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Synthesis and characterization of some naphthalene derivatives bearing naphthoxazole and benzothiazole moieties

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Abstract : Depending upon the electronic nature and steric bulk of the substituents already present, it is possible to synthesize a variety of substituted naphthalene derivatives. Starting from methyl-3-hydroxy-2-naphthoate the present work describes the synthetic route to (E)-4-((2-hydroxy-3-(methoxy-carbonyl) naphthalene-1-yl) diazenyl) benzene-sulphonic acid) [4] in step-I. Subsequent reduction and condensation with appropriate benzene carboxylic acids it is possible to introduce substituted naphthoxazole ring at position-1,2 [7(a-f)]. Ready hydrolysis of the ester group under mild conditions generates a free carboxylic acid group that can be conveniently condensed with 1-amino-2-thiophenol to afford 3-benzothiophenol substituted derivative of [7(a-f)] identified as [10 (a-f)]. All the synthesis processes were carried out according to the well established protocols. Characterizations were performed by elemental analysis, FT-IR and ^{1}HNMR spectroscopy.

(**Keywords:** Naphthoxazole, benzothiazole, benzene carboxylic acids, spectroscopy)

Introduction

Oxazole moiety constitutes one of the most important building blocks for a number of biologically active compounds[1]. Many compounds possessing polycyclic entities with oxazole ring are proven to have potent antibacterial as well as antituberculosis prooperties[2] and also some of them exhibit anticancer activity[3]. Some of the oxazoles are reported to be excellent antioxidants[4]. Naphthoxazoles are known since Fisher successfully synthesized 2-methylnaphtho[1,2-d] oxazole and its isomer 2-methylnaphtho[2,1-d] oxazole[5] in 1905. In the years to follow a number of synthetic routes have been developed for the synthesis of these class of compounds[6]. Some workers have synthesized fused hetero-benzoxazoles under one step photochemical conditions[7,8]. Benzothiazoles are also reported to exhibit many beneficial biological activities and researchers have put a lot of time and energy to explore their synthesis and biological properties. Dong H.,Quan B. *et al*. synthesized 5-methyl-3-substituted-1,2,4-triazolo[3,4-b] benzothiazoles[9]. A group of rsearchers[10] successfully synthesized 1-amino-3H-pyridino[2,1-b]-[1,3]benzothiazoles starting with 2-cyanomethylbenzothiazole, formaldehyde and a reactive methylene component. During survey of literature one can find the synthesis of 2-oxo-2H-pyrimidino[2,1-b]benzothiazole-3-carbonitriles[11]. Some substituted benzothiazoles are reported as potent inhibitors of HIV-I protease[12]. Geronikaki A., Babaev E., *et al.* [13] have accomplished the synthesis of some morpholine substituted benzothiazoles. A few ethoxycarbonyl substituted benzothiazoles are found to possess anticancer activity[14] as well. Reaction of 2-hydrazinobenzothiazole, trimethyl orthoformate on silica gel in xylene afford 1,3,4-triazolo[2,1-b]benzothiazole[15]. Although our this project does not target the evaluation of biological activities of these class of compounds yet one can not deny the importance of finding new novel synthetic routes to these compounds.

Experimental :

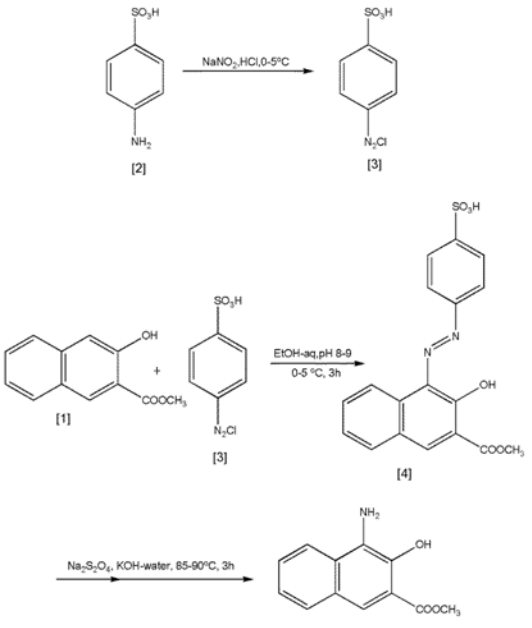
(a) Materials and Methods : All the reagents used were of AR Grade. Methyl-3-hydroxynaphthoate,

sulphanilic acid, 2-aminothiophenol , phosphorus trichloride, sodium hydrosulfite, potassium hydroxide and sodium bicarbonate were purchased from Sigma-Aldrich and used as received. Benzene carboxylic acids and all the solvents were purchased from local supplier for CDH, New Delhi, India and solvents were dried according to standard protocols before use. Methanol, benzene and rest of the chemicals were procured from departmental laboratory. Solvents whwreever necessary were distilled and dried before use. Unless mentioned otherwise, the reagents were used as received.

