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Synthesis and Antimicrobial activity of 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone

A.K. Wanjari

Department of Chemistry, Mahatma Fule Art`s, Commerce and Sitaramji Chaudhari Science College, Warud, Amravati University, MH, India

Abstract : Heterocyclic compounds are used as a building block with a wide application in pharmaceutical industry, medicinal and drug research. This research paper explore the synthesis and antimicrobial activity of 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl) ethanone. The synthesis of 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl) ethanone carried out by using 4-chlorophenol as a starting material which is well knows as a active pharmaceutical ingredients. The synthesised compound tested for the gram positive and gram negative bacteria. The identification of the synthesized compound has been done by using chemical characterization and spectral data.
Keywords : -chlorophenol, thiourea, isothiocynates, 4-chloroacetate, 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone.

Introduction

Sulphur and Nitrogen containing heterocyclic compound are useful building blocks in medicinal and pharmaceutical chemistry, these compound are well known for biologically active compounds[1-4]. The Sulphur and Nitrogen containing heterocyclic compounds have already proven their antimicrobial, antifungal and anti-inflammatory activities[5-6]. Antimicrobial agents, since their discovery have substantially reduced the threats posed by infectious diseases. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds[7]. The thiobiureto, pyridino, dithiaozoyl and bezonido nucleus containing drugs shows remarkable application in medicinal and pharmaceutical sciences[8-9]. Our interest in dithiazole chemistry revolves around the construction of dithiazole systems that can be converted into new heterocyclic systems via ring transformation[10]. Bisdithiazole system considered as a possible precursors to developed heterocyclic system[11]. This is the first time such a product type has been observed in bisdithiazole chemistry, which raises new questions about the possibilities of the use of bisdithiazoles in synthesis. In the present study, 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone has been synthesized from Chalcones by using thiourea and

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isothiocynates. Present study also focus on the development of green route by minimizing time span and increasing purity of the 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone to maintain green chemistry parameter. Benzothiazole have great importance in pharmaceutical utilities, and their synthesis shows considerable interests[12-14]. Considering these all facts present study were undertaken for the feasible and eco-friendly synthesis and antimicrobial analysis of 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone.

Experimental

All the chemicals used are analytical grade, glassware's are qualigens, and melting points are evaluated by using digital melting point apparatus and hot paraffin bath to avoid error. Purity of the synthesize compound calculated by using TLC plate. Perkin-Elmer spectrophotometer in KBr pellets is used for recording IR spectra, H1 NMR spectra recorded by using CDCL3 with TMS as a internal standard.

Preparation of 1-(5-chloro-2-hydroxyphenyl)ethanone: A mixture of 4-chlorophenol (1 mmol), $(CH_3CO)_2O$ (5 mmol), CH_3COONa (2 mmol) and 10 ml solvent was stirred at room temperature for about 10 Hrs. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate as a mobile phase. After completion of reaction, the mixture was filtered and filtrate was concentrated and obtained 4-chlorophenyl acetate after re-crystallization using ethyl acetate as a solvent. Using friedal craft acylation method to the 4-chlorophenyl acetate (1 equivalent) slowly added $AlCl_3$ –solvent free (1.2 equivalent) in fuming hood at 110^oC and reaction was stirred for 10 min, after adding ice water to the reaction mixture and filtration the 1-(5-chloro-2-hydroxyphenyl)ethanone was obtained with 93% yield.

Preparation of 1-(3,5-dichloro-2-hydroxyphenyl)ethanone:

Arrange the reaction set-up in ice bath then to the 1-(5-chloro-2-hydroxyphenyl)ethanone 10 ml of acetic acid, 5 gram of sodium acetate were added and stirring the reaction mixture for 10 minutes to gets reaction mixture completely dissolve. After attaining the reaction temperature below 20^oC chlorine in glacial acetic acid (50 ml) added dropwise into the reaction mixture by keeping temperature below 20^oC. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate as a mobile phase. After completion of reaction ice water was added into it which give pale yellow colour solid after filtration which on re-crystallization using ethyl acetate gives 1-(3,5-dichloro-2-hydroxyphenyl)ethanone with 75% yield.

Preparation of 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea)

A mixture of 1-(3,5-dichloro-2-hydroxyphenyl)ethanone (1 equivalent), thiourea (2 equivalent) and ethanol (20ml) was refluxed for 2 hrs. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate as a mobile phase. After completion of reaction it gives pale yellow coloured solid after filtration in hot condition and recrystalise with ethanol give 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea) with 78% yield.

