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ORIGINAL PAPER

Synthesis and Antibacterial Activity of 1-(2-Diazo-6-ethoxybenzothiazolyl) Substituted Benzene Derivatives

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ABSTRACT

*The title compounds were prepared by a two step synthesis scheme. 2-Amino-6-ethoxy benzothiazole **1** on diazotization gives 6-ethoxybenzothiazolyl-2-diazonium chloride, which on reaction with cold solution of various coupling agents in dilute NaOH furnishes 1-(2- diazo-6-ethoxybenzothiazolyl) substituted benzene derivatives **2**. The structures of all these compounds have been supported by their elemental analysis and spectral studies. Synthesized products were evaluated for their antibacterial activity against Escherichia coli., Klebsiella pneumoniae, Pseudomonas aureus and Staphylococcus aureus and compared with standard drugs.*

Key words: *Benzothiazole, Antibacterial, Azo Dyes.*

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1. INTRODUCTION

Benzothiazole derivatives possess potent biological activities such as anti-inflammatory[1], antitumor agents[2-4], antihistamines[5], antibacterial[6, 7], schistosomicidal agents[8], antituberculotic[9] and insecticides[10]. Benzothiazoles also show significant effects against cancer[11]. Similarly azo compounds also exhibit microbial activities such as antibacterial[12], antiviral[13], antifungal[14] etc. Looking to the importance of these compounds, the present work was aimed to synthesize and screen the antibacterial activity of some new benzothiazole derivatives containing azo group in their structure. For this purpose 2-amino-6-ethoxybenzothiazole **(1)** was prepared by the method reported in the literature[15, 16]. The compound **(1)** was converted into corresponding diazonium chloride by diazotization reaction and it was further coupled with various

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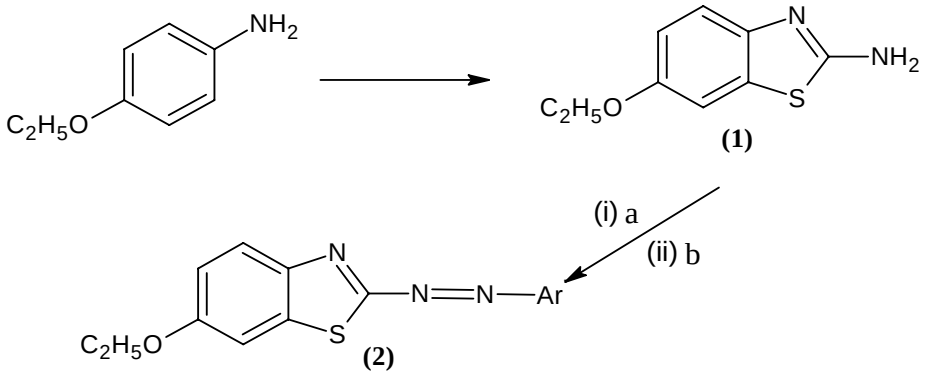
coupling agents (Aniline, *o*-Chloroaniline, á-Naphthol, â-Naphthol and N,N-Dimethylaniline) to get the title compound 2 (Scheme- 1). These compounds were screened for their antibacterial activity against *Escherichia coli., Klebsiella pneumoniae, Pseudomonas aureus* and S*taphylococcus aureus*.

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compounds has been checked by thin layer chromatography. IR spectra were recorded on Shimadzu 8201 Pc spectrophotometer (ë $_{max}$ in cm^{-1}) using KBr disc. ^1H NMR spectra are recorded in $CDCl_3$ on a Brucker DRX-300 MHz using TMS as internal standard.

Synthesis of 2-amino-6-ethoxybenzothiazole (1)

A mixture of p-ethoxy aniline (0.1 mol) and ammonium thiocyanate (0.2 mol) in acetic acid (150mL) were taken in a three neck round bottom flask and allowed to cool up to 0-5 ºC in an ice bath. Now 25 mL bromine (20 mL dissolved in 100 mL acetic acid) was added drop wise through dropping funnel with constant stirring. After the addition of bromine stirring was continued for 24 hours and the contents were filtered. The solid obtained after filtration was dissolved in hot water and filtered again. The filtrate was neutralized by saturated solution of sodium carbonate. 2-Aminobenzothiazole precipitated was washed with water and recrystallised with ethanol (Scheme 1), yield 75%[15, 16].



(a) $NaNO_2$ / HCl, 0ºC, **(b)** ArH / dil. NaOH, 0º– 5ºC,

ArH: - Aniline, o-Chloro aniline, á-Naphthol, â-Naphthol and N, N-Dimethyl aniline.

Scheme 1

Synthesis of 1-*(2-diazo-6-ethoxybenzothiazolyl) substituted benzene derivatives* ***(2)***

A solution of compound **(1)** (0.05 mol) in 5N HCl (20mL) was cooled to 0ºC. To this solution was added a cold solution of sodium nitrite (1.0gm) drop wise with constant stirring. When the addition was complete, the resultant reaction mixture was left in ice- chest for 1hr. To the ice cold solution, a cold solution of Aniline / o-Chloro aniline / á–Naphthol / â-Naphthol / N, N-Dimethyl aniline (0.05mol) in dilute NaOH was added drop wise with constant stirring. When the addition was complete, the resultant reaction mixture was vigorously stirred and filtered off. It was dried and recrystallized from ethanol. Physico-chemical data of synthesized compounds are given in Table 1.

