Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [10] September 2023 : 189-193

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Synthesis, Characterization and Evaluation of Biological activity of 5, 5 - diphenyl imidazolidine - 2, 4 - dione

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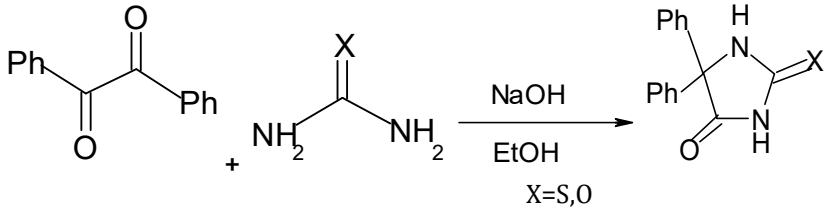
ABSTRACT
Phenytoin is the anticonvulsants class of drugs. The FDA approved phenytoin in 1939 for the treatment of epilepsy. Due to its narrow therapeutic index, the drug has use in the treatment of generalized tonic-clonic seizures, complex partial seizures, status epilepticus, trigeminal neuralgia and behavior disorders. The base catalyzed reaction between benzil, urea and acid, base is used for synthesis of phenytoin. This protocol gave rapid access to the phenytoin (5, 5-diphenylimidazolidine-2,4-Dione) compound in very good yield (> 70 %).
Keywords: *Phenytoin, Anti-fungal, urea, 5, 5-diphenylimidazolidine-2, 4-Dione, Plant pathogen*

Received 23.07.2023 Revised 21.08.2023 Accepted 21.09.2023

INTRODUCTION

Phenytoin (5,5-diphenylimidazolidine-2,4-Dione) is the prime example of anticonvulsant agent. Phenytoin (diphenyl Hydantoin or Dilantin) was first synthesized by Heinrich Biltz in 1908[1]. In 1938 H. Houston Merritt and Tracy Putnam discovered various uses of phenytoin. Phenytoin was synthesized by condensation of benzil and urea in presence of base (30% NaOH) and water as a green solvent. The extra 30% cost is calculated if solvent other than water is used. Removal of solvent after synthesis is most difficult and non-assured procedure. The reaction is proceeding via intramolecular cyclization to form an intermediate heterocyclic Pinacol, which on acidification yields phenytoin (Hydantoin) as a result of 1, 2-phenyl shift in Pinacol rearrangement reaction[3,4,5,8]. Using green solvent like water, synthesis of biologically active moiety with high percentage yield as well as purity is one of the objectives of green chemistry. Phenytoin is a first anticonvulsant agent acting as a sodium channel blocker. Phenytoin can also be used to control seizures occurring during neurosurgery when given at 100-200 mg intra-muscularly at 4 hours intervals. Phenytoin (PHT), sold under the brand name Dilatin among others, is an anti-seizures medication. It is used for the prevention of tonic-clonic seizures and focal seizures[2], but not absence seizures. The intravenous form is use for status an epileptic that does not improve with benzodiazepines. It may also be used for certain heart problems or neuropathic pain. It can be taken intravenously or by mouth. The intravenous form generally begins working within 30 minutes and is effective for 24 hours. Blood level can be measured to determine the proper dose. Phenytoin and its derivatives are important intermediates in the preparation of several amino acids[11] also they are the basic material of new generation of weather-proof high temperature stable epoxy resins[6]. Phenytoin derivatives are used in many consumer products like cosmetics, hair spray also utilized in medications and photographic films[7]. In reported work the synthesis of hydantoin or thiohydantoin by the reaction of Benzil, Urea or Thiourea in presence of Sodium Hydroxide as a base and water or ethanol as a solvent under reflux.



