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Synthesis and Characterization of Some Benzoxazole Derivatives

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ABSTRACT

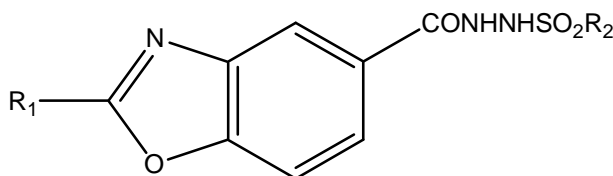
The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. In the current research work, the title compounds *N*[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide, were synthesized by electrophilic aromatic substitution on *p*-hydroxy methyl benzoate (I) with concentrated nitric acid and concentrated sulfuric acid under reflux condition. Compound (II) on reduction with sodium dithionate with alcohol gives 3-amino-4-hydroxy-benzoic acid methyl ester (III). Reaction of compound (III) with two appropriate aliphatic acids (formic acid and acetic acid) produced corresponding 2-substituted benzoxazole-5-carboxylic acid methyl esters. The reaction of compounds (IV) with hydrazine hydrate in ethanol on refluxing yielded the corresponding 2-substituted benzoxazole-5-carboxylic acid hydrazides. On further reaction of compounds (V) with the different sulfonyl chloride derivatives afforded the corresponding eight *N*[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide. The identification and characterization of the synthesized compounds were carried out by Elemental analysis, melting point, Thin Layer Chromatography, FT-IR, NMR and Mass data to ascertain that all synthesized compounds were of different chemical nature than the respective parent compound.

Keywords- Benzoxazole, Thin Layer Chromatography, FT-IR, NMR.

INTRODUCTION

The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. Benzoxazoles have been reported to show a broad spectrum of biological activities. Notable among these are antihistaminic [1],

antifungal[2], Cyclooxygenase Inhibiting[3], antitumor[4], antiulcer[5], anticonvulsant[6], hypoglycemic[7], anti-inflammatory[8,9] and antitubercular activity[10]. The pharmacological properties of Benzoxazoles encouraged our interest in synthesizing several new compounds. In the present study we synthesized a series of some novel eight derivatives of *N*[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide.



N[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide

MATERIALS AND METHODS

All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra[11] of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer. ¹H-NMR spectra[12] were recorded on Bruker Avance-300 MHz Spectrophotometer using dimethyl sulfoxamide as solvent at Indian Institute of Technology(IIT), Mumbai. Mass Spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer at Indian Institute of Technology(IIT), Mumbai. The compounds were also subjected to C, H, N and S analysis(ThermoFinnigan) at IIT Mumbai.

