Synthesis and Biological activity of some new Heterocyclic Compounds

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Abstract: 5-(3,5-Dibromo-2-hydroxyphenyl)-2,3,4-trihydro-1,2,4-triazole-3-thione(4) and 3-[(5-bromo-or 3,5-dibromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolinidin-2-thiones(7a,b)were prepared via the reaction of 2,3,5trisubstituted benzaldehyde thiosemicarbazones(2a,b)with bromine in acetic acid and ethylchloroacetate in presence of fused sodium acetate. While 5-(4-methylphenyl-2-[3,5-dibromo-2-hydroxy-phenylmethylene)-hydrazion]-thiazole(5) prepared via reaction of (2b) with 4-methyl phenacylbromide. Acylation of (2b) and (5) with acetic anhydride gave the corresponding diacetyl derivatives (3) and (6).
Keywords: thiosemicarbazone, thiazole, imidazolidin-2-thione, Acylation, bromination.

Introduction:

Sulpha drugs are well recognized for their various physiological activities [1,2].Likewise, triazole derivatives are known for their antibacterial, fungicidal and pesticidal properties [3],while thiazole and imidazolidines are associated with various biological activities [4-8].Keeping these in view, triazole(4), thiazole(5) and imidazolidinones(7) were synthesized starting from substituted benzaldehyde thiosemicarbazones(2) with a solution of bromine in AcOH, 4-methylphenacyl bromide and ethylchloroacetate in presence of AcONa, it was found that the thiosemicarbazone (2b) and thiazole(5) are converted into diacetyl derivatives (3) and(6) by the action of acetic anhydride .The electron impact (EI) ionization mass spectral fragmentation of some synthesized compounds was described.

Result and Discussion:

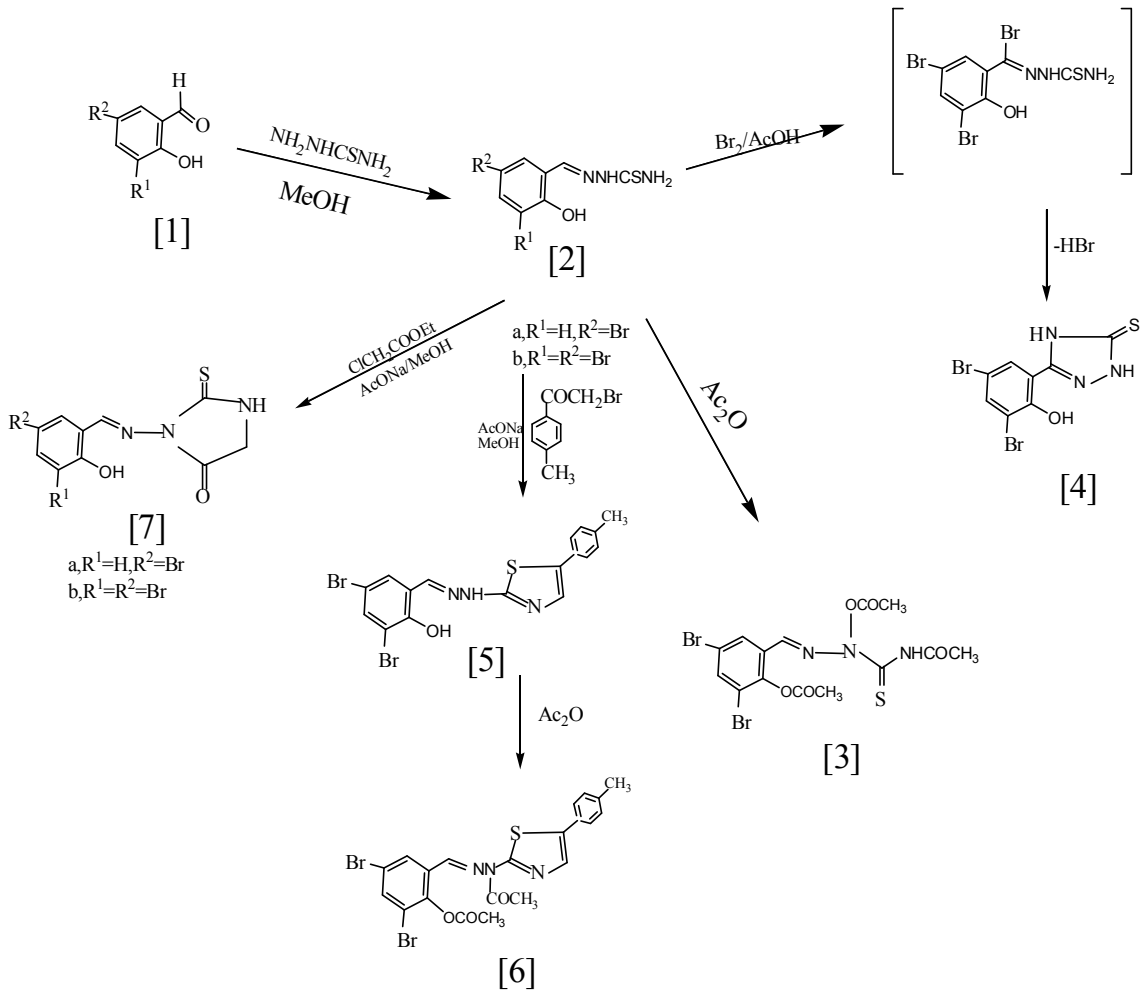
2-hydroxy-5-bromo-benzaldehyde thiosemicarbazone (2a) and 2-hydrox -3,5-dibromo -benzaldehyde thiosemicarbazone(2b) were prepared via the condensation of 5-bromo-2-hydroxy- benzaldehyde and of 3, 5-dibromo-2-hydroxy- benzaldehyde with thiosemicarbazide[9]. 2-acetoxy-3,5-dibromo benzaldehyde-2,4-diacetyl thiosemicarbazone(3) was prepared via actylation of (2b) with acetic anhydride.

