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Synthesis characterization of some nitro-substituted-1, 3-thiazines and their antimicrobial activities.

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ABSTRACT

Some new nitro-substituted 1,3 thiazines have been synthesized by the condensation of 2-hydroxy-3-nitro-5-chlorochalcones with thiourea, phenylthiourea & diphenylthiourea in ethanol containing aqueous KOH solution. The structures of newly synthesized nitro-substituted have been analyzed on the basis of their analytical data, molecular weight determination study and UV, IR & NMR spectral results. The newly synthesized titled compounds were screened for their antibacterial activity against some common pathogens *viz* . . *S. aureus* ,*B. subtilus* . *E. Coli* and *P. aerugiuosa*.

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

INTRODUCTION

In organic chemistry a series of heterocyclic compounds containing an unsaturated six membered ring which contain two carbon one nitrogen and one sulphur atom are termed as thiazines. Various methods have been worked out for their synthesis[1] .Their derivatives have wide variety of biological properties such as Antiparkinsonian[2] Anti-Inflammatory[4,] antibacterial .[7-9] Taking this into consideration the nitro -substituted thiazines were synthesized and assayed for their anti-microbial activity against some common pathogens viz: *S. aureus* ,*B. subtilus* . *E. Coli* and *P. aerugiuosa*. The reaction of various formes of thiourea with chalcone gives 1-3 thiazines. It is found that the presence of 4-phenyl nitro -substitute and 2-substituted imino group in thiazine enhanced the biological activities.

Material and method

Preparation of 2-hydroxy-3-nitro-5-chloroacetophenone (2a)

2-Hydroxy-5-chloroacetophenone (3g) was dissolved in glacial acetic acid (3ml). bromine in acetic acid was added drop wise with constant stirring to this reaction mixture . The temperature of the reaction mixture was maintained below 0°C. The mixture was allowed to stand for 1hour. It was poured into ice cold water with stirring. A yellow solid then obtained was filtered, dried and crystallized from ethanol.

Preparation of 2-hydroxy-3-nitro- 5-chlorochalcones (3a-c)

2-Hydroxy-3-nitro-5-chloroacetophenone (3a), (0.1M) was dissolved in ethanol (50 ml) and aldehyde (Benzaldehyde,Propanaldehyde & Valeraldehyde separately) (0.1M) was added to the above solution and the mixture was heated to boiling. Aq. sodium hydroxide solution (40%, 40 ml) was added drop wise 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 separated was filtered and washed with sodium bicarbonate (10%) followed by water. The crude product was crystallized from ethanol acetic acid mixture (3a-c).

Preparation of 4-(2-hydroxy-3-nitro-5-chlorophenyl)-6-(alkyl or aryl)-2-imino- 3,6 dihydro-1, 3-thiazines (4a-c)

2-Hydroxy-3-nitro-5-chlorochalcone (3a-c), (0.01M) and thiourea (0.01M) were dissolved in ethanol (25 ml).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 1:1 HCl. The product was filtered, dried and crystallized from ethanol (4a-c).

Preparation of 4-(2-hydroxy-3-nitro-5-chlorophenyl)-6-(alkyl or aryl)-2-iminophenyl- 3,6 dihydro-1, 3-thiazine (5a-c)

2-hydroxy-3-nitro-5-chlorochalcone (4a-c), (0.01M) dissolved in ethanol (25 ml) were added to phenylthiourea (0.01M).To this aq. KOH solution (0.02M) was added . 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-c).

Preparation of 4-(2-hydroxy-3-nitro-5-chlorophenyl)-6-(alkyl or aryl)-2-iminophenyl-6H-3-phenyl-1, 3-thiazine (6a-c)

Compounds (6a-c) were synthesized similarly as (5a-c), except that phenylthiourea, diphenylthiourea was used.

The compounds (3a,3b,3c,4a,4b,4c,5a,5b,5c,6a,6b & 6c) thus synthesized were assigned on the basis of elemental analysis molecular weight determination results and spectral data are as follows. Physical characterization data of all the compounds are given in Table 1.

Characterization of the compounds:

Melting points of all synthesized compounds were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer 1000 Spectrophotometer in KBr. NMR spectra were recorded on Bruker advance 400 NMR spectrometer using TMS as internal cal shistandard and chemical shift were expressed in δ ppm.

1. Compound 2a:

I.R. (KBr): cm^{-1} 3400 (-OH phenolic), 1720 (>C=O in ketone),701 (Ar-Br), 1324 (-OH bending in phenol), 650 (C-Cl stretching).
PMR: δ 2.75; (s, 3H, $-COCH_3$); 7.35 -7.73 (m, 2H, ArH); 12.61 (s, 1H, Ar-OH).
U. V.: λ max 344 nm.