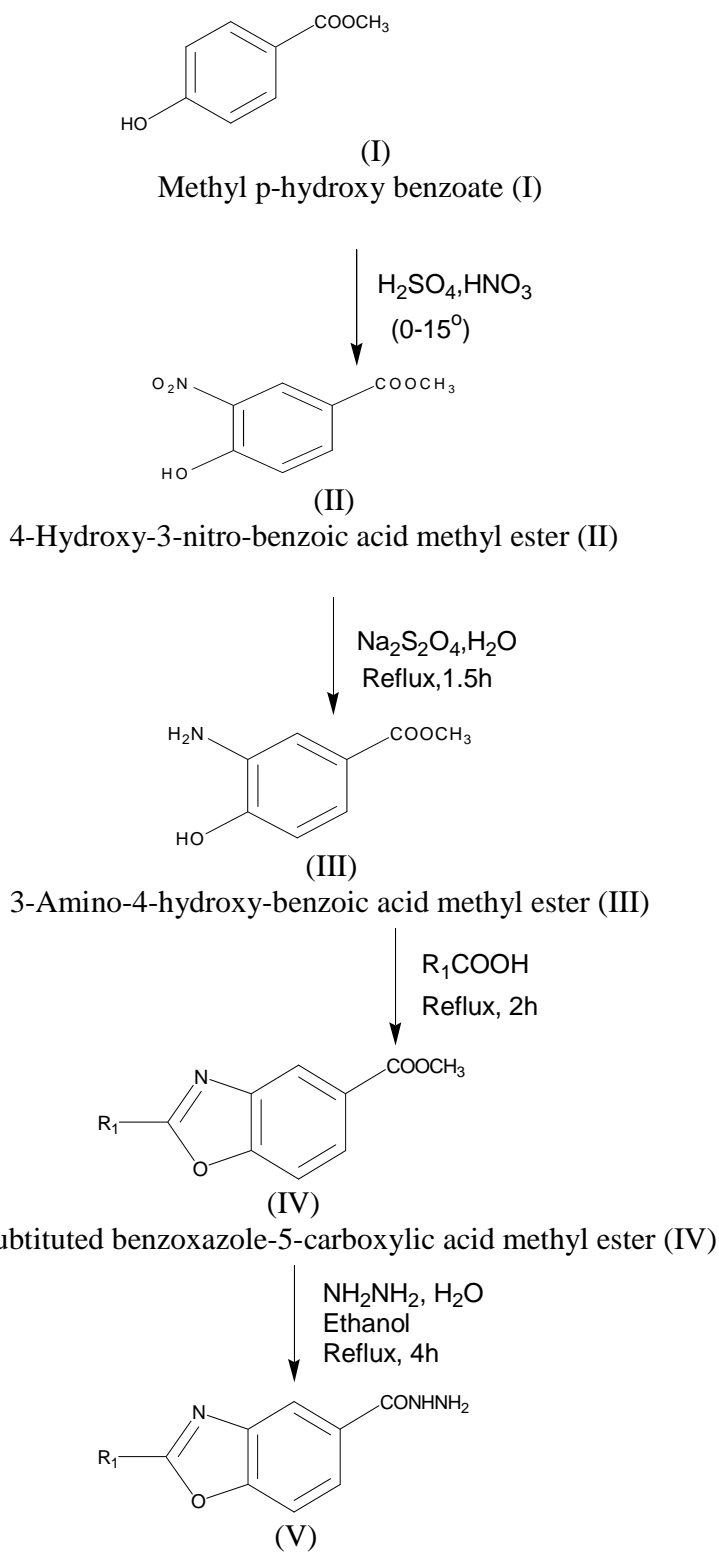
• Synthesis and Characterization of Compounds:

1) 4-Hydroxy-3-nitro-benzoic acid methyl ester (II)

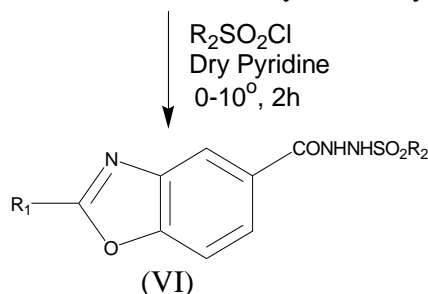
In a 1 lit. three necked round bottom flask equipped with water condenser, mechanical stirrer and thermometer, of p-hydroxy methyl benzoate (10 g, 0.74 mol) was placed. A mixture of concentrated sulphuric acid (6.2 ml) and concentrated nitric acid (6.2 ml) in a dropping funnel, cool the flask in an ice bath to 0-10° and then run in the nitrating mixture in p-hydroxy methyl benzoate with stirring, while maintaining the temperature of the reaction between 5 to 15°; the addition continued upto 1 h. Poured the reaction mixture in to of crushed ice (70 g). Filtered off the crude m-nitro, p-hydroxy methyl benzoate at the pump and wash with cold water. Transfer the solids into 500 ml flask and stirred it with ice cold methanol in order to remove a small amount of ortho isomer and other impurities. The mixture was filtered with suction and washed with little methanol and dried in the air. Then the product was recrystallised using methanol as solvent.

Percentage Yield- 84%, **M.P.** 65-67°, **R_f**-0.76 (Ethyl acetate: methanol, 1:1),

scheme of synthesis:



2-substituted benzoxazole-5-carboxylic acid hydrazide (V)



N[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide (VI)

2) 3-Amino-4-hydroxy-benzoic acid methyl ester (III)

In a 500 ml three necked flat bottom flask equipped with reflux condenser with guard tube, compound II (10 g) was dissolved in boiling alcohol (50%, 100 ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colorless. Then the alcohol was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting colorless, shiny product was filtered, washed with cold water, dried and recrystallise using methanol as solvent.

