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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL 4–[(SUBSTITUTED BENZOTHIAZOL-2-YL) HYDRAZONO]–3–METHYL–5–(SUBSTITUTED PHENYL IMINO)–4, 5–DIHYDROISOXAZOLE

S. Sareen[1], V. Khatri[2], V. Sareen[2]

[1]Vivekanand Institute of Technology (East), Department of Chemistry, Jaipur
[2]Department of Chemistry,University of Rajasthan, Jaipur
Email: sareenparmod@yahoo.com

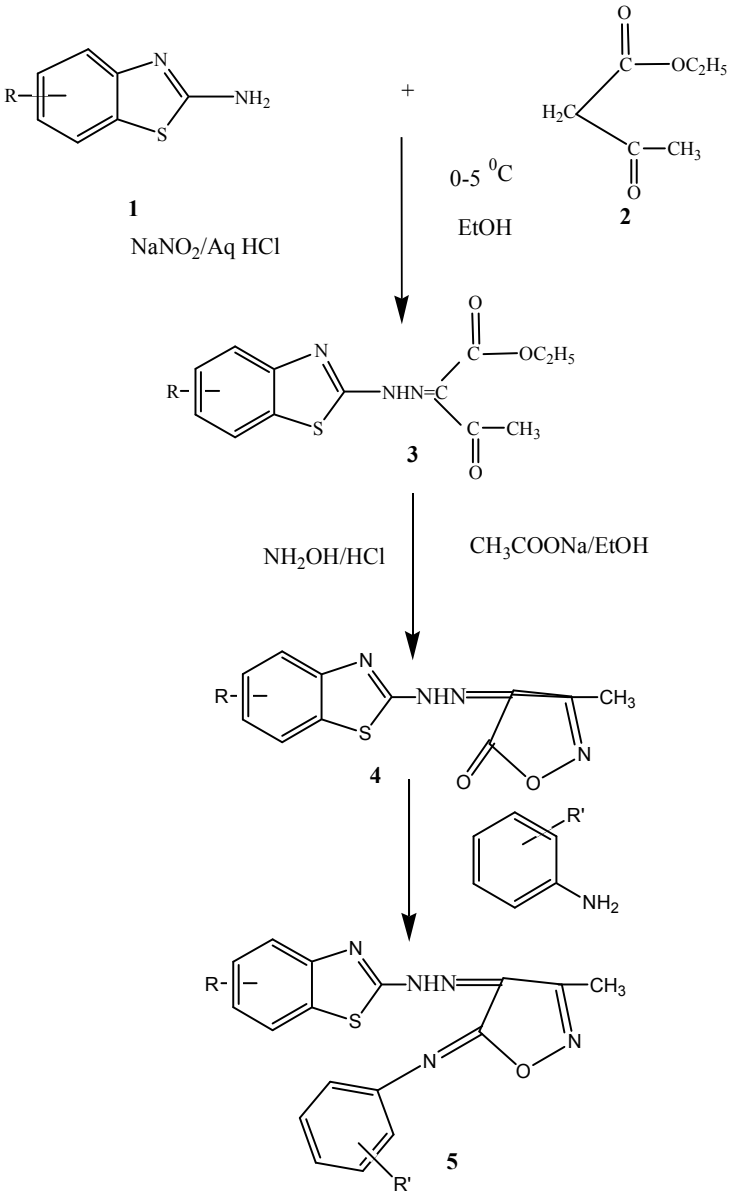
ABSTRACT
This paper deals with synthesis of 2- [(substituted benzothiazol-2-yl) hydrazono] butyric acid ethyl ester **3** from 2-aminosubstituted benzothiazole and ethyl acetoacetic ester in presence of HNO_2 and ethanol. 4-[(substituted benzothiazol-2-yl)-hydrazono]-3-methyl-4H-isoxazol-5-ones **4** were prepared by the condensation of 2-[(substituted-benzothiazol-2-yl)-hydrazono]-3- oxobutyric acid ethyl ester in ethanol with hydroxyl amine hydrochloride in the presence of sodium acetate. Equimolar quantities of **4** and substituted anilines were refluxed in acetic acid to give **5**.

