysts are also interest in terms of stereospecificity.

Key-words : Synthesis, benzil, 5,5-diphenyl-2-thiohydantoin, catalyst influence, Biltz reaction.

Introduction

Heterocyclic molecules play an important role in human life. Synthetic heterocyclic compounds are very useful in pharmaceuticals, chemotherapeutic agents, dyestuffs, photographic, co-polymers and other products¹⁻³. Their preparation methods from the main, historical ones such as the Bucherer–Bergs⁴, or Biltz⁵ syntheses to more modern ones, such as multicomponent reactions (MCRs), which enabled libraries of hydantoinic compounds to be obtained through simple routes.^{6,7} Phenytoin or hydantoin is used to treat various types of convulsions and seizures. It acts on the brain and nervous system in the treatment of epilepsy and to damp the unwanted, runaway brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage gated sodium channels⁸. Directly associated with the structure of hydantoin, there is that of 2-thiohydantoin (2-thioxo-imidazolidin-4-one according to IUPAC) obtained by replacing the oxygen in position 2 with sulfur. The thiohydantoin was obtained similarly to hydantoin, but in the presence of thio-based reactants, or by transformation of the hydantoin scaffold by common thionation reactions (e.g., Lawesson's method). Among thiohydantoin, 2-thiohydantoin is widely known for their various pharmaceutical applications⁹. Reviews on their preparation were already reported^{10,12}. In order to enhance and improve their synthesis, the development of new synthetic methods leading to thiohydantoin and their derivatives has attracted much attention.

The present study involves the improvements and variations of the synthetic conditions of 5,5-diphenyl-2-thiohydantoin with exploring the catalysts and solvents impact on the yield of products. Synthesized compounds were characterized by physical properties, elemental analysis, ¹H and ¹³C NMR spectroscopy.

Experimental

Reagents

Marketed by the Sigma-Aldrich, Acros Organic, Janssen Chimica, Fluka AG-Buchs SG companies, ... the substrates, reagents, catalysts and solvents were used directly without any other purification after their obtaining. As substrates, we used benzaldehyde then benzil; reagents are sodium cyanide and thiourea. Catalysts such as nitric acid, cupric sulfate, soda, potash, aniline, hydrochloric acid, sulfuric acid, sodium methanolate, potassium tert-butoxide and solvents as pyridine, 95° ethanol and then absolute ethanol were used.

Physico-chemical characterization

Some theoretical properties based on the design, pharmacokinetics and drug availability properties rules^{13,14} were explored before the synthesis of the compound. The temperatures (or melting points) (T_f) of the synthesized products were determined using a Heizbank apparatus, Wagner & Munz (KOFER system type WME) and were not corrected. ¹H proton and ¹³C carbon nuclear magnetic resonance (NMR) spectra were recorded using a spectrophotometer Brüker at frequencies of 300-400 MHz and 75-100 MHz respectively. The measurements were carried out on samples dissolved in deuterated dimethylsulfoxide (DMSO) or deuterated chloroform (CDCl₃) with tetramethylsilane taken as a reference. The chemical shifts (δ) are given in parts per million (ppm). The multiplicity of signals is given by singlet (s), doublet (d), multiplet (m), etc.

Methods

Before being used as a substrate, the benzil was prepared by the benzoin condensation reaction according to the methods (A and B) described by Ashnagar *et al.*⁸

A- In a 1000 mL round-bottomed flask, ethanol (200 mL 95%), benzaldehyde (150 g, 142.5 mL, 1.41 mol) and a solution of sodium cyanide (15 g) in water (150) were placed and refluxed for 3 hours. Then, the contents of the flask were cooled in an ice bath. Benzoin was precipitated as a solid material and collected over a Buchner funnel. It was washed several times with cold distilled water to remove the excess sodium cyanide. A second batch of benzoin was obtained by heating the mother liquor on a hot plate. The batches were added together and recrystallized from 95% ethanol. Pure benzoin was obtained as a white crystalline material.

