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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 (^{1}H NMR and ^{13}C 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/H_2SO_4 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.

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Introduction

Heterocyclic molecules play an important role in human life. Synthetic heterocyclic compounds are very useful in pharmaceuticals, chemotherapeutic agents, dyestuffs, photographics, co-polymers and other products[1-3].Their preparation methods from the main, historical ones such as the Bucherer−Bergs[4], or Biltz[5] 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 channels[8]. 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 thiohydantoins were obtained similarly to hydantoins, but in the presence of thiobased reactants, or by transformation of the hydantoin scaffold by common thionation reactions (e.g., Lawesson's method). Among thiohydantoins, 2-thiohydantoins are widely known for their various pharmaceutical applications[9]. 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 thiohydantoins 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, ^{1}H and ^{13}C NMR spectroscopy.

Experimental

Reagents

Marketed by the Sigma-Aldrich, Acros Organic, Janssen Chimica, Fluka AG-Buchs SGcompanies, ... 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 (KOFLER system type WME) and were not corrected. ^{1}H proton and ^{13}C 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 ($CDCl_3$) 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.

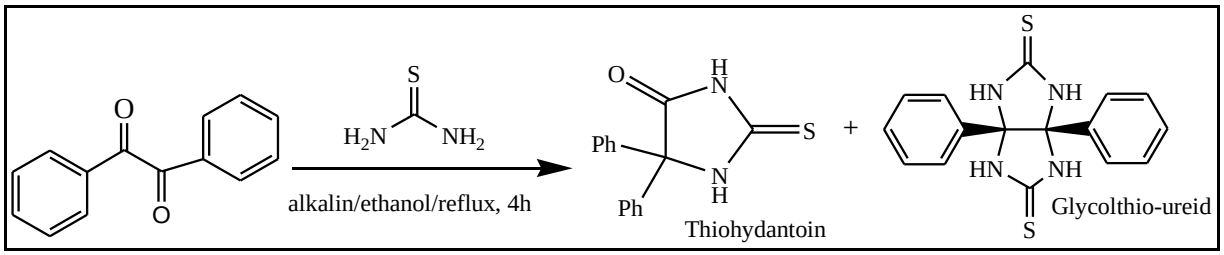
B- Benzoin (50 g, 0.235 mol) was placed in a 1000 mL Erlenmeyer flask and concentrated nitric acid (250 mL) was added into it in a fumecupboard. The mixture was heated on a hot plate with occasional shaking until all the red coloured nitrogen oxide gas was evolved (about 2 hours). The mixture was transferred 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 HNO_3 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 3 : 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 weigt 210.22 (M < 500 $g.mol^{-1}$), lipophilicity 3.38 (*C.logP*< 5), numbers of hydrogen bond acceptor (2) and donors (0).

5,5-diphenyl-2-thiohydantoin :molecular weigt 268.33 (M < 500 $g.mol^{-1}$), lipophilicity 2.28 (ClogP < 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 lowerthan that (89%) obtained in litterature[8].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.

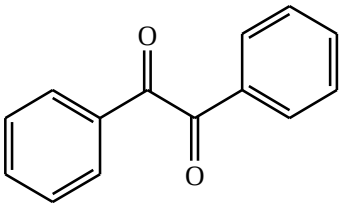


Figure 1 : Structure of benzil

Clear yellow crystals : R : 87,17%; T_f : 94 ± 1°C.**^{13}C NMR** ($CDCl_3$, 100 MHz, δ (ppm)) : 195.1 (C=O), 138.5 ; 133.7 ; 129.5 ; 129.1 (C-$_{Ar}$). **^{1}H NMR** ($CDCl_3$, 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).

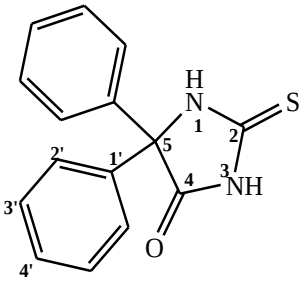


Figure 2 : Structure of 5,5-diphenyl-2-thiohydantoin (thiohydantoin)

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

Catalyseurs / Solvants	**NaOH 30%**	**KOH 30%**	**t-ButOK**	**Aniline/KOH (a)**	**Aniline/H_2SO_{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. **^{13}C 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 ($C_{5'}$). **^{1}H NMR**(DMSO-$_{d6}$, 400 MHz, δ : ppm) : 12.2 (s, 1H; **H**-N_3) ; 11.36 (s, 1H, **H**-N_1) ; 7.3-7.6 (m, 10H, **H**-Ar).

- Synthesis with**15 mL of KOH30%**

White crystal : m.p : 231 ± 1°C. **^{13}C 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 ($C_{5'}$). **^{1}H 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.**^{13}C 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 ($C_{5'}$).**^{1}H 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 ofaniline and 5 mL of KOH 30%**

White crystal,m.p : 232 ± 1°C.**^{13}C 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 ($C_{5'}$).**^{1}H 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*anilineand* after 1hour for stirring*2 mL of* H_2SO_{4conc}97%.**

White crystal,m.p : 232 ± 1°C.**^{13}C 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 ($C_{5'}$).**^{1}H 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.

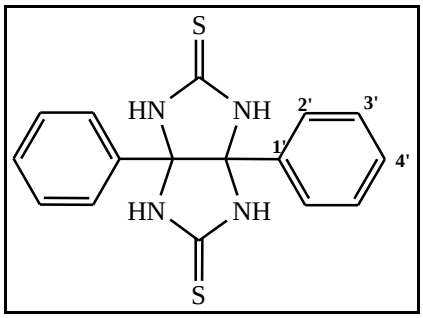


Figure 3 : Glycol-thioureid

White crystal, yield ~ 3 et 11%.**^{13}C NMR**($CDCl_3$, 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 ($C_{4'}$).**^{1}H NMR**($CDCl_3$, 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 (H_2SO_{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 ^{1}H 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-Nx 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 ^{13}C 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 srtucture 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.

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