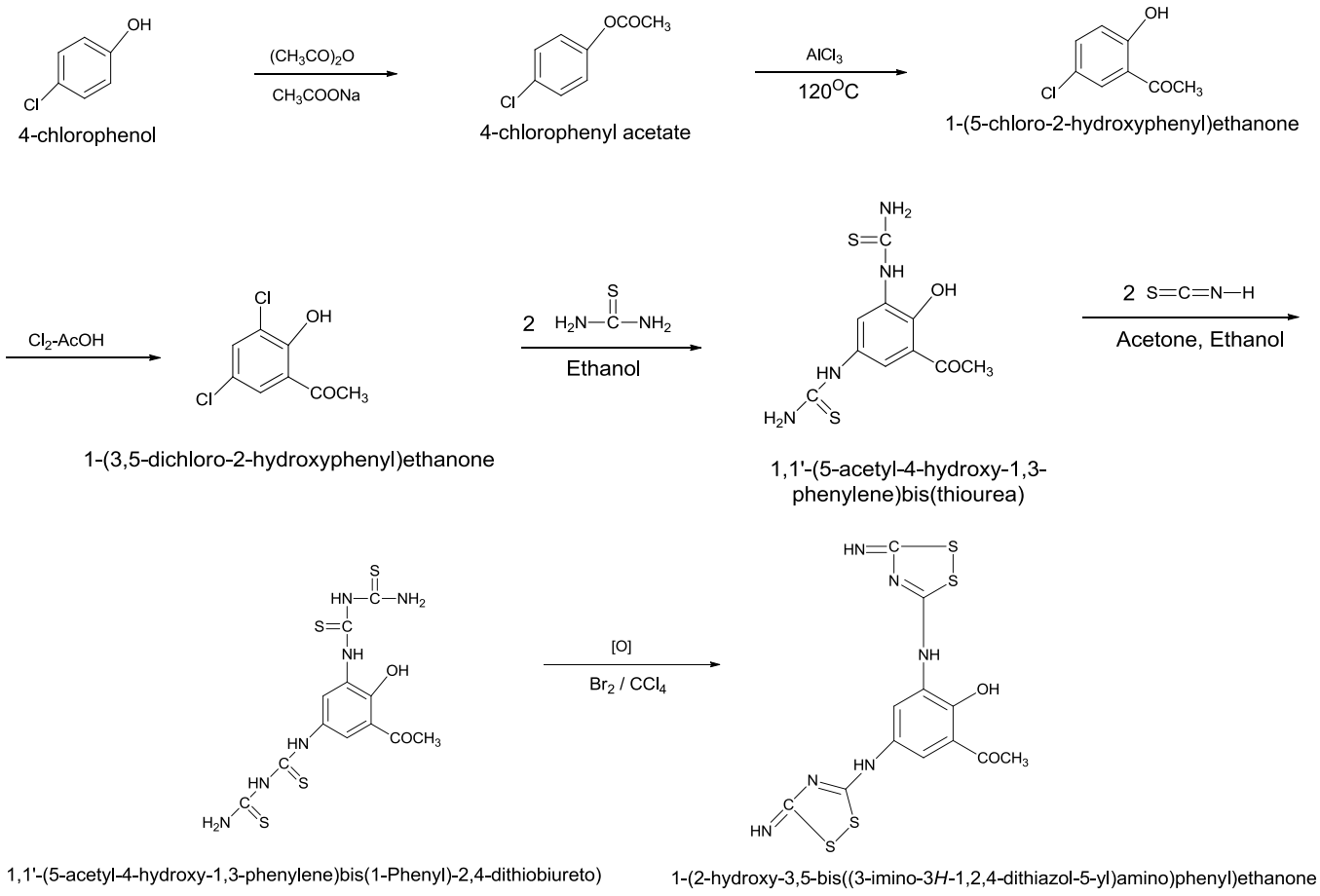
Preparation of 1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto

A mixture of 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea) (1 equivalent) and isothiocyanate (1 2 equivalent) was refluxed using acetone-ethanol (20 ml) as a solvent medium for 1 hrs in round bottom flask. The progress of the reaction was monitored by TLC using n-hexane:ethyl acetate as a mobile phase. After completion of reaction the reaction mixture was filtered off in hot condition which give 73% yield of 1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto.

Preparation of 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone:

1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto (1 equivalent) was taken in china dish and made a paste of it by adding 10% bromine in carbon tetrachloride in fuming hood till the reaction mixture persist the colour of bromine and kept it in at room temperature for 2 hrs it gives dark yellowish crystals with 73% yield.

Scheme for the synthesized compounds



Elucidation of synthesized compounds by NMR and IR spectroscopy

1-(5-chloro-2-hydroxyphenyl)ethanone: IR (KBr) CM^{-1}: 3196.62 cm^{-1}(Phenolic -OH), 1674.23 cm^{-1} (-C=O-stretching), 1475 (aromatic ring C=C) cm^{-1}, 1168 cm-1 (C-Cl stretching in aromatic). ^{1}HNMR ($CDCl_3$) ppm: Ar-H proton at δ7.00-7.69 ppm, -OH proton at δ 5.35 ppm and -CH_3 proton at δ 2.35 ppm.

