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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME CHLOROSUBSTITUTED-1, 3-THIAZOLES

A V GAJBHIYE* AND P R RAJPUT

**Department of chemistry, MGV's A.S.C. College, Nampur, Nashik(D), M.S., India.*
Department of chemistry, Vidyabharti Mahavidyalaya, Camp, Amravati, M.S., India.

ABSTRACT

A Simple and convenient protocol is described for preparation of some new 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4'-chlorobenzyl)-2-amino-1,3-thiazole and 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4'-chlorobenzyl)-2-aminophenyl-1,3-thiazole, were synthesized by refluxing dibrominated chalcone with thiourea or N-phenyl thiourea in good yields. The newly synthesized titled compounds were screened for their antibacterial activities against pathogens such as *staphylococcus aureus*, *p.aeruginosa*, *salmonella typhi*. Some of the compounds displayed pronounced biological activity. All these compounds have been characterized on the basis of their UV, IR and NMR spectral results.

KEYWORDS: Thiazoles, antibacterial activities, chalcone, thiourea, phenyl thiourea.

A V GAJBHIYE
Department of chemistry, MGV's A.S.C. College, Nampur, Nashik(D), M.S., India.

INTRODUCTION

Thiazole is a five membered ring system in which two heteroatoms (N and S) are placed in the ring at 1, 3-positions. Small ring heterocycles containing nitrogen and sulphur atoms have been under investigation for a long time because of their important medicinal properties. Among the wide range of heterocycles explored to develop pharmaceutically important molecules, thiazoles have played an important role in medicinal chemistry. Thiazoles and its derivatives display a wide range of biological activities such as sedative[1], anaesthetic[2], cardiotonic[3], anti-bacterial[4], antifungal[5] and anti-inflammatory[6], and some are known to be used as pharmaceutical as well as agrochemical products[7-9]. Since, discovery and development of effective as well as safe drugs has brought a progressive era in human healthcare that is accompanied by the appearance of drug resistant bacterial strains, there is constant need of new antibacterial agents having novel mechanisms of action to act against the harmful pathogens. 1, 3-thiazole heterocycle is an interesting building block in a variety of natural and synthetic compounds found to possess good antibacterial[10-12] potential. In the present study, in this article, we described a highly efficient synthesis of thiazoles in simple way with less no. of steps by refluxing dibrominated chalcone with thioureas in good yield (Scheme I). Also further investigated them for their antimicrobial activity.

EXPERIMENTAL

All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. All the glasswares used in the present work were of pyrex quality. Purity of compounds was monitored on silica gel coated TLC plate. Melting points were determined in glass capillary tubes and are uncorrected. PMR spectra were recorded on a Bruker Avance II 400 spectrophotometer in DMSO and U.V. spectra on a spectrophotometer (Schimadzu U.V.1601). IR spectra were recorded on a Perkin-Elmer FT IR 1600. Physical characterization data of all the compounds is given in table 1.

Table 1
Characterization data of newly synthesized compounds

Compound	Molecular formula	M.P(ºC)	Yield (%)	Rf
1a	$C_8H_6O_2Cl_2$	53	75	0.83
2a	$C_{15}H_9Cl_3O_2$	190-193	70	0.86
3a	$C_{15}H_9Br_2Cl_3O_2$	204-207	75	0.82
4a	$C_{18}H_{18}Cl_3N_2OS$	180-184	70	0.70
5a	$C_{24}H_{22}Cl_3N_2OS$	145-147	75	0.75

The synthetic routes which furnished the target compounds are shown below along with their U.V., IR and NMR data (Scheme-1)

Preparation of 2'-hydroxy-3', 5'-dichloroacetophenone (1a)

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

I.R. (KBr): 3050 cm^{-1}(-OH phenolic), 1645 cm^{-1}(C=O in ketone), 1300 cm^{-1} (C-O), 730 cm^{-1} (C-Cl stretching)
PMR: δ12.73(s, 1H, Ar-OH); δ7.25-7.63(m, 2H, Ar-H); δ2.60(s, 3H, -CH_3).
U.V.: 343 nm

Preparation of 2'hydroxy-3', 5'-dichloro-4-4'-chlorophenylchalcone (2a)

2'-Hydroxy-3', 5'-dichloroacetophenone (1a), (0.1M) was dissolved in ethanol (50 ml) and p-chlorobenzaldehyde (0.1M) was added and the mixture was heated to boiling. Aqueous potassium 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 thus separated was filtered, washed with sodium bicarbonate (10%) followed by water and finally crystallized from ethanol (2a).

