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Synthesis and Antibacterial Assay of Some Chlorosubstituted 4-Aroyl/Alkoylisoxazoles

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ABSTRACT :
Aroyl/alkoylacetophenones (2a-b) undergo intramolecular Claisen condensation to form 1-(2'-hydroxy-3',5'-dichlorophenyl)-3-aryl/alkyl-1,3-propane-diones (4a-b) which on treatment with aliphatic aldehydes in ethanol containing little piperidine form 3-aroyl/alkoylchromanones (5a-b), 3-aroyl/ alkoylchromones (6a-b). Further the compounds (6a-b) on treatment with $NH_2OH.HCl$ in DMSO containing small amount of piperidine gave 4-aroyl/ alkoyl isoxazoles (8a-b). Thenewly synthesized clorosubstituted isoxazoles were screened for their antibacterial activities against some *Gram positiveStaphylococcus aureus and Streptococcus sp.* and *Gram negativePseudomonas sp.* and *Solmonella typhi* pathogens. All the newly synthesized compounds were found to be active against test pathogens.

KEYWORDS -*Chromanones, Chromones, isoxazoles, antibacterial assay.*

INTRODUCTION : Isoxazoles are the compounds having five membered ring containing both nitrogen and oxygen in the 1,2 positions. Various methods have been worked out for their synthesis[1-7] Derivatives of isoxazoles have played a crucial role in the history of heterocyclic chemistry and have been extensively instrumental as pharmacophores and synthons in the field of organic chemistry and drug designing. Several isoxazole derivatives have been found to possess significant activities such as antibacterial[8],antitubercular[9],antiviral[10],insecticidal[11],antimicrobial[12],antiinflammatory[13],antiparasitic[14],antiprotozoal[15],antiproliferative[16]. Taking into consideration the widespread applications of chlorosubstituted isoxazoles as antibacterial, antifungal, antiparasitic agents in the field of medicine and agriculture, it was thought interesting to synthesize some new chlorosubstituted isoxazoles and study their antibacterial activity.

The newly synthesized clorosubstituted isoxazoles were screened for their antibacterial activities against some *Gram positiveStaphylococcus aureus and Streptococcus sp.* and *Gram negativePseudomonas sp.* and *Solmonella typhi* pathogens. All the newly synthesized compounds were found to be active against test pathogens.

EXPERIMENTAL:

SCHEME :

The synthetic routes which furnished the target compounds are as under along with their IR and NMR data.

Synthesis of 2-hydroxy-3,5-dichloroacetophenone (2b):

2-Hydroxy-5 chloroacetophenone (3g) was dissolved in acetic acid (5ml), sodium acetate (3g) was added to the reaction mixture and chlorine in acetic acid reagent (40ml) was added dropwise with constant stirring. Mixture was allowed to stand for 30 minutes. Then it was poured into cold water. A pale yellow solid product thus separated was filtered and crystallized from ethanol to get (2b).

IR (KBr): 3040 cm^{-1} [strongly intramolecular hydrogen bond of O-H stretching],1660 cm^{-1} [>C=O stretching in o-hydroxy- arylketone], 1345 cm^{-1} [O-H bending in phenol], 650 cm^{-1}[C-Cl stretching];

^{1}H NMR ($CDCl_3$): δ 2.60 [S, 3H, Ar-COC**H**$_3$],δ 0.87 to 7.64 [m, 2H Ar-**H**], δ 12.11 [s, 1H Ar-O**H**].

Physical and analytical data of the synthesized compounds are summarized in the following table 1.

Synthesis of 2-benzoyloxy-3,5-dichloroacetophenone (3a):

A mixture of 2-hydroxy-3,5-dichloroacetophenone (0.04 mol) benzoyl chloride (0.05 mol) was dissolved in NaOH (10%) (30 ml). The reaction mixture was shaken for half an hour, the product was then filtered, washed with $NaHCO_3$ (10%) and purified by recrystallization with ethanol to give 2-benzoyloxy-3,5-dichloroacetophenone (3a).

IR (KBr): 2930.9cm^{-1} [C-H stretching, -CH_2], 1230-1245 cm^{-1} [>C=O stretching], 3150-3425.9 cm^{-1} [-O-H stretching], 1305.5 cm^{-1} [-CH_3 bending], 1229.4cm^{-1}[C=O stretching], 860.4 cm^{-1} [C-Cl str.].

^{1}H NMR [$CDCl_3$]: δ 2.13 [s, 3H –C**H**$_3$],δ 12.08 – 12.74 [s, 1H, O-**H**],δ 7.20- 7.85 [m, 7H Ar-**H**].