1-(3,5-dichloro-2-hydroxyphenyl)ethanone: IR (KBr) CM^{-1}: 3132.31 cm^{-1}(Phenolic -OH), 1670.16 cm^{-1} (-C=O-stretching), 1468 (aromatic ring C=C) cm^{-1}, 1159 cm-1 (C-Cl stretching in aromatic). ^{1}HNMR ($CDCl_3$) ppm: Ar-H proton at δ7.57-7.71 ppm, -OH proton at δ 5.35 ppm and -CH_3 proton at δ 2.50 ppm.

***1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea)*:** IR (KBr) CM^{-1}: 3106.67 cm^{-1}(Phenolic -OH), 1645.11 cm^{-1} (-C=O-stretching), 1434 (aromatic ring C=C) cm^{-1}, 1178 cm-1 (C-N). ^{1}HNMR ($CDCl_3$) ppm: Ar-H proton at δ5.79-6.19 ppm, -OH proton at δ 5.35 ppm and Ar-NH proton t δ 4.0 ppm, -NH_2 proton t δ 8.56 ppm, -CH_3 proton at δ 2.51 ppm.

***1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto*:** IR (KBr) CM^{-1}: 3118.83 cm^{-1}(Phenolic -OH), 1741 cm^{-1} (-C=O-stretching), 1602 (aromatic ring C=C) cm^{-1}, 1856 cm^{-1} (C-N), 3234 cm^{-1} (-NH stretching), 1073.0 cm^{-1} (C-S-stretching). ^{1}HNMR ($CDCl_3$) ppm: Ar-H proton at δ5.79-6.19 ppm, -OH proton at δ 5.35 ppm and Ar-NH proton t δ 4.0 ppm, -NH_2 proton t δ 8.53 ppm, -CH_3 proton at δ 2.54 ppm.

***1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone*:** IR (KBr) CM^{-1}: 3201.45 cm^{-1}(Phenolic -OH), 1782 cm^{-1} (-C=O-stretching), 1608 (aromatic ring C=C) cm^{-1}, 1518 cm^{-1} (C-N), 3310 cm^{-1} (-NH stretching), 1438.0 cm^{-1} (C-S-stretching). ^{1}HNMR ($CDCl_3$) ppm: Ar-H proton at δ5.79-6.19 ppm, -OH proton at δ 5.35 ppm and Ar-NH proton t δ 4.7 ppm, -NH_2 proton t δ 7.48 ppm, -CH_3 proton at δ 2.50 ppm. The physical characterizations of all the synthesized compounds are shown in table number 1.

Antimicrobial Activity

The 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea), 1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto and 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone compounds were evaluated for in vitro antimicrobial activity. The antimicrobial activities of these compounds were screened by using cup-plate agar diffusion method in DMF, using standard Co-Trimazin 25 µg/ml against gram positive and gram negative bacteria such as E. *coli*, S. *typhi*, S. *abony*, P. *aeruginosa*, and B. *subtilis*. The antimicrobial activities of all the synthesized compounds are shown in table number 2.

Table No. 1: Physical data of characterization of compounds

Sr. No	Name of Compound	M.P in ^{o}C	Yield in %	Elemental composition found				
				C	H	N	O	S
1	1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea)	177	78	30.49	5.11	23.71	13.54	27.13
2	1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto	164	73	39.42	3.30	19.70	7.50	30.06
3	1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone	181	73	39.79	2.38	19.88	7.57	30.35

Table No. 2: Antimicrobial Activity

Sr. No.	Name of Compound	Zone of inhibition in mm				
		Bacteria				
		E. coli	***S. abony***	***P. aeruginosa***	***S. typhi***	***B. subtilis***
1	1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea)	14	15	15	14	15
2	1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto	15	14	16	15	16
3	1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone	17	15	16	16	17

Conclusion

The synthesis of proposed structure of 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea), 1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto and 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone by cyclo-addition reaction gives good yields and high purity. The synthesized compounds were screened against the gram positive and gram negative bacteria for the Antimicrobial activity study by using Cup plate method. 1-(2-hydroxy-3,5-bis((3-imino-3H-1,2,4-dithiazol-5-yl)amino)phenyl)ethanone compound shown strong anti-microbial activity than 1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(1-phenyl)-2,4-dithiobiureto and 1,1-(5-acetyl-4-hydroxy-1,3-phenylene)bis(thiourea) even at low concentrations. This study can provide a road map to design and synthesis of many heterocyclic compounds based anti-microbial active compounds

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