

SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF CHLORO-SUBSTITUTED-1, 3-THIAZINES

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ABSTRACT

The synthesis, spectral analysis and biological activities of some 4-phenyl-2-hydroxy-chlorosubstituted-2-imino-1, 3-thiazine with phenyl thiourea and diphenyl thiourea have been carried out in two series. In series I we got 4-(2-hydroxy-3,5-dichlorophenyl-6-(ethyl)-2-iminophenyl-1,3-thiazine and 4-(2-hydroxy-3,5-dichlorophenyl-6-(ethyl)-2-iminophenyl-3-phenyl-1,3-thiazine(3a-6a) from 2-hydroxy-3,5-dichloroacetophenone from phenyl thiourea and in series II 4-(2-hydroxy-3,5-dichlorophenyl)-6-(hexyl)-2-iminophenyl-1,3-thiazine and 4-(2-hydroxy-3,5-dichlorophenyl)-6-(hexyl)-2-iminophenyl-3-phenyl-1,3-thiazine(3b-6b) were synthesized from diphenyl thiourea. All these compounds have been analyzed by UV, IR and NMR for structure assignment. The Antibacterial activities of these compounds were studied.

Keywords: Thiazines, antibacterial activities, phenyl thiourea, diphenyl thiourea.

INTRODUCTION

Thiazine is a six member ring system, which contains two heteroatoms (N & S) placed in the heterocyclic ring at 1, 3 positions. Many workers have synthesized different 1, 3-thiazines¹⁻⁴. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities⁵⁻⁶. Chalcones and their analogues having an α , β -unsaturated carbonyl system are very versatile substrates for the evolution of various reactions⁷ and physiologically active compounds⁸. The reaction of thiourea with α , β -unsaturated ketones results in 1, 3 thiazine⁹⁻¹⁰. It has been well focused that the presence of 4-phenyl chlorosubstituted moieties is an important structural feature also 2-substituted imino group present in thiazine ring, and the resulting molecule would exhibit promising biological activities. Phenyl thiourea and diphenyl thiourea give two series (I, II) in ethanol and aq. alkali. In the present study, various 4-phenyl-2-substituted-amino-thiazines have been synthesized from Chalcones by using phenylthiourea and diphenyl thiourea¹¹ and screened for their antibacterial activities against gram positive and gram-negative pathogens.

EXPERIMENTAL

All the glassware's used in the present work were of Pyrex quality. Melting points were determined in open capillary and are uncorrected. Purity of compounds was monitored on silica gel coated TLC plate. I.R. spectra were recorded on FTIR-FTLA 2000 Spectrophotometer in KBr palates, PMR spectra on spectrometer in CDCl₃ and U. V. spectra on spectrophotometer (Schimadzu U.V. 1601). The analytical data of compounds were highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterization data of all the compounds are given in Table 1.

The synthetic methods used in present work are given below along with their UV, IR and NMR data (Scheme-1 and 2).

2'-Hydroxy 3', 5'-dichloro acetophenone (3a)

2'-Hydroxy 5'-chloro acetophenone (3g) was dissolved in acetic acid (5ml). Sodium acetate (3g) was added to the reaction mixture and then chlorine in acetic acid reagent (40ml, 7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 20 °C. The mixture was allowed to stand for 30 minutes. It was poured into water with stirring. A pale-yellow solid then obtained was filtered, dried and crystallized from ethanol.

I.R. (KBr): 3068 cm⁻¹ (-OH phenolic), 1652 cm⁻¹ (>C=O in ketone), 1304 cm⁻¹ (-OH bending in phenol), 737 cm⁻¹ (C-Cl stretching).

PMR: δ 2.65; (s, 3H, -CH₃); δ 7.25 -7.63 (m, 2H, ArH); δ 12.71 (s, 1H, Ar-OH).

U. V.: 344 nm

Preparation of 2'-Hydroxy 3', 5'-dichloro-4-ethyl chalcone (4a)

2'-Hydroxy 3', 5'-dichloro acetophenone (3a), (0.1M) was dissolved in ethanol (50 ml) and propanaldehyde (0.1M) was added to the above solution and the mixture was heated to boiling. Aq. sodium hydroxide solution (40%, 40 ml) was added dropwise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hour and kept overnight. It was then acidified by hydrochloric acid solution (50%). The solid separate was filtered, acid washed with sodium bicarbonate (10%) followed by water. The crude product was crystallized from ethanol acetic acid mixture (4a).

I.R. (KBr): 3068 cm⁻¹ (-OH phenolic), 1646 cm⁻¹ (>C=O in ketone), 1304 cm⁻¹ (-OH bending in phenol) 1559 cm⁻¹ (-C-CH=CH asymmetric stretching), 647 cm⁻¹ (C-Cl stretching), 2929.5(aliphatic -CH stretching).