Melting points were recorded in open capillary and are uncorrected. Elemental analysis was obtained using Perkin Elmer (USA) 2400 series II CHN analyser. The IR spectra are recorded on a NICOLET-400 D spectrophotometer. ^{1}H NMR spectra are obtained in $CDCl_3$ at 400 MHz on a FT-NMR, R-1500 spectrophotometer and chemical shift (d values are expressed with respect to TMS as internal standard.

(b) Synthesis : For synthesis of title compounds the method reported in literature[16] was reproduced with slight modifications. Reaction schemes (I, II, III) are outlined in figures at appropriate places. Spectral data are summarized in table (1), elemental analysis, yield analysis and melting points are mentioned in table (2). General methods of synthesis for each step is as mentioned bolow :

Step-I : Synthesis of 1-amino-3-methoxycarbonyl-2-naphthol : 0.06 mol (10.38g) of sulphanilic acid[2] was was dissolved in 20% aqueous sodium carbonate solution and warmed up to 50°C to ensure complete dissolution. When the mixture attains room temperature, equimolar $NaNO_2$ solution in water (25mL) was added slowly with stirring and allowed to cool at <5°C.This cooled solution was carefully added to ice-cooled concentrated HCl (12 mL) during a period of 30 minutes with stirring and allowed to stand for about 1.0 h waiting for the completion of reaction to afford product[3]. The diazo-coupling of [3] was carried out with 0.05 mol (10.10g) of methyl-3-hydroxynaphthoate [1] in aqueous ethanol maintaining the pH around 8-9 by using sodium carbonate solution in ice-bath for 3.00 hours to afford [4] in a very good yield 15.12g (0.04 mole,82%) after filteration and drying. Recrystallization from ethanol and drying in vacuum was done prior to yield measurement. Entire azo compound was heated in 20% aqueous KOH at about 60°C for half an hour and added sodium dithionite 6.96g, 0.04 mole in portions over 15 minutes and heated at 90°C for 3.00 to 3.50h. Appearance of beize colour solid indicated the formation of 1-amino-3-methoxycarbonyl-2-naphthol[5] in excellent yield (8.63g, 78%).