I.R. (KBr): 3400cm^{-1}(-OH phenolic), 1647cm^{-1}(C=O in ketone), 579cm^{-1}(C=C stetching), 818 (C-Cl stretching), 3074 cm^{-1}(aromatic –CH stretching).
PMR: δ 7.93(d, 1H, -CO-CH=CH-Ar); δ 7.52 (d,1H, -CO-CH=CH); δ 7.80 (s,1H, Ar-H); δ7.64 (s,1H, Ar-H); δ7.62 (d, 2H, Ar-H); δ7.44 (d, 2H, Ar-H); δ 13.31(s, 1H, Ar-OH).
U.V.: 380 nm.

Preparation of 1-(2'-hydroxy-3', 5'-dichlorophenyl)-2,3-dibromo-3-(4'-chlorophenyl)-propan-1-one (3a)

2'-Hydroxy-3', 5'-dichlorophenyl-4-4'-chlorophenylchalcone(2a), (0.01M) was suspended in bromine in glacial acetic acid reagent (25% w/v)(6.4 ml). The reagent was added dropwise with constant stirring. After complete addition of reagent, the reaction mixture was kept at room temperature for about 30 minutes. The solid product thus separated was filtered and washed with a little petroleum ether to get compound (3a).

I.R. (KBr): 3421cm^{-1}(-OH phenolic), 1651cm^{-1} (C=O in ketone), 1579cm^{-1}(C=C stetching), 837 cm^{-1}(C-Cl stretching), 3086 cm^{-1}(aromatic =CH stretching).
PMR: δ 6.63 (d, 1H, -CO-CH-Br); δ 5.63(d, 1H, -CO-CHBr-CH-Br); δ 7.71(d, 2H, Ar-H); δ 7.41(d, 2H, Ar-H); δ 7.42 (s, H, Ar-H); δ 7.73(s, H, Ar-H); δ 8.32 (s, 1H, Ar-OH).
U.V.: 340 nm

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4'-chlorobenzyl)-2-amino-1,3-thiazole (4a)

1-(2'-hydroxy-3', 5'-dichlorophenyl) -2,3-dibromo-3- (4' -chlorophenyl)-propan-1-one (0.01 mol) and thiourea (0.01 mol) were dissolved in ethanol (25 ml). To this aqueous KOH solution (0.02mol) was added. The reaction mixture then refluxed for 2.5 hours, cooled and diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get compound (4a).

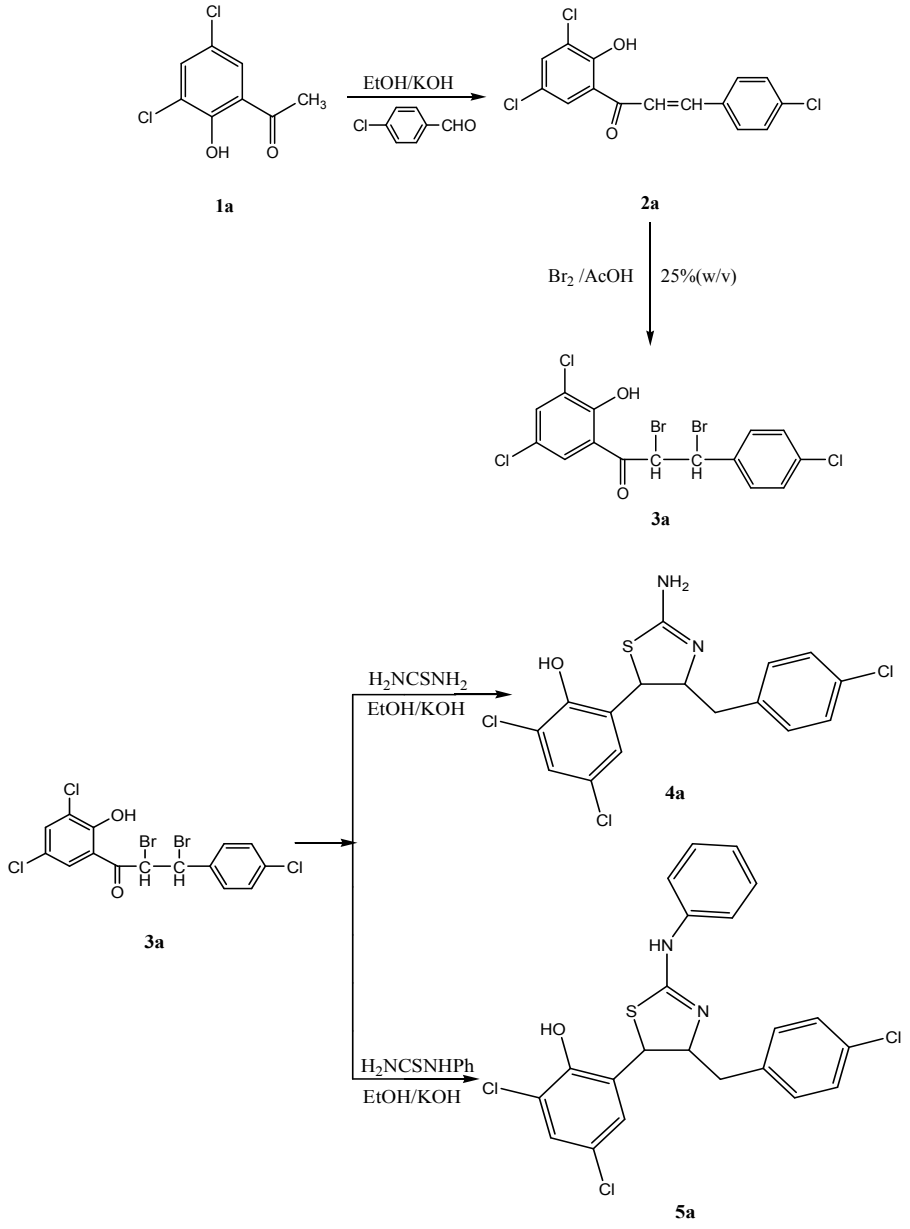
IR: 3600 cm-1(-OH phenolic), 2925 cm-1(N-H stretching), 3074 cm-1(aromatic C-H stretching), 1602 cm-1(C=N stretching), 1511 cm-1(C=C stretching); 831 cm-1(C-Cl)
PMR: δ 13.31(s, 1H, Ar-OH); δ 2.53 (s, 2H, -CH_2-) ; δ8.43 (s,1H, Ar-H); δ 7.80 (s, 1H, Ar-H); δ 7.48 (d, 2H, Ar-H) ; δ 7.93(d, 2H, Ar-H) ; δ 3.64(s, 2H, -NH_2)
UV: 320 nm