Benzil was obtained from benzoin according to the following protocol

B- Benzoin (50 g, 0.235 mol) was placed in a 1000 mL Erlenmeyer flask and concentrated nitric acid (250 mL) was added into it in a fumecupboard. The mixture was heated on a hot plate with occasional shaking until all

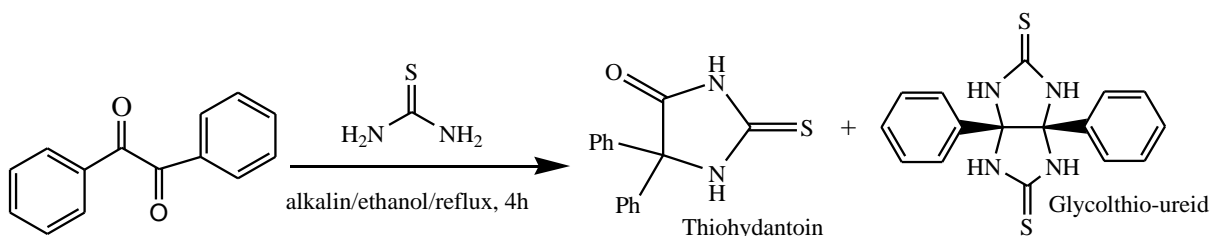
the red coloured nitrogen oxide gas was evolved (about 2 hours). The mixture was transferred to another 2000 mL Erlenmeyer flask which contained 1000 mL distilled water and stirred vigorously until the oil solidified as a yellow crystalline material. It was filtered over a Buchner funnel and washed with a liberal quantity of cold water until all the excess HNO₃ was removed. The solid material was recrystallized from 95% ethanol which resulted yellow needle crystalline material

Synthesis of 5,5-diphenyl-2-thiohydantoin (thiophenytoin)

Thiophenytoin is synthesized (scheme 3) by condensation of benzil with thiourea according to the protocol of Elarfi et al. (2012)¹⁵ with a variation of some catalysts (alkaline solutions) and solvents (ethanol 95° and absolute ethanol).

In a round-bottomed flask equipped with a reflux condenser, a mixture of benzil (0.025 mol), urea or thiourea (0.05 mol) **with a suitable alkaline solution** and 75 mL of ethanol were placed.

The mixture was heated under reflux for 4 hours. After cooling to room temperature, the reaction mixture was poured into 125 mL of cold water and mixed thoroughly. The reaction mixture was allowed to stand for 15 min and it was filtered under suction. Then the filtrate was acidified with concentrated hydrochloric acid and the resulting precipitate was filtered and washed with water. The crude products were recrystallized from ethanol 95°.



Scheme 1 : Synthetic route

Results and discussion

One of our objectives being the valorization of the Biltz's reaction, we used in this work the classical synthesis method (at reflux) to obtain thiohydantoin from the reaction between benzil and thiourea in the presence of several bases as the catalysts in ethanol 95° or absolute ethanol. Benzil and thiohydantoin showed physical properties compatible with reasonable pharmacokinetics and advantageous.

Benzil : molecular weight 210.22 ($M < 500 \text{ g.mol}^{-1}$), lipophilicity 3.38 ($C.\log P < 5$), numbers of hydrogen bond acceptor (2) and donors (0).

5,5-diphenyl-2-thiohydantoin : molecular weight 268.33 ($M < 500 \text{ g.mol}^{-1}$), lipophilicity 2.28 ($C.\log P < 5$), numbers of hydrogen bond acceptor (4) and donors (2).

This benzil used as a substrate in this reaction is obtained by benzoin condensation reaction with a good yield (87.17%) but lower than that (89%) obtained in literature⁸. In terms of melting point, the work of Pavia et al. (2011)¹⁶ and those of Ashnagar et al. (2009)⁸ confirm the characterization of this product (95°C and 92°C respectively) against 94° C obtained.

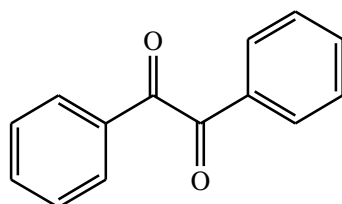


Figure 1 : Structure of benzil

Clear yellow crystals : R : 87,17%; T_f : 94 ± 1°C. ¹³C NMR (CDCl₃, 100 MHz, δ (ppm)) : 195.1 (C=O), 138.5 ; 133.7 ; 129.5 ; 129.1 (C-Ar). ¹H NMR (CDCl₃, 400 MHz, δ (ppm)) : 7.47 (m, 4H_{Ar}) ; 7.59 (m, 2H_{Ar}) ; 7.85 (m, 4H_{Ar}). Ar = aromatic.

Then, thiohydantoin (thiophenytoin) (Figure 2) is obtained with good yields ranging from 67 to 81% in ethanol 95° and from 83 to 93% in absolute alcohol (Table 1).