2. Compound 3a:

I.R. (KBr): cm^{-1} 3455 (-OH phenolic), 2990 (aliphatic –CH stretching).
1705 (>C=O in ketone), 789(Ar-Br stretching),1314 (-OH bending in phenol) 1641.42 (-C-CH=CH asymmetric stretching), 759(C-Cl stretching).
PMR: δ 3.75(d, 1H, -CH=CH); 4.23(d, 1H, -CH=CH) 7.0-8.0 (s, 2H, ArH); 12.7(s, 1H, Ar-OH);
U.V.: λ max 343.5 nm

3. Compound 4a:

I.R (KBr): cm^{-1} 3403 (-OH phenolic), 3236 (N-H stretching); 2950 (Aliphatic C-H stretching); 1304 (OH bending in phenol); . 700.16(Ar-Br stretching), 700 (C-Cl stretching).
PMR: δ 2.70 (s, 1H, $-CH_3$); 4.4 (s, 1H, -NH); 3.6(t,1H,CH-C=C); 5.47(m,1H,CH=CH); 5.70 (m,1H,CH=CH); 6.7 to 8 (s, Ar-H); 4.7 (s, 1H, -NH stretching); 12 (s, 1H, ArOH).

4. Compound 5a:

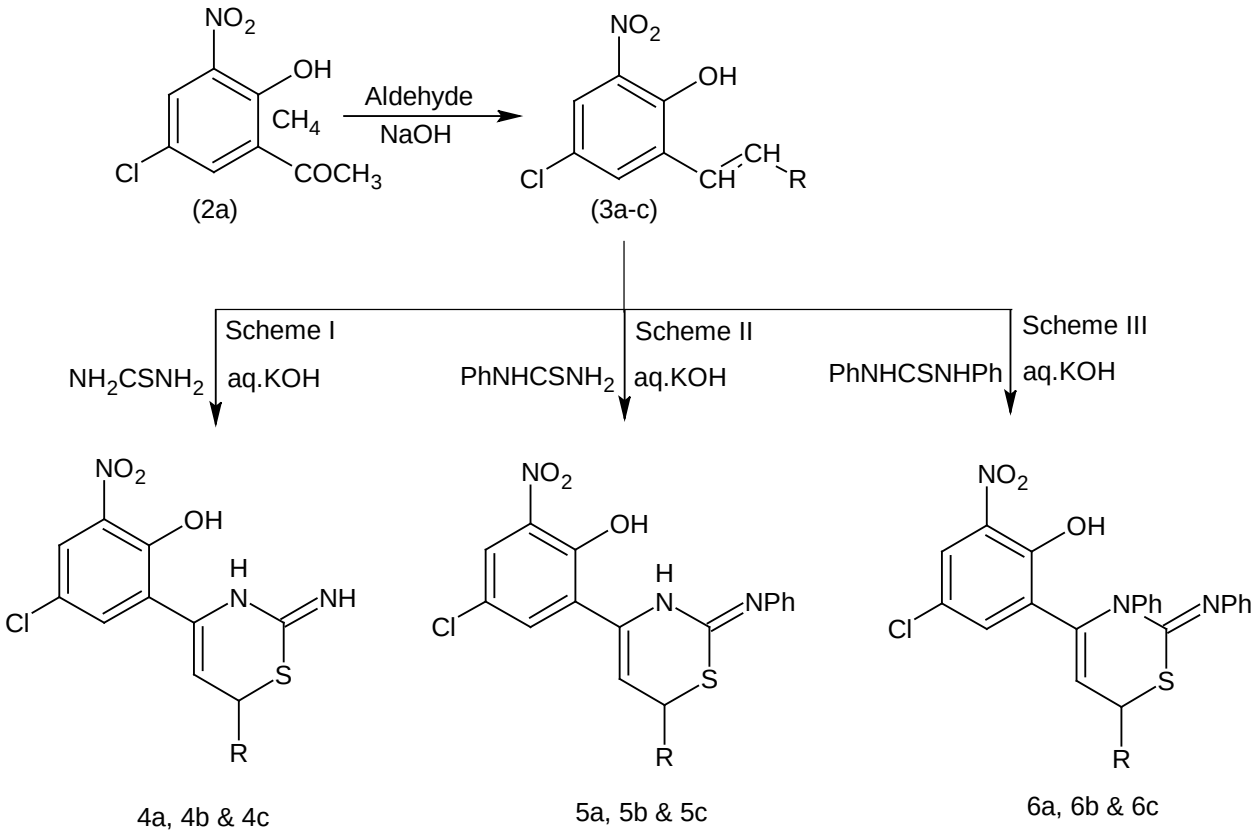
I.R (KBr):cm^{-1} 3440 (-OH phenolic), 3266 (N-H stretching); 2950 (Aliphatic C-H stretching);1660(-C=N stretching)1444(Ar-NO2 stretching); 1312 (-CN stretching) 1304 (OH bending in phenol); 699 (C-Cl stretching).
PMR: δ 2.40 (s, 3H, $-CH_3$); 3.7 (s, 1H, -NH stretching); 3.4(t,1H,CH-C=C); 5.57(m,1H,C=CH-CH3); 5.74(m,1H,CH=CH-CH3); 6.6(d,1H,NH-C=CH); 7.1 to7.8 (m,7H, Ar-H); 10.9 (s, 1H, ArOH).
UV: λ max 330 nm.