INTRODUCTION
Benzothiazole moiety itself is very small but it possesses different biological activities. Its different substituted derivatives are all the more biologically active.[1-5]
2-Aminobenzothiazoles have a wide spectrum of biological activities. The biological profiles of these new generations of benzothiazoles represent much progress with regard to the older compounds. Antimicrobial activity of some substituted thiazoles are well established because they possess (S-C=N) toxophoric ring.
Isoxazoles have a long history of application in pharmaceutical and agrochemical industry.[6] Hikmet Agirbas et al.[7] reported the synthesis and structure bacterial activity relationship investigation of isomeric 2,3,5 - substituted perhydropyrolo[3,4-d] isoxazole-4,6-diones.
The compounds containing isoxazolone nucleus along with benzothiazole enhances their biological activity. Due to broad spectrum of pharmacological and biological activities of both heterocycles we envisaged that the synthesis of new molecules containing both heterocycles could give entry to novel bioactive compounds.
Keeping in view the importance of biological activities associated with benzothiazole and isoxazole derivatives we have synthesized some new halogen containing hyrazono derivatives of isoxazoles[8]. Because of our interest in condensation reactions and in continuation of our work[9, 10] the formation of isoxazolones opened the gates to the formation of the title compounds 4-[substitutedbenzothiazol-2-yl)hydrazono]-3-methyl-5-(substitutedphenyl imino)-4,5-dihydroisoxazole.
All these new compounds synthesized are characterized by IR, ^{1}H NMR and elemental analysis.

RESULT AND DISCUSSION

4-[substituted benzothiazol-2-yl)hydrazono]-3-methyl-5-(substituted phenyl imino)-4, 5-dihydroisoxazole **5** were prepared by the condensation of 4-[(substituted benzothiazol-2-yl)hydrazono]-3-methyl-4H-isoxazol-5-ones and substituted anilines in presence of acetic acid in ethanol.

The names and M.P.'s of these compounds are recorded in **TABLE I.**



R= 4-Cl, 5-Cl, 4-F, 6-F

R'= 4-F, 2-Cl, 2-CF_3, 2,5-Dichloro

SCHEME

IR SPECTRA

IR spectra were recorded on a SHIMADZU 8400S FT-IR spectrometer in KBr pellets.

IR spectra of 4-[substituted benzothiazol-2-yl)hydrazono]-3-methyl-5-(substitutedphenyl imino)-4,5-dihydroisoxazole(5) showed significant characteristic absorption bands in the region of ν_{max} : 3350 (-NH), 1500(>NHN=C), 1625 (>C=N) and 3000-3050 (aromatic) cm^{-1}.

^{1}HNMR

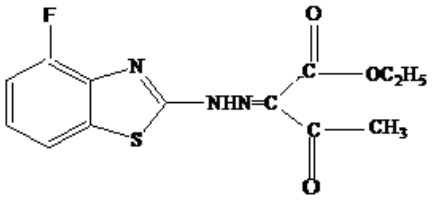
^{1}HNMR Spectra of 4-[substituted benzothiazol-2-yl)hydrazono]-3-methyl-5-(substitutedphenyl imino)-4,5-dihydroisoxazole(5) showed characteristic signals at δ 8.1 (s, 1H, >NHN=C), 1.25 (s, 3H, CH_3), 6.7-7.3 (m,7H, ArH) ppm.

TABLE 1

Compound	Nomenclature	M.P. ^{0}C
5a	4-[(-4-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(4-fluorophenylimino)-4,5-dihydroisoxazole	157
5b	4-[(-4-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2-chlorophenylimino)-4,5-dihydroisoxazole	158
5c	4-[(-4-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2,5-dichlorophenylimino)-4,5-dihydroisoxazole	160
5d	4-[(-5-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(4-fluorophenylimino)-4,5-dihydroisoxazole	226
5e	4-[(-5-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2-chlorophenylimino)-4,5-dihydroisoxazole	229
5f	4-[(-5-Chlorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2,5-dichlorophenylimino)-4,5-dihydroisoxazole	230
5g	4-[(-4-Fluorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2-chlorophenylimino)-4,5-dihydroisoxazole	210
5h	4-[(-6-Fluorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(4-fluorophenylimino)-4,5-dihydroisoxazole	159
5i	4-[(-6-Fluorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2-trifluoromethylphenylimino)-4,5-dihydroisoxazole	151
5j	4-[(-6-Fluorobenzothiazol-2-yl)hydrazono]-3-methyl-5-(2,5-dichlorophenylimino)-4,5-dihydroisoxazole	160

EXPERIMENTAL

Synthesis of 2- [(4-Fluorobenzothiazol-2-yl) hydrazono] butyric acid ethyl ester (3)



2-Amino-4-fluoro benzothiazole (0.01 mole) was dissolved in a mixture of conc. HCl (8ml) and water (6ml) and cooled to 0^{o}C in an ice bath, cold aqueous solution of sodium nitrite (

0.02 mole) was then added. The cold diazonium salt solution was filtered into a cooled solution of ethyl acetoacetate (0.01 mole) and sodium acetate (0.05 mole) in ethanol (25ml) and stirred for 2 hrs. and the resulting solid was filtered, dried and crystallized from ethanol. Yield 60%, M.P. 225^{o}C. All other diazonium compounds were prepared in a similar manner.