Reported Scheme: 1

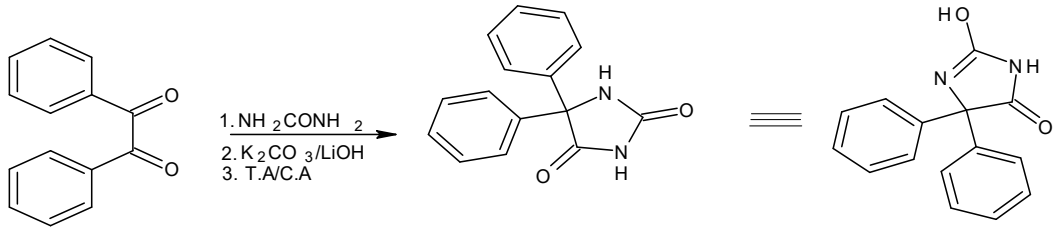
The recent environmental concerns, we devel oped the most economical, efficient and environmentally friendly protocol for the synthesis of 5, 5-diphenylimidazolidine-2, 4-dioneby using different bases like (potassium carbonate, calcium hydroxide, lithium hydroxide, sodium methoxide, sodium ethoxide) with organic acids such as tartaric acid and citric acid. The K2CO3 was reported as a green chemical base[9]. In reported work, used of sodium hydroxide as a base and hydrochloric acid. According to the hazards statements[10],sodium hydroxide and hydrochloric acid causes severe skin burns, eye damage (H314) and may also cause respiratory irritation (H335).This procedure becomes a newer approach to synthesis of 5, 5-diphenylimidazolidine-2, 4-dione which is a key important of this work.

MATERIAL AND METHODS

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed on silica coated glass plate with detection by UV light. ^{1}H NMR spectra were recorded with tetramethyl silane as the internal standard. ^{1}H NMR spectra were recorded at 500MHz on Bruker. Chemical shift (delta) is reported in ppm downfield from DMSO (d = 2.5 ppm) for ^{1}H NMR. The IR spectra were obtained on lambda scientific FTIR-7600 spectrophotometer using potassium bromide pellets. Melting points were recorded on Digital Melting Point Apparatus (Systronics EQ730).

GENERAL PROCEDURE FOR SYNTHESIS OF PHENYTOIN:

1 g (0.0047 mol) of benzil, 0.6 g (0.0095 mol) of urea, 15ml. conc. solution of base, 10 ml. ethanol and 15 ml of distilled water taken in round bottom flask, reflux in oil bath for 3-4 hours. After that reaction mixture cooling to room temperature, was poured into 30 ml cold water with stirring. It was allowed to stand for 10 minutes and filter it to remove the insoluble by-products. The filtrate thus obtained was cooled and acidified by using concentrated acid solution. The precipitates obtained were separated by filtration. The crude product obtained was washed with cold water, recrystallized with ethanol.



Reaction Scheme 2: Synthetic pathway to produce 5, 5-diphenylimidazolidine-2,4-Dione.

Table 1: Comparative Study of 5, 5-diphenylimidazolidine-2,4-Dione

Comp.	*Reactant*	*Reagent*	*Base*	*Acid*	*Time (min.)*	*M.P.(^{0}C)*	*Yield %*
1	Benzil	Urea	LiOH	Tartaric Acid	180-200	297-298	78
2	Benzil	Urea	K_2CO_3	Tartaric Acid	220-230	292-296	70
3	Benzil	Urea	NaOMe	Citric Acid	180-190	296-298	78
4	Benzil	Urea	Ca $(OH)_2$	Citric Acid	170-180	294-298	76
5	Benzil	Urea	NaOEt	Citric Acid	180-190	294-298	80

The Characterization of 5, 5-Diphenylimidazolidine-2, 4-Dione by FTIR, ^{1}H NMR and ^{13}C NMR as follows.

FTIR(KBr):3260,3200,1770,1745,1722,1486,1405,1015,780,760,720,685,650 cm^{-1}.