5. Compound 6a:

IR (KBr): cm^{-1} 3435 (-OH phenolic stretching); 1650 (-C=N stretching); 1313 (-CN stretching); 692 (C-Cl stretching).

PMR: δ 2.5 (s, 3H, -CH_3); 4.8 (s, 1H, NH stretching); 4.17(d,1H,C=C-H); 5.5(d,1H,CH=C); 6.5(d1,H,C=CH) 6.9 to 7.8 (s,12H, Ar-H); 11.99 (s, 1H, ArOH).
UV: λ max 340 nm

Scheme: Synthesis of nitro-substituted 1,3 thiazines



Where R = -C_6H_5, -CH=CH-CH_3, -$(CH_2)_3CH_3$

Aldehyde a = Benzaldehyde; b = Crotonaldehyde; c = Valeraldehyde

RESULTS AND DISCUSSION:

The compounds (3a,3b,3c,4a,4b,4c,5a,5b,5c,6a,6b and 6c were screened for their antibacterial activity against some gram positive bacteria viz. *S. aureus* and *B. subtilus* and gram negative bacteria viz. *E. Coli* and *P. aerugiuosa* species at conc. of 1000 µm gentamycine as a standard. DMF was used as a solvent control using agar plate techniques. The zones of inhibition formed were measured in mm and shown in Table- 2.

Table- 1- Physical and analytical characterization of data of newly synthesized compound

Compd.	Mol.Formula	Mol. Wt.	R	Yield(%)	m.p.(^{0}C)	Found Cal. %		R_f
						C	N	

1a	$C_8H_7O_2Cl$	171	---	75	---	56		0.62
2b	$C_8H_6O_4NCl$	215	---	80	---	44	6.5	0.59
3a	$C_{15}H_{10}O_4NCl$	303	$-C_6H_5$	78	85	59	6.0	0.72
3b	$C_{12}H_{10}O_4NCl$	267	$-CH=CH-CH_3$	70	85	53	6.01	0.90
3c	$C_{13}H_{14}O_6NCl$	283	$-CH_2CH_2CH_2CH_3$	60	102	55	4.55	0.70
4a	$C_{16}H_{12}O_5N_3SCl$	361	$-C_6H_5$	74	170	53	6.55	0.79
4b	$C_{13}H_{12}N_3SO_5Cl$	325	-CH=CH-CH3	70	138	55	7.15	0.52
4c	$C_{14}H_{16}O_5N_2SCl$	317	$-CH_2CH_2CH_2CH_3$	76	145	49	3.56	0.66
5a	$C_{22}H_{16}O_5N_3SCl$	437	$-C_6H_5$	72	140	60	5.56	0.51
5b	$C_{19}H_{16}N_3SO_3Cl$	401	$-CH=CH-CH_3$	70	142	58	4.46	0.35
5c	$C_{20}H_{20}O_5N_3SCl$	417	$-CH_2CH_2CH_2CH_3$	76	120	57	5.79	0.69
6a	$C_{28}H_{20}O_5N_3SCl$	515	$-C_6H_5$	70	132	65	4.83	0.49
6b	$C_{25}H_{20}N_3SO_5Cl$	509	$-CH=CH-CH_3$	71	138	62	5.15	0.34
6c	$C_{26}H_{24}N_3O_5SCl$	469	$-CH_2CH_2CH_2CH_3$	73	157	63	5.00	0.55

Table-2 - Antibacterial activities of synthesized new compound

Compound	Zone of inhibition (mm)			
	E .Coli	*S. aureus*	*S. subtilus*	*P. aeruginosa*
3a	15	14	14	13
3b	16	13	19	12
3c	22	12	14	15
4a	12	13	15	14
4b	17	16	15	17
4c	20	16	12	15
5a	12	13	16	20
5b	14	16	15	15
5c	23	15	13	15
6a	21	26	27	22
6b	25	26	25	24
6c	17	18	15	16

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