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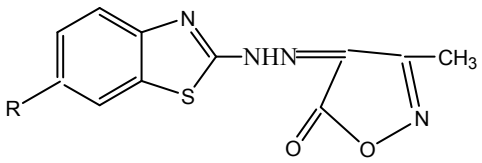
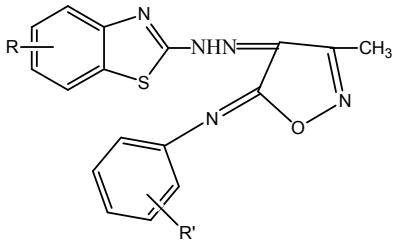
4-[(Substituted-benzothiazol-2-yl)-hydrazono]-3-methyl-4H-isoxazol-5-ones (4)



4-[(Substituted benzothiazol-2-yl)-hydrazono]-3-methyl-4H-isoxazol-5-ones were prepared by the condensation of 2-[(substituted-benzothiazol-2-yl)-hydrazono]-3- oxobutyric acid ethyl ester (0.01 mole) in ethanol (20 ml) with hydroxyl amine hydrochloride (0.01 mole) in the presence of sodium acetate (1g) in water by refluxing for 4-5 hrs. on a water bath. After completion of reaction, reaction mixture was cooled and a solid was obtained which on crystallization from ethanol gave 4-[(substituted benzothiazol-2-yl)hydrazono]-3-methyl-isoxazol-5-ones.
All halogenated hydrazono pyrazolones were prepared in a similar manner.

4-[(Substituted benzothiazol-2-yl)hydrazono]-3-methyl-5-(substituted phenylimino)-4,5-dihydroisoxazole (5)



5

R = 4-Cl, 5-Cl, 4-F, 6-F

R' = 4 F, 2-Cl, 2-CF_3, 2,5-Dichloro

Equimolar (0.01 mol) quantities of **4** and substituted anilines were refluxed in glacial acetic acid (5 ml) for 6 hrs., after cooling pale yellow solid was obtained. It was kept overnight, then it was filtered, washed, dried and recrystallized with ethanol to give **5**. All halogenated imino compounds were prepared in a similar manner.

TABLE 2

Physical and analytical data of compounds prepared

Compound	R	R'	Molecular Formula	Yield, %	Analysis Found (Calculated) N	S
5a	**4-Cl**	**4-F**	$C_{17}H_{11}ClFN_5OS$	**50**	**18.12 (18.06)**	**8.38 (8.26)**
5b	**4-Cl**	**2-Cl**	$C_{17}H_{11}Cl_2N_5OS$	**52**	**17.45 (17.33)**	**7.99 (7.92)**
5c	**4-Cl**	**2,5- Di Cl**	$C_{17}H_{11}Cl_3N_5OS$	**45**	**15.90 (15.92)**	**7.26 (7.28)**
5d	**5-Cl**	**4 –F**	$C_{17}H_{11}ClFN_5OS$	**46**	**18.27 (18.06)**	**8.37 (8.26)**
5e	**5-Cl**	**2-Cl**	$C_{17}H_{11}Cl_2N_5OS$	**51**	**17.30 (17.33)**	**7.90 (7.92)**
5f	**5-Cl**	**2,5- Di Cl**	$C_{17}H_{11}Cl_3N_5OS$	**52**	**15.96 (15.92)**	**7.30 (7.28)**
5g	**4 -F**	**2-Cl**	$C_{17}H_{11}ClFN_5OS$	**48**	**18.00 (18.06)**	**8.25 (8.26)**
5h	**6-F**	**4 F**	$C_{17}H_{11}F_2N_5OS$	**47**	**18.85 (18.87)**	**8.64 (8.62)**
5i	**6-F**	**2-CF_3**	$C_{18}H_{11}F_4N_5OS$	**50**	**16.60 (16.63)**	**7.62 (7.60)**
5j	**6-F**	**2,5- Di Cl**	$C_{17}H_{10}Cl_2FN_5OS$	**45**	**16.60 (16.58)**	**7.64 (7.58)**

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