Preparation of 5-(2'-hydroxy-3', 5'-dichlorophenyl)-4-(4'-chlorobenzyl)-2-aminophenyl-1,3-thiazole (5a)

1-(2'-hydroxy-3', 5'-dichlorophenyl)-2, 3-dibromo-3-(4'-chlorophenyl)-propan-1-one (0.01 mol) and phenyl thiourea (0.01 mol) were dissolved in ethanol (25 ml). To this, aqueous KOH solution (0.02mol) was added. The reaction mixture was then refluxed for 2.5 hours, cooled, diluted with water and acidified with conc. HCl. The product thus separated was filtered and crystallized from ethanol to get compound (5a).

IR: 3620 cm-1(-OH phenolic), 2975 cm-1(N-H stretching), 3100 cm-1 (aromatic C-H stretching), 1615 cm-1(C=N stretching), 1515 cm-1(C=C stretching); 831 cm-1(C-Cl)

PMR: δ 13.31(s, 1H, Ar-OH); δ 2.53 (s, 2H, -CH_2-) ; δ8.43 (s,1H, Ar-H); δ 7.80 (s, 1H, Ar-H); δ 7.48 (d, 2H, Ar-H) ; δ 7.93(d, 2H, Ar-H) ; δ 3.64(s, 1H, -NH-); δ 7.36-7.54(m, 5H, Ar-H)
UV: 370 nm



The compounds (3a, 4a and 5a) were screened for their antibacterial activity against some pathogens such as Staphylococcus aureus, p.aeruginosa, salmonilla 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.

Scheme I

Table 2
Antibacterial activities of synthesized new compounds

Compound	Zones of inhibition(mm)		
	s.typhi	***p.aeruginosa***	***s.aureus***
3a	62.5	125	100
4a	25	200	25
5a	125	50	62.5

RESULTS AND DISCUSSIONS

The newly synthesized compounds (3a, 4a and 5a) were found to be active against test pathogens. A further detailed study in the light of medical sciences is advised to reveal the symbiotic impact of titled compounds in curing human ailments. A new synthetic procedure for the formation of 1,3-thiazole compounds containing 5-phenyl chlorosubtituted moiety and 2-substituted amino group has been developed that achieved in minimum number of steps with better yield. Thus, we believe that this novel procedure opens up a new door for the formation of important heteroaromatic compounds of this series in the interest of academics and pharmaceutical industries.

CONCLUSION

In summary, we have synthesized some thiazoles having 5-phenyl chlorosubstituted moiety and 2-substituted amino moiety. The antifungal screening of thiazoles 3a-5a were found to be active due to the presence of chlorine on phenyl ring.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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