Table 1 Physico-chemical data of synthesized compounds (2a-e)

Compound	*Mol. Formula*	*Melting point* °C	*Analysis (%) found (cal.)* C	H	N	*% yield*
2a	$C_{15}H_{14}N_4OS$	168	60.30 (60.40)	4.43 (4.69)	18.68 (18.79)	49
2b	$C_{15}H_{13}ClN_4OS$	207	60.30 (60.40)	4.28 (4.36)	18.29 (18.79)	59
2c	$C_{19}H_{15}N_3O_2S$	170	65.22 (65.32)	4.18 (4.29)	12.12 (12.09)	58
2d	$C_{19}H_{15}N_3O_2S$	172	65.22 (65.32)	4.18 (4.29)	12.12 (12.03)	62
2e	$C_{17}H_{18}N_4OS$	169	62.02 (62.08)	6.02 (6.09)	17.12 (17.07)	55

ANTIBACTERIAL ACTIVITY

All the synthesized compounds **2a-e** were tested against gram positive bacteria *S. aureus* and gram negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* using Kirby Bauer disc diffusion method. The zone of inhibition was measured in mm. For comparison Streptomycin and Ceftazidime were taken as standard drugs. The compounds were tested at 200 mg/ml concentration. The observations show that compound 2**b** was found more effective against *Escherichia coli*, *Klebsiella pneumoniae* and *S. aureus* and the compound 2**a** was found more effective against *E. coli*, *Klebsiella pneumonia*. The results of activity are summarized in Table 2.

Table 2 The zone of inhibition in mm of the compound as well as standard drugs tested for antibacterial activity

	Zone of Inhibition (mm)			
Compounds	***E. Coli***	***K. pneumoniae***	***P. aeruginosa***	***S. aureus***
2a	22	20	15	15
2b	24	22	20	17
2c	19	17	09	09
2d	20	18	10	08
2e	21	20	13	11
Streptomycin	22	23	25	20
Ceftazidime	24	26	21	26

RESULTS AND DISCUSSION

The structures of all the synthesized compounds have been supported by elemental analysis and their spectral studies. Compounds 2**a-e** shows IR absorption bands at 1605-1635(-N=N, stretching), 3340-3450 (-O-H stretching), broad IR bands at 3400-3440 cm-1(NH Stretching), 1250-1290 (C-O-C stretching).

Spectral Analysis of Compounds 2a-2e

1-(2-diazo-6-ethoxybenzothiazolyl)-4-aminobenzene **2a:** M.F. $C_{15}H_{14}N_4OS$, IR (KBr) ë $_{max}$ in cm^{-1}, a band appeared at 1390 due to the C-S str, 1650 C=N str, 1613 N=N str, 1470, 1598 Ar C=C str, 1290 C-O-C str, 1338 C-NH_2 str; ^{1}HNMR (300MHz, $CDCl_3$): 1.39 (t, 3H, CH_3); 3.98 (q, 2H, Ar-OCH_2), 6.4 (s, 1H, acyclic N-H), 7.30-8.0.(m, 8H, Ar- H)

1-(2-diazo-6-ethoxybenzothiazolyl)-4-amino-3-chlorobenzene **2b**: M.F. $C_{15}H_{13}ClN_4OS$, IR (KBr) ë $_{max}$ in cm^{-1}, a band appeared at 1445 C-S str, 1645 C=N str, 1631 N=N str, 1479 Ar C=C str, 1218 C-O-C str, 1340 C-NH_2 str , 1098 C-Cl; ^{1}HNMR (300MHz, $CDCl_3$): 1.49 (t, 3H, CH_3); 3.96 (q, 2H, Ar- OCH_2), 5.63 (s, 1H, -OH), 6.4 (s, 1H, acyclic N-H), 7.33-7.45 (m, 7H, Ar- H).

1-(2-diazo-6-ethoxybenzothiazolyl)-4-hydroxynaphthalene **2c**: M.F. $C_{19}H_{15}N_3O_2S$, IR (KBr) ë $_{max}$ in cm^{-1}, a band appeared at 1370 C-S str, 1662 C=N str, 1635 N=N str, 1470, 1580 Ar C=C str, 1242 C-O-C str, 3402 OH str; ^{1}HNMR (300MHz, $CDCl_3$) : 1.46 (t, 3H, CH_3); 3.89 (q, 2H, Ar-OCH_2), 5.65 (s, 1H, -OH), 7.30-7.68.(m, 4H, Ar -H), 7.80-8.0.(m, 10H, Ar -H).

1-(2-diazo-6-ethoxybenzothiazolyl)-2-hydroxynaphthalene **2d**: M.F. $C_{19}H_{15}N_3O_2S$, IR (KBr) ë $_{max}$ in cm^{-1}, a band appeared at 1360 C-S str, 1642 C=N str, 1620 N=N str, 1490 Ar C=C str, 1279 C-O-C str, 3350 OH str; ^{1}HNMR (300MHz, $CDCl_3$) : 1.40 (t, 3H, CH_3); 3.92 (q, 2H, Ar- OCH_2), 5.68 (s,1H,-OH), 7.23-7.58.(m, 4H, Ar- H), 7.65-7.80.(m, 10H, Ar -H).

1-(2-diazo-6-ethoxybenzothiazolyl)-4(N,N'-dimethylamino)benzene **2e**: M.F. $C_{17}H_{18}N_4OS$, IR (KBr) ë $_{max}$ in cm^{-1}, a band appeared at 1380 C-S str, 1658 C=N str, 1608 N=N str, 1490, 1602 Ar C=C str, 1282 C-O-C str; ^{1}HNMR (300MHz, $CDCl_3$): 1.35 (t, 3H, CH_3); 3.90 (q, 2H, Ar- OCH_2), 5.62 (s, 1H, -OH), 2.78 (s, 6H, N-$(CH_3)_2$); 7.30-7.39 (m, 8H, Ar -H).

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