5-(3,5-Dibromo-2-hydroxy-phenyl)-2,3,4-trihydro-1,2,4-triazole-3-thione (4) was prepared via the bromination of 3,5-dibromo-2-hydroxy- benzaldehyde thiosemicarbazone(2b)with bromine in acetic acid, followed by cyclization with removal hydrogen bromide [10] (scheme 1).

Treatment of 3,5-dibromo-2-hydroxy- benzaldehyde thiosemicarbazone(2b) with 4-methylphenacyl bromide in presence of fused sodium acetate in methanol under reflux, yielded the corresponding 5-(4-methylphenyl-2-[3,5-dibromo-2-hydroxy-phenylmethylene)-hydrazion]-thiazole (5).

Acylation of compound (5) with acetic anhydride under reflux gave the corresponding 5-(4-methyl-phenyl)-2-[(3,5-dibromo-2-acetyloxy-phenylmethylene)-acetylhydrazino]-thiazole (6)(scheme1).

The reaction of thiosemicarbazones(2a,b) with ethylchloroacetate in presence of fused sodium acetate in methanol under reflux, afforded the corresponding 3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(7a) and 3-[(3,5-dibromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(7b) ,respectively.



Scheme 1

Antimicrobial studies

Applying the agar plate diffusion technique[14] for some of the newly synthesized compounds was screened in Vitro for antimicrobial activity against:

I)- Gram positive bacteria such as:

1-Bacillus Subtilis.

2-Staphylococcus Aureas.

II)- Gram negative bacteria such as:

1-Escherichia Coli species.

2-Pseudomonas species.

III)- Fungi such as:

1-Candida albicans.

Procedure:

Nutrient agar medium had been utilized for growing test organisms. This medium was of the following composition (g/L) peptone (5.0 gm), beef extract (3.0 gm), sodium chloride (5.0 gm); agar (18.00 gm) and water (100 CC). Each compound was tested at the prementioned concentration dissolved in dimethyl formamide, while dimethyl formamide itself was used as control for comparison.

Bacterial suspensions from activity growing cultures were prepared using sterile distilled water. The media was prepared, poured into 9 cm diameter plates, allowed to solidify and then one mL/ plate of bacterial suspension was transferred aseptically to these plates incubated at 27 °C for 24 hours. The compounds were tested at 100 µg/mL concentration and the activity was determined by measuring the zone of inhibition.

The screening results given in the following tables indicated that all the compounds exhibited antimicrobial activities against one or the other type of bacteria and fungi.

Table (1): Antimicrobial Activities of some synthesized compounds [2a to 7a]

Compound	***Pseudomona Sp.***	***Escherchia coli***	***Bacillus Subtilis***	***Staphylococcus Aureus***	***Candida albicans***
[2a]	_	_	_	++++	_
[2b]	_	_	_	_	_
[3]	+++	+	_	_	_
[4]	+++	+	_	++++	_
[5]	_	_	_	++++	_
[6]	+++	+	_	+++++	_
[7a]	_	_	_	++++	_
[7b]	_	_	_	++++	_

Experimental Section

NMR spectra were recorded on general Electric QE 300 instrument and chemical shifts were given with respect to TMS. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and a Biorad FTS7 (KBr).Mass spectra were obtained on a Joel JMSD-300 spectrometer operating at 70 eV. Microanalyses were conducted using elemental analyzer, Heneaus CHN-OS Rapid. Melting points were determined on a MEL-TEMP II and uncorrected.