Synthesis of 2-anisoyloxy-3,5-dichloroacetophenone (3b):

A mixture of 2-hydroxy-3,5-dichloroacetophenone (2b) (0.04 mol) and anisic acid (0.05) kept suspended in dry pyridine (30ml) and to this $POCl_3$ (3ml) was added dropwise with constant stirring and occassional cooling. The reaction mixture was kept overnight and then worked up by dilution and acidified with ice cold HCl (50%) to neutralize pyridine. The solid product thus obtained then filtered and washed with $NaHCO_3$. It was purified by crystallization from ethanol to give 2-anisoyloxy-3,5-dichloro-acetopheonone (3b).

IR (KBr): 2957.9 cm^{-1}(C-H str.), 1727.8 -1630 cm^{-1}(C=O str.), 1433.2 cm^{-1}(-CH_2 bending), 866.2 cm^{-1}(C-Cl str.);

^{1}H NMR ($CDCl_3$): δ 1.25 – 2.45 (m, 4H, -C**H**$_2$-C**H**$_2$-), δ2.66 (t, 2H, -CO-C**H**$_2$), δ2.17 (s, 3H, -C**H**$_3$), δ7.26 – 7.65 (dd, 2H, Ar-**H**).

Synthesis of 1-(2-hydroxy-3,5-dichlorophenyl)-3-phenyl-1,3-propanedione (4a):

A mixture of 2-benzoyloxy-3,5-dichloroacetophenone (3a) and dry pyridine was warmed upto 60 ^{0}C and pulvurised KOH was added slowlywith constant stirring and then kept overnight. After digestion the reaction mixture was acidified with cold 1:1 dil HCl. The product thus obtained was filtered and washed with $NaHCO_3$ solution. Finally it was crystallized from ethanol to get (4a).

IR (KBr): 3150 cm^{-1} [O-H stretching], 1730.2 – 1709.*0* cm^{-1} [CO-CH_2-CO str.], 1610 cm^{-1}[C=C str.], 1245 cm^{-1}[C-O str.], 820 cm^{-1}[C-Cl stretching];

^{1}H NMR ($CDCl_3$): δ 3.96 [s, 2H, CO-C**H**$_2$-CO], δ 6.66 – 7.99 [m, 7H, Ar-**H**], δ 12.08 – 12.80 [s, 1H, Ar-O**H**], δ 15.71 [s, 1H, -C=C-OH enol].

Similarly compound 4b was also synthesized and its spectral characterization data is as under-

1-(2-Hydroxy-3,5-dichlorophenyl)-3-(4'-methoxyphenyl)-1,3-propanedione(4b):

IR(KBr): 3288cm^{-1} (Intramolecular H-bonded O-H str.), 1639 cm^{-1}(>C=O str.), 1558 cm^{-1} (C=O str.), 1217 cm^{-1}(>C-O str.), 868.8 cm^{-1} (C-Cl str);

^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3H, Ar-O C**H**$_3$), δ 4.60 (s, 2H, -CO-C**H**$_2$-CO-), δ 6.6 (s, 1H, -C=C**H**), δ 6.8-8.0 (m, 6H, Ar-**H**).

Synthesis of 3-benzoyl-2-(2'-propyl)-6,8-dichlorochromanone (5a):

A mixture of 1-(2-hydroxy-3,5-dichlorophenyl-3-phenyl-1,3-propanedione (4a) (0.01 mol) and propionaldehyde (0.02 mol) was refluxed in DMSO (25 ml) and piperidine (0.5ml) for 15-20 minutes. After cooling the reaction mixture was acidified with dil. HCl (1:1) and the product thus separated was crystallized from ethanol to get the compound 5a.

IR (KBr): 3150–3425.9 cm^{-1}[O-H stretching], 2957.4 cm^{-1} [C-H str. In alkane], 1639 cm^{-1} ,[>C=O str.], 1435.1 cm^{-1} [-CH_2 bending],1234.5 cm^{-1}, [C-O-C str. In ether], 866 cm^{-1}[C-Cl str.];

^{1}H NMR ($CDCl_3$): δ 12.08–12.74 [O-**H**], δ 2.85–1.96 [m, 4H, -CH_2-C**H**$_2$-C**H**$_2$-], δ 6.77 [m. C**H**$_A$-CH, chromanone ring], δ 5.39 [d, CH- C**H**$_B$. Chromanones ring], δ 7.25 – 7.98 [m, 7H, Ar-**H**].