PMR: δ 2.56-2.67 (d, 1H, -CH=CH); δ 7.0-8.0 (s, 2H, ArH); δ 12.6 (s, 1H, Ar-OH);

U.V.: 340.5 nm

Preparation of 4-(2'-hydroxy-3'5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-1, 3-thiazine (5a)

2'-hydroxy-3', 5'-dichlorophenyl-4-ethylchalcone (4a), (0.01M) dissolved in ethanol (25 ml) were added to phenylthiourea (0.01M). To this aq. KOH solution (0.02M) was added (prepared from KOH in small amount of distilled water). The reaction mixture was refluxed for 2.5 hours, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol (5a).

I.R (KBr): 3067 (-OH phenolic), 3206 (N-H stretching); 2950 (Aliphatic C-H stretching); 1304 (OH bending in phenol); 696 (C-Cl stretching).

PMR: δ 2.70 (s, 1H, -CH₃); δ 6.7 to 8 (s, Ar-H); δ 4.7 (s, 1H, -NH stretching); δ 12-7 (s, 1H, ArOH).

UV: 338.5 nm

Preparation of 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(ethyl)-2-iminophenyl-3-phenyl-1, 3-thiazene (6a)

Synthesis of (6a) compound was similar in manner as (5a), except that phenylthiourea, diphenylthiourea was used.

IR (KBr): 3068 (-OH phenolic stretching); 3206 (-NH stretching); 1648(-C=N stretching); 1052 (-CN stretching); 641 (C-Cl stretching).

PMR: δ 2.72(s, 1H, -CH₃ stretching), δ 7 to 8 (s, Ar-H); δ 4.8 (s, 1H, NH stretching); δ 12.7 (s, 1H, ArOH).

UV: 273 nm

Preparation of 2'-hydroxy-3', 5'-dichloro-4-hexylchalcone (4b):

2'-hydroxy 3', 5'-dichloro acetophenone (3a), 0.1M was dissolved in ethanol (25 ml), heptanaldehyde (0.1 M) was added to the above solution and the mixture was heated to boiling. Aq. sodium hydroxide solution (40%, 40 ml) was added dropwise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hour and kept overnight. Then it was acidified by hydrochloric acid solution (50 %). The solid separated was filtered, acid washed with sodium bicarbonate 10% followed by water. The crude product was crystallized from ethanol **IR (KBr)-**; 3068 (-OH phenolic), 2926 (aliphatic-CH stretching), 1646 (>C=O Stretching), 641 (C-Cl stretching).

PMR: -δ 2.6 (s, 3H, -CH₃), δ 7.4 to 7.8 (m, 2H, Ar-H), δ 12.7 (s, 1H, Ar-OH)

UV:-342 nm

Preparation of 4-(2'-hydroxy-3', 5'-dichloro -phenyl)-6-hexyl-2-iminophenyl-1, 3-thiazene (5b): - 2'-hydroxy-3', 5'-dichloro-4-hexyl chalcone (4b), (0.01 M) dissolved in ethanol (25 ml), and added phenyl thiourea (0.01M). To this solution aq. KOH solution (0.02 M) was added (prepared from KOH in small amount of distilled water). The reaction mixture was refluxed for 2.5 hours, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol (5b).

IR (KBr): 3068 (-OH phenolic stretching); 3300 (NH stretching); 1305 (-OH bending in phenol); 1022 (C-S stretching); 736 (C-Cl stretching).

PMR: δ 2.7 (s, 3H, -CH₃); δ 7 to 8 (s, -ArH); δ 6.1 (s, 1H, NH stretching); δ 12.7 (s, 1H, Ar-OH)

UV: 294nm

Preparation of 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(hexyl)-2-iminophenyl-3-phenyl-1, 3-thiazene (6b):

Synthesis of (6b) compound was similar in manner as procedure (5b), except that phenylthiourea was used diphenylthiourea.

IR (KBr): 3067 (-OH phenolic stretching); 3206 (NH stretching); 2950 (aliphatic C-H stretching); 1304(OH bending in phenol); 1045 (C-S stretching); 696 (C-Cl stretching).

PMR: δ 2.70 (s, 1H, -CH₃); δ 7 to 8 (s, -ArH); δ 4.7 (s, 1H, NH stretching); δ 12.7 (s, 1H, Ar-OH).

UV: 273 nm.

RESULTS AND DISCUSSION

The compound (3a-6a) and (3b-6b) were screened for their antibacterial against gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *E. Coli* and *P. aeruginosa* species at conc. of 1000 μ m gentamycine as a standard. DMF was used as solvent control using agar plate techniques. The zones of inhibition formed were measured in mm and are shown in Table 2. Presence of phenolic group and N, S hetero atoms increase the antibacterial activity of compound from (5a-6a) and (5b-6b).