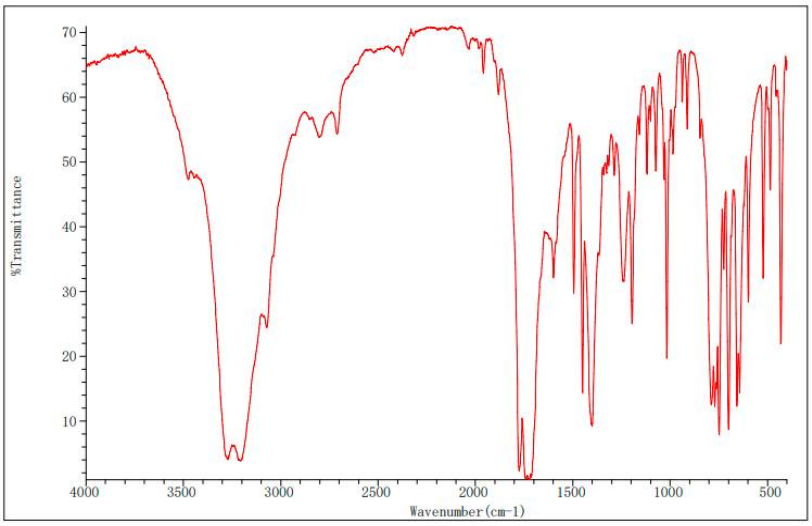


Fig 1: FTIR Spectrum

^{1}H NMR (500 MHz, DMSO-d_6)d: 11.15 (s, 1H), 9.35(s, 1H), 7.38(m,10 H)

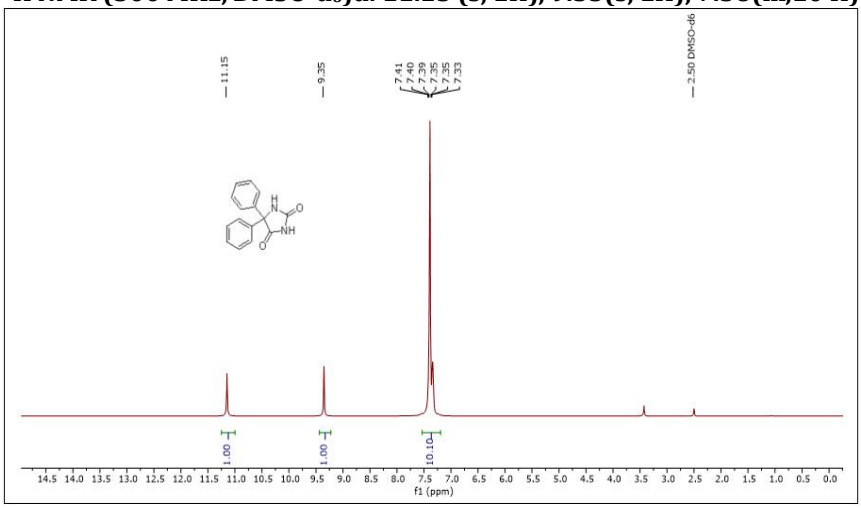


Fig 2:^{1}H NMR Spectrum

^{13}C NMR (126 MHz, DMSO-d_6) d: 174.91, 156.09, 139.99, 128.57, 128.10, 126.66, 70.30.