2, 3,5-trisubstituted benzaldehyde thiosemicarbazones (2a,b)

A mixture of 2,3,5-trisubstituted benzaldehyde (1)(0.01 mol), thiosemicarbazide (0.01 mol) in methanol (30 ml) was heated under reflux for 3 hrs., then cool . The solid formed was filtered off, dried and purified by re-crystallization with methanol to give (2).

5-bromo-2-hydroxylbenzaldehyde thiosemicarbazone (2a); yield 89%, m.p. 195^{o}C, ^{1}H-NMR (dmsod6): δ 11.73 – 11.62 (br-S, 1H, OH), 10.29 – 10.23 (br. S, 1H,NH); 7.23 – 8.44 (m,4H, Ar H an CH=N); 3.34 (S, 2H, NH2) ppm.

3,5,-dibromo-2-hydroxybenzaldehyde thiosemicarbazone (2b); yield 87%; m.p: 230^{o}C, ^{1}H-NMR(DMSO-d6): δ, 11.76 -11.63 (br. S, 1H, OH), 10.30 – 10.25 (br. S, 1H, NH), 7.20 – 8.49 (m, 3H, Ar-H and CH=N), 3.37 (S, 2H, NH_2) ppm.

2-acetoxy-3,5-dibromo benzaldehyde-2,4-diacetyl thiosemicarbazone(3)

A solution of (2b) in acetic anhydride (25 ml) was heated under reflux for 2-3 hrs. Then cooled and poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by recryslalization from absolute Ethanol to give (3) as pale brown crystalls.The yield 67%, m.p. 80^{o}C, ^{1}H-NMR(DMSO-d6): δ,2.2(s,3H,$COCH_3$), 2.3(s,3H,$COCH_3$), 2.45(s,3H,$COCH_3$), 6.9(s,1H,Ar-H),7.5(s,1H,Ar-H),8(s,1H,=CH)and 11.9(s,1H,NH) ppm.

5-(3,5-dibromo-2-hydroxyphenyl)-2,3,4-trihydro-1,2,4-triazole-3-thione(4)

A solution of 2b (0.01 mol) in acetic acid (30 ml) was heated at 25-35oC. a solution of bromine (0.01 mol) in acetic acid (10 ml) was added drop wise with stirring during 30 min. after addition the mixture was stirred for 2hr. the reaction mixture poured into water. The resulting solid was filtered off, washed with water and purified by ethanol to give (4) as pale yellow crystals, yield 57%, m.p.: 205^{o}C, ^{1}H-NMR (DMSO-d6): δ, 7.72 (S, 1H,ArH), 8.06 (S, 1H, ArH); 10.5 (S,1H, NH), 10.9 (S, 1H, NH), 11.99 (S, 1H, OH) ppm.

5-(4-methylphenyl-2-[3,5-dibromo-2-hydroxy-phenylmethylene)-hydrazion]-thiazole(5).

A mixture of (2) (0.01 mol) and 4-methylphenacyl bromide (0.01 mol) in methanol (50 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 6hr. the reaction mixture was cooled and poured into water. The resulting solid was filtered off, washed with hot water, dried and purified by suitable solvent to give (5). yield 62%; MP: 210^{o}C, as brown crystalls ^{1}H-NMR (DMSO-d6): δ, 1.8 (S, 3H, CH_3), 7.12-8.01 (m, 7H, ArH and thiazole H), 8.42 (S, 1H, CH=N), 10.20 (S, 1H, NH), 11.9(S, 1H, OH) ppm.

3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7a) and 3-[(3,5-dibromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione(7b).

A mixture of (2) (0.01 mol) and ethylchloroacetate (0.01 mol) in methanol (50 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 6hr. the reaction mixture was cooled and poured into water. The resulting solid was filtered off, washed with hot water, dried and purified by suitable solvent to give (7a and 7b).
3-[(5-bromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7a), yield 83%, m.p. 310^{o}C, as very pale yellow crystalls,. ^{1}H-NMR (DMSO-d6): δ, 3.9 (S, 2H, CH_2CO), 7.01- 7.80 (m, 3H, Ar H), 8.60 (S, 1H, CH=N), 10.92 (S, 1H, NH), 12.00-12.12 (br.S, 1H, OH) ppm.
3-[(3,5-dibromo-2-hydroxy-phenylmethylene)-amino]-4-oxo-imidazolidin-2-thione (7b), yield 79%, m.p. 295^{o}C as white crystalls. ^{1}H-NMR (DMSO-d6): δ, 3.4 (S, 2H, NCH_2CO), 7.52 (S, 1H, ArH), 7.85 (S, 1H, ArH), 8.63 (S, 1H, CH=N), 11 (S, 1H, NH), 12.10-12.17 (br.S, 1H, OH) ppm

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