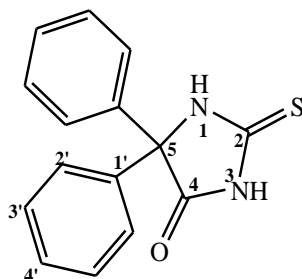


Figure 2 : Structure of 5,5-diphenyl-2-thiohydantoin (thiohydantoin)

Table 1 : Yield (in%) of thiophenytoin according to catalysts and solvents

Solvents	Catalysts				
	NaOH 30%	KOH 30%	t-ButOK	Aniline/KOH (a)	Aniline/H ₂ SO _{4conc} (b)
EtOH 95°	76.31	73.07	81.05	79.27	67.54
EtOH (absolute)	85.54	83.11	93.17	-	-

a, 5mL/5mL (v/v) et b, 15mL/2mL (v/v).

Characterization of 5,5-diphenyl-2-thiohydantoin

- Synthesis with 15 mL of NaOH 30%

White crystal : m.p : 232 ± 1°C. ¹³C NMR (DMSO-d₆, 100 MHz, δ : ppm) : 181.35 (C=S) ; 175.11 (C=O) ; 138.31 (C_{1'}) ; 128.41 (C_{2'}) ; 128.75 (C_{3'}) ; 126.52 (C_{4'}) ; 72.90 (C_{5'}). ¹H NMR (DMSO-d₆, 400 MHz, δ : ppm) : 12.2 (s, 1H, H-N₃) ; 11.36 (s, 1H, H-N₁) ; 7.3-7.6 (m, 10H, H-Ar).

- Synthesis with 15 mL of KOH 30%

White crystal : m.p : 231 ± 1°C. ¹³C NMR (DMSO-d₆, 100 MHz, δ : ppm): 181.25 (C=S) ; 175.15 (C=O) ; 138.31 (C_{1'}) ; 128.41 (C_{2'}) ; 128.75 (C_{3'}) ; 126.53 (C_{4'}) ; 72.91 (C_{5'}). ¹H NMR (DMSO-d₆, 400 MHz, δ : ppm): 12.2 (s, 1H, H-N₃) ; 11.36 (s, 1H, H-N₁) ; 7.3-7.5 (m, 10H, H-Ar).

- Synthesis with 5 mL of solution t-BuOK

White crystal, m.p : 232 ± 1°C. ¹³C NMR (DMSO-d₆, 100 MHz, δ : ppm) : 181.25 (C=S) ; 175.15 (C=O) ; 138.31 (C_{1'}) ; 126.82 (C_{2'}) ; 128.75 (C_{3'}) ; 126.50 (C_{4'}) ; 72.91 (C_{5'}). ¹H NMR (DMSO-d₆, 400 MHz, δ : ppm) : 12.2 (s, 1H, H-N₃) ; 11.4 (s, 1H, H-N₁) ; 6.9-7.6 (m, 10H, H-Ar).

- Synthesis with 5 mL of aniline and 5 mL of KOH 30%

White crystal, m.p : 232 ± 1°C. ¹³C NMR (DMSO-d₆, 100 MHz, δ : ppm): 181.30 (C=S) ; 175.25 (C=O) ; 138.34 (C_{1'}) ; 128.39 (C_{2'}) ; 128.72 (C_{3'}) ; 126.53 (C_{4'}) ; 72.91 (C_{5'}). ¹H NMR (DMSO-d₆, 400 MHz, δ : ppm): 12.2 (s, 1H, H-N₃) ; 11.4 (s, 1H, H-N₁) ; 7.3-7.5 (m, 10H, H-Ar).

- Synthesis with 5 mL of aniline and after 1 hour for stirring 2 mL of H₂SO_{4conc} 97%.

White crystal, m.p : 232 ± 1°C. ¹³C NMR (DMSO-d₆, 100 MHz, δ : ppm): 181.25 (C=S) ; 175.14 (C=O) ; 138.31 (C_{1'}) ; 128.75 (C_{2'}) ; 129.59 (C_{3'}) ; 126.53 (C_{4'}) ; 72.90 (C_{5'}). ¹H NMR (DMSO-d₆, 400 MHz, δ : ppm): 12.2 (s, 1H; H-N3) ; 11.4 (s, 1H, H-N1) ; 7.0-7.9 (m, 10H, H-Ar).