Percentage Yield- 70%, **M.P.** 110-112°, **R_f**-0.67 (Saturated methanol),

3) 2-substituted benzoxazole-5-carboxylic acid methyl ester (IV)

Compound III (0.01mol) was heated with an appropriate aliphatic acid (formic acid and acetic acid) in excess under reflux for 2h. The reaction mixture was cooled and poured in crushed ice (100 gm) with stirring. The product thus separated was filtered under suction and washed with cold water. The products were recrystallised by using methanol as a solvent.

The following two compounds were prepared by the above mentioned procedure,

a) Benzoxazole-5-carboxylic acid methyl ester (IVa)

Percentage Yield- 80%, **M.P.** 74-76°C, **R_f**-0.7 (Saturated methanol),

b) 2-methyl-benzoxazole-5-carboxylic acid methyl ester (IVb)

Percentage Yield- 60%, **M.P.** 70-72°C, **R_f**-0.7 (Saturated methanol),

4) 2-substituted benzoxazole-5-carboxylic acid hydrazide (V)

A mixture of an appropriate 2-substituted benzoxazole-5-carboxylic acid methyl ester IV (0.001 mol) in alcohol (25 ml) and hydrazine hydrate (99%, 0.015 mol) was heated under reflux on water bath for 4 hours. The alcohol was reduced to half of its volume and cooled. The product separated was filtered and washed with small portions of cold alcohol and then with cold water, repeatedly and dried. The resultant product was recrystallised using methanol as solvent. Using above mentioned procedure following two compounds were synthesized.

a) Benzoxazole-5-carboxylic acid hydrazide (Va)

Percentage Yield- 90%, **M.P.** 108-110°C, **R_f**-0.6 (Methanol)

b) 2-methyl-benzoxazole-5-carboxylic acid hydrazide (Vb)

Percentage Yield- 80%, **M.P.** 144-146°C, **R_f**-0.7 (Methanol)

5) *N* [substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide (VIa-h)

To a cooled and stirred solution of compound VIa and VIb (4 g) in pyridine (25 ml) toluene sulfonyl chloride was slowly added (3.8 ml). After two hours the solution was poured into mixture of ice and concentrated hydrochloric acid and water; the pale yellow colored precipitate was recovered. Washed with dilute hydrochloric acid and water, and was recrystallised using ethanol as a solvent.

Compound (VIa)

***N* [(4-methyl phenyl)sulfonyl]-1,3-benzoxazole-5-carbohydrazide.**

Percentage Yield- 38%, **M.P.** 72-74°C, **R_f**-0.63 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹:** 3390 (-NH- str.), 1315 and 1398 (-S-O str.), 1730 (-CO- str.), 1625 (C=N str.), 3085 (Ar-H str.), 835 (C=C bending), 1165 (ether group in ring); **¹H NMR:** (CDCl₃) δ 7.34-7.95 (m, 8H), δ 8.0 (s, 2H), δ 2.35 (d, 3H).; **FAB-MS:** (m/z, 100%): 331 (M⁺).

Compound (VIb)

***N* [(4-methyl phenyl)sulfonyl]-1,3-benzoxazole- 2-methyl-5-carbohydrazide.**

Percentage Yield- 57%, **M.P.** 78-80°C, **R_f**-0.60 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹:** 3319 (-NH- str.), 1315 (-S-O str.), 1730 (-CO- str.), 1625 (C=N str.), 3010 (Ar-H str.), 2230 (C-C str.); **¹H NMR:** (CDCl₃) δ 7.34-7.95 (m, 7H), δ 8.0 (s, 2H), δ 2.35 (d, 6H).

Compound (VIc)

***N* [(4-acetamido phenyl) sulfonyl]-1,3-benzoxazole-5-carbohydrazide.**

Percentage Yield- 74%, **M.P.** 92-94°C, **R_f**-0.57 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹:** 3327 (-NH- str.), 1352 (-S-O str.), 1730 (-CO- str.), 1116 and 1172 (CONH str.), 3010 (Ar-H str.); **¹H NMR:** (CDCl₃) δ 7.44-7.95(m, 8H), δ 8.0 (s, 3H), δ 2.02 (d, 3H).