Table-1: Characterization data of synthesized new compound

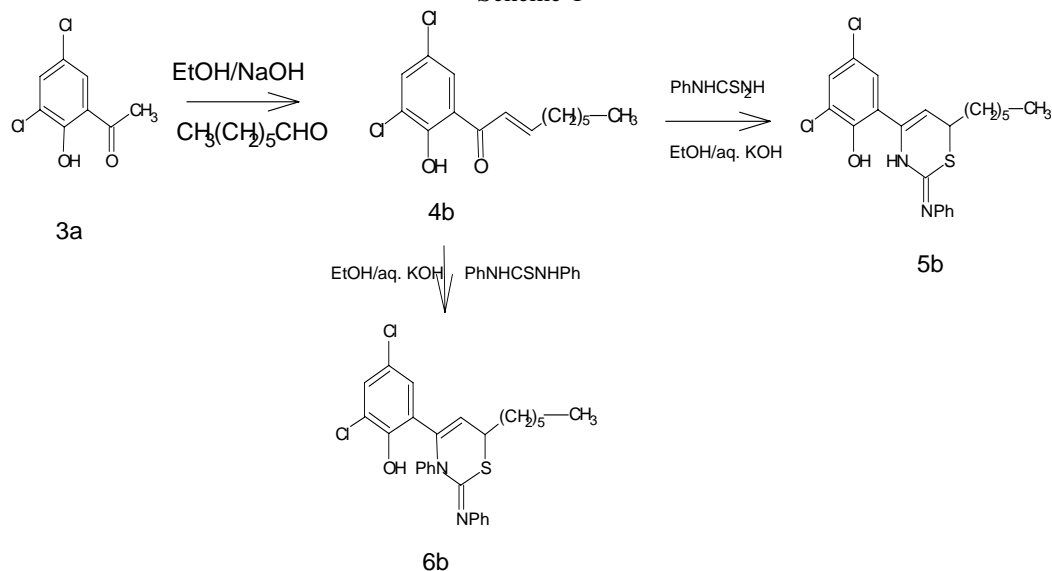
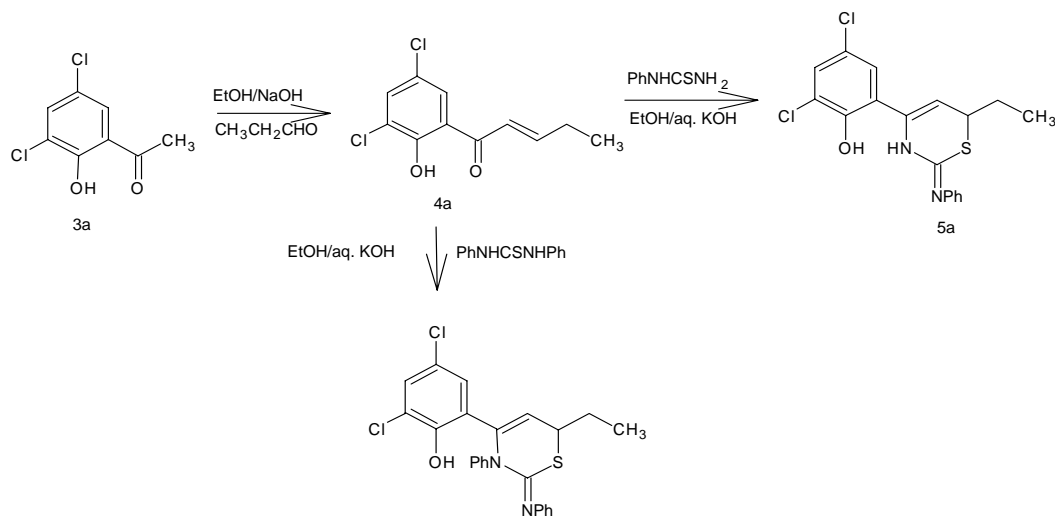
Compound	Molecular Formula	M.P. (°C)	Yield (%)	Rf
3a	C ₈ H ₆ O ₂ Cl ₂	53	75	0.84
4a	C ₁₁ H ₁₀ O ₂ Cl ₂	98	70	0.83
5a	C ₁₈ H ₁₆ ON ₂ SCl ₂	98	75	0.76
6a	C ₂₄ H ₂₀ ON ₂ SCl ₂	122	70	0.82
4b	C ₁₅ H ₁₈ O ₂ Cl ₂	122	70	0.82
5b	C ₂₂ H ₂₄ ON ₂ SCl ₂	114	75	0.77
6b	C ₂₈ H ₂₈ ON ₂ SCl ₂	94	80	0.81

Table-2: Antibacterial activities of synthesized new compound

Compound	Zone of inhibition (mm)			
	<i>E. Coli</i>	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>S. subtilis</i>
3a	09	06	06	08
4a	10	08	09	08
5a	10	08	08	07
6a	14	15	14	14
4b	14	15	14	15
5b	15	15	14	15
6b	15	14	15	15

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