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Application of green solvent in synthesis of thiophenytoins using aryl thioureas

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ABSTRACT

Phenytoin (5,5'-dipenylimidazolidine-2,4-dione) and Thiophenytoin (5,5-diphenyl-2-thioimidazolidine-4-one) are the prime examples of anticonvulsant agent. According to reported procedure, they are synthesized by condensation of benzil and urea in presence of base (30% w/v NaOH) using ethanol as solvent which itself acts as CNS stimulant. Removal of solvent after synthesis is most difficult and non-assured process. Therefore in the present work by application of green chemistry principles thiophenytoins were synthesized by condensation of benzil and sub. aryl thioureas in presence of base and water as green solvent. These compounds were characterized on the basis of its spectral (UV,IR, ^{1}H NMR) data.

Keywords: Thiophenytoin, Aryl thiourea, Green chemistry, Green solvent, Spectral study.

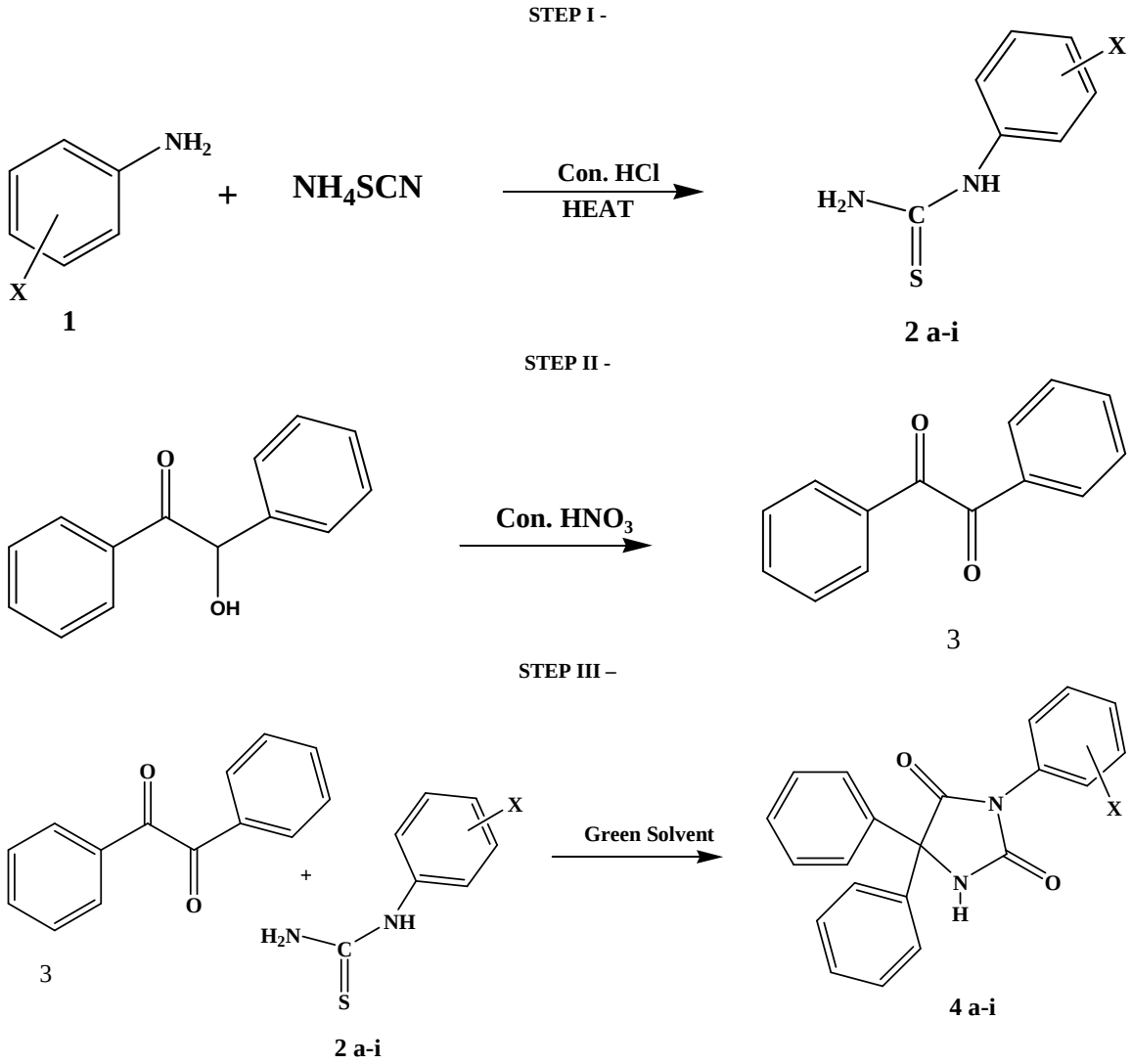
INTRODUCTION

Green chemistry is the design of chemical products and process that eliminates the use and generation of hazardous substances [1]. Using green solvent, like water, synthesis of biologically active moiety with high percentage yield as well as high purity is one of the objectives of green chemistry. Purity of few drugs for CNS acting required high profile of purity and safety for pertaining biological activity [2].

Phenytoin is one of the most widely used drugs in the therapy of epilepsy. However, its low solubility in water, both as free acid and sodium salt, makes its administration to patients difficult and seldom satisfactory. Phenytoin is given orally as sodium salt in a strong alkaline solution, since it requires a p^H between 10 and 12 to be maintained in solution [3].