Compound (VI d)

***N* [(4-actamido phenyl) sulfonyl]-1,3-benzoxazole-2-methyl-5-carbohydrazide.**

Percentage Yield- 40%, **M.P.** 89-90°C, **R_f**-0.54 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹:** 3324 (-NH- str.), 1322 (-S-O str.), 1730 (-CO- str.), 1629 (C=N str.), 3110 (Ar-H str.), 3180 (CONH str.), 1165 (ether in ring); **¹H NMR:** (CDCl₃) δ 7.44-7.95 (m, 7H), δ 8.0 (s, 3H), δ 2.02 and 2.35 (d, 6H).

Compound (VIe)

***N* [(4-chloro phenyl) sulfonyl]-1,3-benzoxazole-5-carbohydrazide.**

Percentage Yield- 75%, **M.P.** 110-112°C, **R_f**-0.53 (Ethanol:Ethyl acetate); **IR (KBr):** 3216 cm⁻¹ (-NH- str.), 1339 cm⁻¹ (-S-O str.), 3090 cm⁻¹ (Ar-H str.), 772 cm⁻¹ (C-Cl str.); **¹H NMR:** (CDCl₃) δ 7.44-7.95 (m, Ar-H, 8H), δ 8.0 (s, 2H).

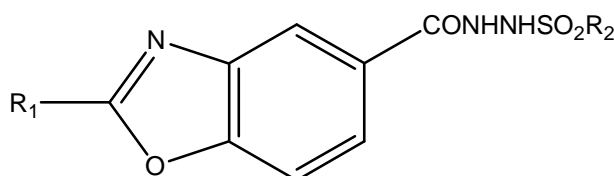
Compound (VI f)

***N* [(4-chloro phenyl) sulfonyl]-1,3-benzoxazole-2-methyl -5-carbohydrazide.**

Percentage Yield- 72%, **M.P.** 102-104°C, **R_f**-0.62 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹:** 3204 (-NH- str.), 1354 and 1329 (-S-O str.), 1730 (-CO- str.), 3180 (CONH str.), 3097 (Ar-H str.), 767 (C-Cl str.); **¹H NMR:** (CDCl₃) δ 7.44-7.95 (m, 7H), δ 8.0 (s, 2H), δ 2.35 (d, 3H)

Compound (VIg)*N* [benzene sulfonyl]-1,3-benzoxazole-5-carbohydrazide.**Percentage Yield**- 30%, **M.P.** 68-70°C, **R_f**-0.62 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹**: 3350 (-NH- str.), 1329 (-S-O str.), 1730 (-CO- str.), 3174 (CONH str.), 3097 (Ar-H str.), 674 (C-C bending).; **¹H NMR**: (CDCl₃) δ 7.03-7.95 (m, Ar-H, 9H), δ 8.0 (s, 2H).**Compound (VIh)***N* [benzene sulfonyl]-1,3-benzoxazole- 2-methyl-5-carbohydrazide.**Percentage Yield**- 40%, **M.P.** 66-68°C, **R_f**-0.72 (Ethanol:Ethyl acetate); **IR (KBr) cm⁻¹**: 3204 (-NH- str.), 1346 (-S-O str.), 1730 (-CO- str.), 1625 (C=N str.), 3085 (Ar-H str.), 2990 (C-C str.), 1165 (ether group in ring); **¹H NMR**: (CDCl₃) δ 7.03-7.95 (m, 8H), δ 8.0 (s, 2H), δ 2.35 (d, 3H).**RESULTS AND DISCUSSION**

- Lead Nucleus with Different substituents (R₁ and R₂) were summarized in Table No.1:

*N* [substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide**Table.No.1**

COMPOUND	R1	R2
VIa	H	Tosyl
VIb	CH ₃	Tosyl
VIc	H	4-aceta amido
VId	CH ₃	4-aceta amido
VIe	H	4-chloro
VI f	CH ₃	4-chloro
VIg	H	Benzene
VIh	CH ₃	Benzene

- Physical data of compound. No. II_a-II_f were summarized in Table No.2:

Table.No.2

Comp. No.	R ₂	Molecular formula	mp(°C)	Yield(%)	R _f value
VIa	Tosyl	C ₁₅ H ₁₃ N ₃ O ₄ S	72-74	48%	0.63
VIb	Tosyl	C ₁₆ H ₁₅ N ₃ O ₄ S	78-80	57%	0.60
VIc	4-aceta amido	C ₁₆ H ₁₄ N ₄ O ₅ S	92-94	72%	0.57
VIId	4-aceta amido	C ₁₇ H ₁₆ N ₄ O ₅ S	88-90	40%	0.54
VIe	4-chloro	C ₁₄ H ₁₀ ClN ₃ O ₄ S	110-112	75%	0.53
VIIf	4-chloro	C ₁₅ H ₁₂ ClN ₃ O ₄ S	102-104	72%	0.64
VIg	Benzene	C ₁₄ H ₁₁ N ₃ O ₄ S	69-70	38%	0.62
VIh	Benzene	C ₁₅ H ₁₃ N ₃ O ₄ S	66-68	40%	0.72

• Elemental analysis of compound. No. II_a-II_i were summarized in Table No.3:
Table.No.3

Compd No.	R ₂	Molecular formula	Elemental Analysis (%)					
			Calculated			Found		
			C	H	N	C	H	N
VIa	Tosyl	C ₁₅ H ₁₃ N ₃ O ₄ S	52.9	4.04	13.08	52.5	4.04	13.12
VIb	Tosyl	C ₁₆ H ₁₅ N ₃ O ₄ S	55.6	4.34	12.07	55.2	4.38	12.11
VIc	4-aceta amido	C ₁₆ H ₁₄ N ₄ O ₅ S	53.63	3.91	15.64	53.67	3.87	15.68
VIId	4-aceta amido	C ₁₇ H ₁₆ N ₄ O ₅ S	52.57	4.12	14.43	52.61	4.16	14.47
VIe	4-chloro	C ₁₄ H ₁₀ ClN ₃ O ₄ S	45.94	2.94	12.37	45.90	2.98	12.41
VIIf	4-chloro	C ₁₅ H ₁₂ ClN ₃ O ₄ S	47.81	3.37	11.81	47.85	3.41	11.85
VIg	Benzene	C ₁₄ H ₁₁ N ₃ O ₄ S	51.31	3.28	13.81	51.35	3.32	13.85
VIh	Benzene	C ₁₅ H ₁₃ N ₃ O ₄ S	53.12	3.75	13.12	53.16	3.79	13.08

In the present investigation (VIa-VIh) compounds were synthesized.

4-Hydroxy-3-nitro-benzoic acid methyl ester (II) was synthesized in an excellent yield by electrophilic aromatic substitution on p-hydroxy methyl benzoate (I) by concentrated nitric acid and concentrated sulfuric acid under refluxed condition. Compound (II) on reduction with sodium dithionite with alcohol afforded 3-amino-4-hydroxy-benzoic acid methyl ester (III). Reaction of compound (III) with two appropriate aliphatic acids (formic acid and acetic acid) gives corresponding 2-substituted benzoxazole-5-carboxylic acid methyl esters (IVa and IVb).The

reaction of compounds (IV) with hydrazine hydrate in ethanol on refluxing gives the corresponding 2-substituted benzoxazole-5-carboxylic acid hydrazides (Va and Vb). On further reaction of compounds (V) with the different sulfonyl chloride derivatives afforded the corresponding eight *N* [substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide (VIa-VIh).

The purity and homogeneity of all the synthesized compounds were confirmed by their sharp melting points (uncorrected), thin-layer chromatography.

The chemical structure was confirmed by infra-red absorption spectra of all the compounds synthesized. The aromatic Ar-H stretching for all the derivatives was found to be at the range of 3050-3200 cm^{-1} . The presence of asymmetric ether disubstituted ring is confirmed by the peak at the range of 1160-1080 cm^{-1} . The presence of sulfone group was confirmed by the peaks at the range of 1315-1398 cm^{-1} . The presence of N-H stretching was confirmed by the peaks at the range 3350-3390 cm^{-1} . The presence of amide linkage (-CONH-) is indicated by the peaks at the ranges near about 3180 cm^{-1} . Also some $^1\text{H-NMR}$ spectra's were useful for some protons in the compounds such as δ 7.30-8.0 indicates the presence of phenyl ring protons, the signals at δ 8.0 indicated the presence of amide linkage, Peak at δ 2.0 shows that presence of amine linkage. And a mass spectrum of the compounds gives mass of compounds.

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