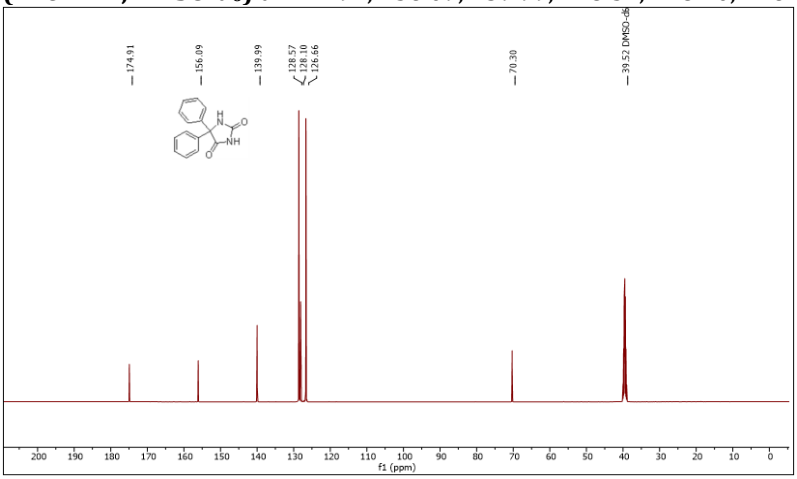


Fig 3:^{13}C NMR Spectrum

To check the anti-fungal properties of phenytoin compound. This phenytoin product was tested in Mahatma Phule Krishi Vidyapeeth, Rahuri, Department of Plant Pathology and Microbiology, laboratory

against some Plant Pathogens. This result indicates that, the Phenytoin shows anti-fungal properties on some plant pathogens. The plant pathogens were grown on potato dextrose agar and product was tested by Poison food technique. The result is given as follows.

Table 2: Antifungal activity of synthesized compound

Sr. No.	Name of Product	Plant Pathogen against which product is tested	Concentration of the product tested	Result
1.	Phenytoin (5,5-diphenyl-imidazolidine-2,4-dione)	*Macrophomina Spp.*	4 ppm	Inhibition zone was not observed.
			12 ppm	Inhibition zone was not observed.
			18 ppm	Inhibition of fungal growth was observed.
2.	Phenytoin (5,5-diphenyl-imidazolidine-2,4-dione)	*Aspergillus niger*	4 ppm	Inhibition of fungal growth was observed.
			12 ppm	Inhibition of fungal growth was observed.
			18 ppm	Inhibition zone was not observed.
3.	Phenytoin (5,5-diphenyl-imidazolidine-2,4-dione	*Aspergillus flavous*	4 ppm	Inhibition of fungal growth was observed.
			12 ppm	Inhibition of fungal growth was observed.
			18 ppm	Inhibition zone was not observed.

RESULT AND DISCUSSION

This is a modified procedure for synthesis of Phenytoin. The key point of this reaction is the used as LiOH, NaOMe, $Ca(OH)_2$, NaOEt and K_2CO_3 conc. base solution instead of NaOH. The citric acid and tartaric acid conc. acid solution are used instead of HCl **(Table 1).** The base LiOH, NaOMe, Ca $(OH)_2$, NaOEt shows good yield as well as less reaction time compared to K_2CO_3 which is weak base. The product Phenytoin were confirmed based on TLC, Melting point, FTIR, ^{1}H-NMR and ^{13}C-NMR data. Phenytoin was biologically active compound. We study here the anti-fungal properties of phenytoin against three plants pathogens. Different concentration of product solution tested against plant pathogens; it clearly shows zone of inhibition of fungal growth. The results indicate that the phenytoin has good anti-fungal properties **(Table 2).** We have developed highly efficient, eco-friendly newer protocol for the synthesis of Phenytoin. This protocol gives access to the synthesis of phenytoin derivatives by using different base and acid in very good yield in short reaction time. Phenytoin also shows anti-fungal properties against some plant pathogens.

CONCLUSION

We have developed highly efficient, eco-friendly newer protocol for the synthesis of Phenytoin. This protocol gives access to the synthesis of phenytoin derivatives by using different base and acid in very good yield in short reaction time. Phenytoin also shows anti-fungal properties against some plant pathogens.

ACKNOWLEDGEMENT

The authors are gratefully acknowledged to Dr. Shamama Parveen, President of RECWS Aurangabad and Dr. Shaikh Kabeer Ahmed, Principal Sir Sayyed College, Aurangabad, for providing laboratory facilities.

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CITATION OF THIS ARTICLE

Sachin S F, Surendra N. T.Synthesis, Characterization and Evaluation of Biological activity of 5, 5 - diphenyl imidazolidine - 2, 4 – dione. Bull. Env. Pharmacol. Life Sci., Vol 12[10] September 2023: 189-193.