Phenytoin (5, 5-diphenylimidazolidine-2,4-dione) is the first anticonvulsant agent often cited as a prime example of anticonvulsant acting as a sodium channel blocker [4-5]. Generally, according to reported procedure, it is synthesized by condensation of benzil and urea in presence of base (30% w/v NaOH) using ethanol as solvent which itself acts as CNS stimulant [6]. Removal of solvents after synthesis is most difficult and non-assured process. In case of Phenytoin transformation in polymorphism plays an important role when solvent other than water is used. About 30% extra cost is calculated if solvent other than water is used.

Therefore in present work, substituted thiophenytoins were synthesized by condensation of benzil and substituted aryl thioureas [7] in presence of base (30% w/v NaOH) and water, a green solvent [8]. Newly synthesized thiophenytoins are confirmed by their physical data and spectral data.



MATERIALS AND METHODS

All the chemicals used for synthesis were of LR (Laboratory Reagent) grade. TLC (Thin Layer Chromatography) was performed on microscopic glass slides coated with silica gel-G, using chloroform: ethyl acetate (7:3) as a solvent systems and the spots were visualized by exposure to iodine vapours. The IR spectrum of synthesized compounds were recorded on Shimadzu 8400-S FT-IR Spectrophotometer using potassium bromide.

The ^{1}H NMR was recorded in DMSO-D6 using NMR Varian-Mercury 300MHz spectrometer.

Step I- General procedure for the synthesis of substituted Aryl thiourea 2a-i :
To aniline (25 mL), concentrated hydrochloric acid (25 mL) was added and the solution was warmed. A saturated solution of ammonium thiocyanate in water (30 g in 60 mL) was added slowly in above solution. The mixture was boiled until the solution got turbid. The turbid solution was poured in cold water. The separated precipitate as phenylthiourea was filtered and crystallized from aqueous ethanol (80%) so as to obtain pure compound.

Step II- General procedure for the synthesis of Benzil from Benzoin 3 :
Benzoin (5.0 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 (44 g, 0.21 mol, 89%). Its m.p. was found to be 92°C (literature 95°C).

Its IR (mull in nujol) hadn− (cm^{-1}): 3050 (C=CH, aromatic), 1680 (C=O, s), 1595, 1585, 1450 (C=C aromatic, m).

Step III- General procedure for the synthesis of Thiophenytoin (5,5-diphenyl-2-thioimidazolidine-4-one) 4a-i : Benzil (0.025 mol) and Aryl thiourea (0.05 mol), 15 ml of 30% w/v sodium hydroxide solution and 40 ml of water was placed in a 250 ml round bottom flask and heated for 2 hours. After cooling to room temperature, the reaction mixture was poured into 100 ml of water with stirring. It was allowed to stand for 15 minutes and filtered under suction to remove the insoluble by-product. The filtrate thus obtained was cooled and acidified by using concentrate hydrochloric acid. The precipitates obtained were separated by filtration. The crude product obtained was washed with cold water.

The physical data and yield of synthesized compounds are summarized in **Table I**

UV, IR and ^{1}H NMR spectra of synthetised thiophenytoins are given as below

UV Spectra shows λ_{max} values of compounds 4 a-i were bet'n region 250 - 300

IR Spectra IR (KBr) in cm^{-1}: 746.90, 663.05, 611.72 (4b-4i) (C-H, monosubstituted phenyl ring); 1514.52-1498.18 (C-N stretching); 1742.59- 1703.52 (C=O stretching); 1693.41-1670.21 (C=S stretching); 2957.17-2937.32 (C-H Stretching of aromatic ring); 3846.61-3741.32 (N-H Stretching)

^{1}HNMR Spectra (δ in ppm) ; 6.97- 7.64 (m, 15-14H, Ar-H)

Table I

Sr.No.	X	Molecular formula	Yield	M.P. in ^{o} C
4a	H	$C_{21}H_{16}N_2OS$	85	200
4b	2-NO_2	$C_{21}H_{15}N_3O_3S$	90	205
4c	3-NO_2	$C_{21}H_{15}N_3O_3S$	85	203
4d	4-NO_2	$C_{21}H_{15}N_3O_3S$	93	210
4e	2-Cl	$C_{21}H_{15}N_2OSCl$	95	230
4f	3-Cl	$C_{21}H_{15}N_2OSCl$	88	215
4g	4-Cl	$C_{21}H_{15}N_2OSCl$	90	235
4h	4-OH	$C_{21}H_{16}N_2O_2S$	87	220
4i	4-Br	$C_{21}H_{15}N_2OSBr$	92	213

RESULTS AND DISCUSSION

Subtistuted Thiophenytoins (5,5-diphenyl-2-thioimidazolidine-4-one) 4**a-i** were synthesized by condensation of benzil **3** and Substituted aryl thioureas 2**a-i** in presence of 30% w/v NaOH solution and water as a green solvent. It was obtained as a solid melting in the range 200-230 ^{0}C. The reaction between different substituted aniline and ammonium thiocyninde result in the formation of substituted aryl thioureas 2**a-i** and Benzil **3** was synthesized from Benzoin.

The structures of the newly synthesized compounds **4a-i** were established on the basis of spectral data like The solid state IR (KBr, cm^{-1}), The ^{1}H NMR (DMSO, ppm) , U V Spectra.The physical characterizations of **4a-i** given in **Table I**

CONCLUSION

Thiophenytoin (5,5-diphenyl-2-thioimidazolidine-4-one) is the prime examples of anticonvulsant agent but their syntheses involve non-green approach along with some hyzardous output. Therefore in present work, thiophenytoins were synthesized by condensation of benzil and substituted aryl thioureas in presence of base (30% w/v NaOH) and water, a green solvent. Newly synthesized thiophenytoins are confirmed by their physical data and spectral analysis like M.P., UV, IR and ^{1}H NMR.

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