Synthesis of 3-anisoyl-2(2'-propyl)-6,8-dichlorochromanone(5b):

Compound 5b was synthesized in similar way as compound 5a. Its spectral analysis is presented as below-

IR (KBr): 2925.4 cm^{-1} [C-H str. In alkane], 1735 cm^{-1} [>C=O str.], 1304.6 cm^{-1}[-CH_3 bending], 1234.5 cm^{-1} [C-O-C stre. In ether], 869 cm^{-1} [C-Cl stretching];

^{1}H NMR $CDCl_3$: δ 3.85-2.15 [unresolvable complex multiplets -C**H**$_2$-C**H**$_2$-C**H**$_3$], δ1.4-0.9 [t, 6H,-C**H**$_3$], δ 6.56 [m, C**H**$_A$-CH, chromanone ring],δ 5.35 [d, CH-C**H**$_B$, chromanone ring], δ 7.26-7.65 [d, 2H, Ar-**H**].

Synthesis of 3-benzoyl-2-(2'-propyl)-6,8-dichorochromone (6a):

3-Benzoyl-2-(2'-propyl)-6,8-dichlorochromanone (5a) (0.01 mol) was refluxed for 10 min. with a crystal of Iodine in DMSO (20ml). After cooling the reaction mixture was diluted with water. The solid product thus separated, filtered, washed with sodium thiosulphate solution and crystallized with ethanol to get (6a).

IR (KBr): 1734 cm^{-1}[>C=O str.], 1603.8 cm^{-1}[>C=C< str.], 1234.4 cm^{-1}[C-O str.], 872.5 cm^{-1}[C-Cl str.], 2957.3 cm^{-1}[C-H str.], 1434.7 cm^{-1}[-CH_2 bending] ,1304 cm^{-1}[-CH_3 bending .

^{1}H NMR $CDCl_3$: δ 7.5 - 7.9 [m,1H,Ar-**H**], δ 0.91 [t, 3H, -CH_2-CH_2-C**H**$_3$], δ1.30 [m, 2H,-CH_2,C**H**$_2$-CH_3], δ 2.66 [t, 2H, -C**H**$_2$-CH_2-CH_3].

Synthesis of 3-Anisoyl-2-(2'-propyl)-6,8-dichlorochromone (6b):

Compound 6b was synthesized in similar way as compound 6a. Its spectral analysis is presented as below-

IR (KBr): 1734 cm^{-1}[>C=O str.],1649.8 cm^{-1} [>C=O str.], 1603 cm^{-1}[>C=C< str.], 869.3 cm^{-1} [C-Cl str.], 2943 cm^{-1}[C-H str.], 1304.3 cm^{-1}[-CH_3 bending].

^{1}H NMR $CDCl_3$: δ 3.7-1.25 [unresolvable multiplets 12H, -C**H**$_2$-C**H**$_2$-C**H**$_2$-] , δ 6.96-7.2 [dd, 2H, Ar-**H**], δ 2.66 [t, 2H,-C**H**$_2$,CH_2-CH_3].

Synthesis of 3-(2-hydroxy-3,5-dichlorophenyl)-4-benzoyl-5-(2'-propyl)-isoxazole (8a):

A mixture of 3-Benzoyl-2-(2'-propyl)-6,8-dichlorochromanone (6a) (0.01 mol) and $NH_2OH.HCl$ (0.02 mol) was refluxed in DMSO (20ml) containing 1 ml piperidine for 1.5 hours. After cooling, the reaction mixture was acidified with dil. HCl. The solid product was filtered and washed with sodium bicarbonate (5%) solution. The product was crystallized from ethanol to get the compound (8a).

IR (KBr): 3400.0 cm^{-1}[strongly intramolecular H-bonded O-H str.], 3061 cm^{-1} [C-H stretching in aromatics], 2934.1 cm^{-1} [C-H stretching in aliphatics], 1655 cm^{-1} [C=O str str.], 1609.7 cm^{-1} [C=N str.], 1555.7 cm^{-1} [C=C str.], 1452.3 cm^{-1} [-CH_2 bending], 1379.4 cm^{-1} [-CH_3 bending], 860.2 cm^{-1} [C-Cl str.].

^{1}H NMR ($CDCl_3$): δ 1.2 [t, 3H, -CH_2-CH_2-C**H**$_3$], δ 1.4-2.3 [m, 2H, -CH_2-C**H**$_2$-CH_3], δ 2.65 [t, 2H, -C**H**$_2$-CH_2-CH_3], δ 6.82-8.02 [m, 12H, Ar-**H**], δ 9.45 [s,1H, Ar-O**H**].

Synthesis of 3-(2-hydroxy-3,5-dichlorophenyl)-4-anisoyl-5-(2'-propyl)-isoxazole (8b): The compound 8b was synthesized in similar way as the compound 8a. Its spectral analysis is presented as below-

IR (KBr): 3354.0 cm^{-1}[O-H str.], 2923 cm^{-1}[C-H str. In alkane], 1558 cm^{-1}[C=N str.], 1454.5 cm^{-1}[-CH_2 bending], 868 cm^{-1} [C-Cl str.].