Characterization of glycol-thioureid

The glycol-thioureid formed during certain reactions showed following spectral characteristics. Its yield has varied depending on the base and the alcohol used.

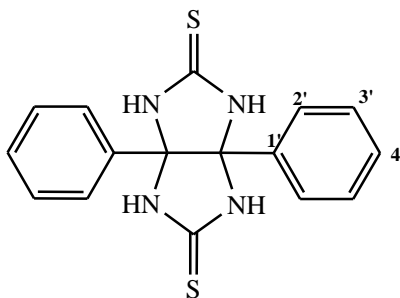


Figure 3 : Glycol-thioureid

White crystal, yield ~ 3 and 11%. ¹³C NMR (CDCl₃, 100 MHz, δ : ppm) : 182.43 (C=S), 89.86 (C sp³), 135.46 (C_{1'}) ; 127.62 (C_{2'}) ; 128.41 (C_{3'}) ; 126.82 (C_{4'}). ¹H NMR (CDCl₃, 400 MHz, δ : ppm) : 9.8 (s, 4H, H-N) ; 6.5-7.5 (m, 10H-Ar).

We have generally noticed during this study that the yields of all the products obtained with various catalysts in absolute alcohol are higher than their corresponding ones in ethanol 95°. This is because the aqueous medium causes dilution of the alkaline solution. It should be noted in this work that the best synthesis yield of thiohydantoin is obtained with potassium tert-butoxide (t-BuOK) in the presence of absolute ethanol (93.17%) but with the presence of the secondary product, glycol-thioureid even if in very low yield (<4%). Concurring results have been shown by Gbaguidi *et al.* (2011)¹⁷, but the reaction is performed in the presence of potassium hydroxide in dimethylsulfoxide (DMSO). Generally, the adduct product is present in all syntheses when a single catalyst is used. It should also and above all be pointed out that the syntheses made in the presence of a mixture of aniline and potash (KOH) then aniline and concentrated sulfuric acid (H₂SO_{4conc}) in ethanol 95° only led to the thiophenytoin, without side product, with good yields (79 and 67% respectively). According to our research, recent methods of mixing catalysts have not been thoroughly investigated. So, this method can be valued because it leads to a specific reaction. We deduced from these works that to orient the reaction towards the formation of thiophenytoin alone and with good yield (83-89%), it is necessary on the one hand to work in a strongly basic and less aqueous medium or to carry out the reaction with mixing the catalysts.

After the syntheses, we proceeded to the structural characterization of the products by spectrometric analysis methods. In the various ¹H NMR spectra of all the synthetic products obtained, we had singlets observed with chemical shifts δ between 11.3-11.4 and 12.2 ppm (2 x 1H) confirming the presence of the H-N_x in position 1 and 3 respectively. Aromatic protons (10H) appear as a multiplet between 6.9-7.9 ppm. These data obtained are in agreement with the results of Ghanbari *et al.* (2014)¹⁸. In the uncoupled ¹³C NMR spectra, we find peaks of carbonyl (C=O) and thiocarbonyl (C=S) carbons around the chemical shifts δ between 175.25 and 175.11 ppm then between 181.35 and 181.25 ppm respectively, peaks which are different from that C=O (δ = 195 ppm) of benzyl, the reaction substrate. Aromatic carbons are observed at chemical shifts between 125 and 140 ppm; as an example, the thiophenytoin obtained in the presence of t-BuOK shows peaks of benzene carbons at δ (ppm): 138.31 (C_{1'}); 126.82 (C_{2'}); 128.75 (C_{3'}); 126.50 (C_{4'}). Peaks which appear around 72.92-72.90 ppm correspond to that of the tetrahedral quaternary carbon (C_{5'}) of the ring formed. This also justifies the formation of the product because this type of Csp³ also did not exist in any substrates and reagents. This analysis is confirmed through the spectra of the products synthesized by Liton and Islam (2006)¹⁹ and Faghihi *et al.* (2002)²⁰. All physico-chemical properties and spectrometric analyses confirmed the structure of synthesis molecules studied.

Conclusion

In this work, thiohydantoin was synthesized with good yields by exploration of alkaline catalysts. We noted the role of the solvent that interacts in this reaction, absolute ethanol improves the yield compared to EtOH 95°. Syntheses with mixtures of catalysts are also of interest in terms of stereospecificity. In view of its observations, additional studies are planned exploring the mechanism of reactions with the mixture of catalysts.