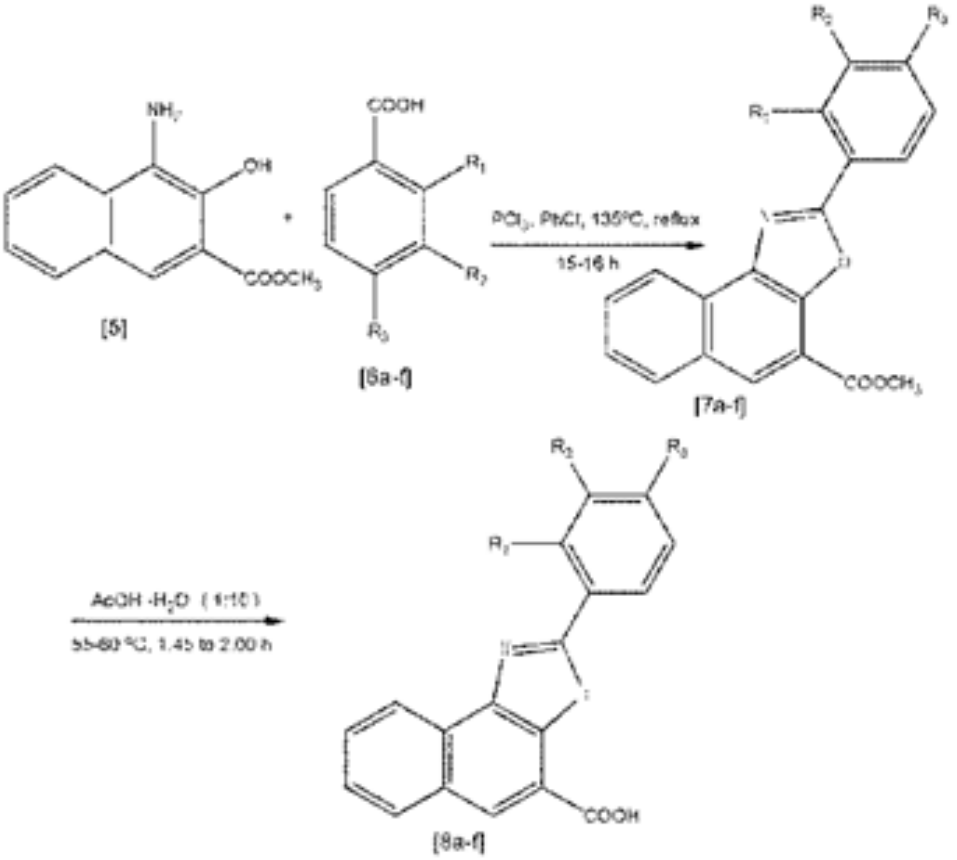


Scheme for step-I : Synthesis of 1-amino-3-methoxycarbonyl-2-naphthol.

Step-II : Synthesis of 2-aryl substituted naphtho[1,2-d]oxazole-4-carboxylic acids [8a-f] : In each reaction 0.004 mole of [5] (868 mg) was reacted with equal moles of benzene carboxylic acids [6a-f]. Whereever mentioned in this paper the symbols have following significance.

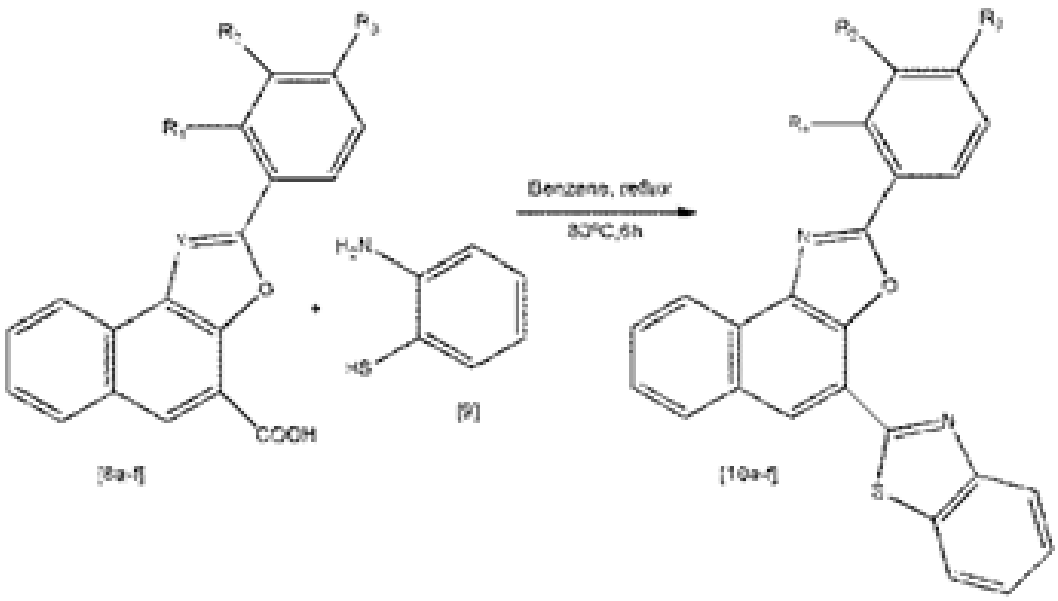
(a) $R_1 = R_2 = R_3 =$ (b) $R_1 = OH$, $R_2 = R_3 = H$
(c) $R_1 = R_2 = H$, $R_3 = OH$ (d) $R_1 = R_3 = H$, $R_2 = NO_2$,
(e) $R_1 = R_2 = H$, $R_3 = Cl$ (d) $R_1 = R_2 = H$, $R_3 = NH_2$

Reactants were introduced to 100 mL round bottom flask containing chlorobenzene solvent (10 mL) and stirred for 15 minutes at room temperature. Added 0.004 mole (0.8g) of PCl_3 and refluxed at about 135°C for periods ranging from15 to 16 hours[17]. Each condensation product [7a-f] was separately subjected to mild alkaline hydrolysis using acetic acid-water (1:10 by volume) at 55-60 °C for a period varying from 1.45 to 2.00 h. The free carboxylic acid group is readily generated upon completion of the reaction. The reported yields are for crude products in completely dry state.