^{1}H NMR $CDCl_3$: δ 0.92 [t, 3H, -C**H**$_3$], δ1.20-2.5 [complex multiplet 8H, -CH_2-C**H**$_2$-C**H**$_3$], δ 6.96 – 7.37 [m, 7H, Ar-**H**], δ13.30 [s, 1H, Ar-O**H**].

All the newly synthesised compounds(5a,5b, 6a, 6b, 8a and 8b) were screened for their antibacterial activity against some *Gram positive* pathogens viz. *Staphylococcus aureus* and *Streptococcus sp.* and some *Gram negative* pathogens viz. *Pseudomonas sp.* and *Solmonella Typhi.* at conc.of 1000 µm 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.

RESULTS AND DISCUSSION :

The newly synthesized compounds (5a, 5b, 6a, 6b, 8a and 8b) were found to be active against test pathogens. However a further detailed study in the light of Medical sciences is advised.

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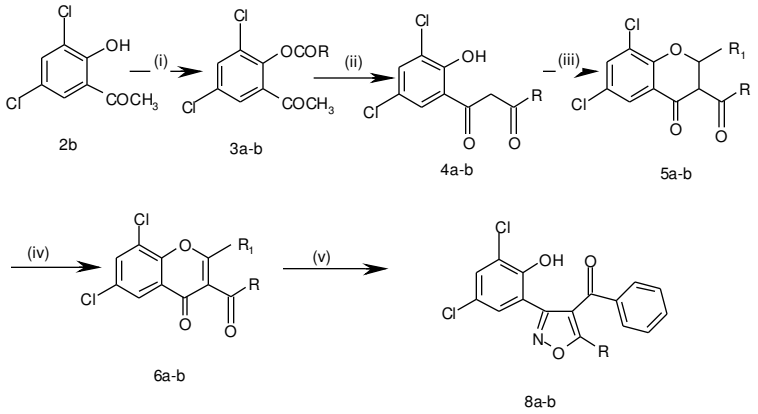
SCHEME :



Where, R; a= C_6H_5 ; b= CH_3-O-C_6H_5 ; R_1 = CH_3-CH_2-CH_2

i] 2a=C_6H_5COCl, 10% NaOH.
2b= $CH_3OC_6H_4COOH$, Dry pyridine,$POCl_3$

ii] KOH, Pyridine

iii] CH_3-CH_2-CH_2OH [Propionaldehyde] , piperidine

iv] DMSO + I_2

v] $NH_2OH.HCl$ + DMSO + Piperidine

Table 1 : Physical and Analytical characterization data of newly synthesized compounds –

Compounds	Mol. Fourmula	Mol Wt.	R	R'	Yield %	M.P. ^0C	Found (Calculated)%	
							C	N
2b	$C_8H_6Cl_2O_2$	205			75	53		
3a	$C_{15}H_{10}O_3Cl_2$	309	-C_6H_5		75	65	58.25	
3b	$C_{16}H_{12}O_4Cl_2$	338	-C_6H_5-OCH_3		75	117	56.63	
4a	$C_{15}H_{10}O_3Cl_2$	309	-C_6H_5		75	113	58.25	
4b	$C_{16}H_{12}O_4Cl_2$	339	-C_6H_5-OCH_3		60	119	56.63	
5a	$C_{19}H_{16}O_3Cl_2$	363	-C_6H_5	-CH_2-CH_2-CH_3	70	114	62.80	
5b	$C_{20}H_{18}O_4Cl_2$	393	-C_6H_5-OCH_3	-CH_2-CH_2-CH_3	60	107	61.06	
6a	$C_{19}H_{14}O_3Cl_2$	361	-C_6H_5	-CH_2-CH_2-CH_3	60	110	63.15	
6b	$C_{20}H_{16}O_4Cl_2$	391	-C_6H_5-OCH_3	-CH_2-CH_2-CH_3	60	90	61.38	
8a	$C_{19}H_{15}O_3NCl_2$	385	CH_2-CH_2-CH_3	-C_6H_5	60	180	59.22	5.97
8b	$C_{20}H_{13}O_4NCl_2$	347	CH_2-CH_2-CH_3	-C_6H_4-OCH_3-	60	196	69.10	6.62

TABLE-2

ANTIBACTERIAL ACTIVITIES OF SYNTHESISED NEW COMPOUNDS :

Zones of inhibition (mm)

Compounds	Staphylococcus aureus	Streptococcus sp.	Pseudomonas sp.	Solmonella typhi
5a	14	12	14	14
5b	14	15	15	14
6a	15	15	16	16
6b	14	15 15	16	
8a	16	17 16	17	
8b	17	18	17	17

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