Références

- 1- Sivakumar RP. Synthesis, Spectral Characterization and Biological activities of 1,3,5-Triazines based Mannich Base Compounds. *International Journal of ChemTech Research*, 2021,14(3): 343-354.
- 2- Ahluwalia VK, Kidwai M. *New Trends In Green Chemistry*, Anamaya publisher New Delhi, 2nd edition, 2007, 250: 5-18.
- 3- Ahluwalia VK. *Green Chemistry Environmentally Benign Reactions*, published by India books, 2nd edition, 2006, 1-10.
- 4- Bucherer HT, Lieb VA. Syntheses of Hydantoins. II. Formation of Substituted Hydantoins from Aldehydes and Ketones. *J. Prakt. Chem.*, 1934, 141: 5-43.
- 5- Biltz H. Constitution of the Products of the Interaction of Substituted Carbamides on Benzil and Certain New Methods for the Preparation of 5,5-Diphenylhydantoin. *Ber. Dtsch. Chem. Ges.*, 1908, 41: 1379-1393.
- 6- Hulme C, Bienaymé H, Nixey T, Chenera B, Jones W, Tempest P, Smith AL. Library Generation Via Postcondensation Modifications of Isocyanide-Based Multicomponent Reactions. *Methods Enzymol.*, 2003, 369: 469-496.
- 7- Hulme C, Ma L, Romano JJ, Morton G, Tang S-Y, Cherrier M-P, Choi S, Salvino J, Labaudiniere R. Novel Applications of Carbon Dioxide/MeOH for the Synthesis of Hydantoins and Cyclic Ureas Via the Ugi Reaction. *Tetrahedron Lett.*, 2000, 41: 1889-1893.
- 8- Ashnagar A, Gharib Naseri N, Amini M. Synthesis of 5,5-diphenyl-2,4-imidazolidinedione (Phenytoin) from Almond. *International Journal of ChemTech Research*, 2009, 1(1): 47-52.
- 9- Wang ZD, Sheikh SO, Zhang Y. A simple synthesis of 2-thiohydantoins. *Molecules*, 2006, 11: 739-750.
- 10- Savjani JK, Gajjar AK. Pharmaceutical Importance and Synthetic Strategies for Imidazolidine-2-thione and Imidazole-2-thione Derivatives. *Pak. J. Biol. Sci.*, 2011, 14: 1076-1089.
- 11- Metwally MA, Abdel-Latif E, Thiohydantoins: Synthetic Strategies and Chemical Reactions. *J. Sulfur Chem.*, 2012, 33: 229-257.
- 12- Muccioli GG, Poupaert JH, Wouters J, Norberg B, Poppitz W, Scribad GKE, Lambert DM. A rapid and efficient microwave-assisted synthesis of hydantoins and thiohydantoins. *Tetrahedron*, 2003, 59: 1301-1307.
- 13- Lipinski AC, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*, 2001, 46: 3-26.
- 14- Lipinski AC, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv. Rev.*, 1997, 23: 3-25.
- 15- Elarfi MG, Al-Difar HA, Elhag Ahmed ME. Synthesis of hydantoin and thiohydantoin. *Der Chemica Sinica*, 2012, 3(2): 299-300.
- 16- Pavia DL, Lampman GM, Kriz GS, Engel RG. A small scale approach to organic laboratory techniques. Brooks/Cole, Cengage learning, Canada, 3rd edition, 2011, 265-286.
- 17- Gbaguidi FA, Kpoviessi SDS, Kapanda CN, Muccioli GG, Lambert DM, Accrombessi GC, Mansourou M. and Jacques JH. A high yield synthesis of phenytoin and related compounds using microwave activation. *African Journal of Pure and Applied Chemistry*, 2011, 5(7): 168-175.
- 18- Ghanbari MM, Safari J. and Roohi Z. One-pot synthesis of imidazolidine-2-thiones, hydantoins and thiohydantoins under solvent-free and grinding conditions. *Open Access Library Journal*, 2014, 1(705): 1-5.
- 19- Liton AK, and Islam MR. Synthesis of hydantoin and thiohydantoin related compounds from benzil and study of their cytotoxicity. *Bangladesh Journal of Pharmacology*, 2006, 1(1): 10-15.

- 20- Faghihi K, Zamani K. and Mallakpour S. Synthesis and characterization of optically active poly(amide-imide)s with hydantoin and thiohydantoin derivatives in the main chain. Iranian Polymer Journal, 2002, 11(5): 339-347.

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