Scheme for step-II : Synthesis of 2-aryl substituted naphtho [1,2-d]oxazole-4-carboxylic acids [8a-f].

Separate reactions of varients [8a-f] are carried out starting with 0.002 mole and equimolar quantities of 1-amino-2-naphthol, refluxing in benzene for nearly 6.00 hours. Progress of reactions were monitored by TLC using appropriate mixture of ethyl acetate and hexane. Best combination for TLC proves to be 6-9% ethyl acetate mixtures. The final products were recrystallized using methanol (a,d,e), petroteum ether (b,c) and acetonitrile for (f). Dry products exhibit reasonable to very good yields indicated at proper place in table.



Scheme for step-III : Synthesis of 4-(4-benzo[d]thiazol-2-yl) naphtho [1,2-d]oxazole-2-yl-) derivatives [8a-f].

Results and Discussions :

Arene diazonium compounds find several utilities in synthetic organic chemistry, specially in preparation of a large number of dye stuffs and pigments. However there are a few instances about their electrophilicy particularly on naphthalene ring systems. In step-I of our synthetic endeavour we have successfully exploited the electrophilicity of benzene diazonium chloride of sulphanilic acid. The quaci-activated ring of the naphtholic ester shows electrophilic substitution at more reactive position-1 of the ring to produce [4] in very satisfactory yield. Sodium dithionite has been used as a preferred choice for reduction of azo compounds under mild conditions by many researchers and cited under references. In our case it also proved tobe a very good reductant for generation of primary amino group at position-1 of the naphthalene ring to furnish [5]. Although it appeared challenging to carry out cyclization between [5] and substituted benzoic acids [6a-f] with protection ot the ester group at position-3 of the ring, the reaction conditions mentioned in scheme for step-II proved its worth. Later on mild alkaline hydrolysis of {7a-f] followed by acidification with glacial acetic acid resulted in conversion of ester to free carboxylic acids [8a-f]. Corresponding yield analysis reveals the fact that condensation in step-II is favoured by electron releasing groups on benzene carboxylic acid component. In step-III conventional practice for synthesis of benzothiazoles has been employed and the yields are moderate to very satisfactory as per our expectations. Finally the characterizations by elemental analysis and spectroscopic methods established the synthesis of desired compounds.

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Spectral data for compounds : 4, 8a-f, 10a-f			
Compound	Systematic IUPAC Name	FT- IR (KBr) , (cm^{-1})	^{1}HNMR($CDCl_3$), 400MHz δ(ppm), TMS
4	(E)-4-((2-hydroxy-3-(methoxycarbonyl)naphthalene-1-yl)diazenyl)benzenesulphonic acid $C_{18}H_{14}N_2O_6S$	3112, Ar(C-H), 1577, (N=N).	2.18 (s,1H,SO_3H) 4.64 (s,1H,OH) 5.21(m,3H,COOMe) 7.71-8.90(m,9H,Ph)
8(a)	2-phenylnaphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{11}NO_3$	3016, Ar(C-H), 2994, COOH 1646, C=N, 1532, Ar C-C 1244, C-O,	12.14 (s,1H,COOH) 7.52-8.65(m,9H,Ph)
8(b)	2-(2-hydroxyphenyl)naphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{11}NO_4$	3120 OH(phenolic), 3014, COOH, 3008, Ar(C-H), 1638, C=N, 1542, Ar C-C, 1256, C-O,	5.42 (s,1H,OH) 7.66-8.84(m,9H,Ph) 11.46(s,1H,COOH)
8(c)	2-(4-hydroxyphenyl)naphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{11}NO_4$	3264 OH(phenolic), 3162, COOH, 2998, Ar(C-H), 1672, C=N, 1522, Ar C-C, 1248, C-O,	5.84 (s,1H,OH) 7.74-8.96(m,9H,Ph) 11.84(s,1H,COOH)
8(d)	2-(3-nitrophenyl)naphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{10}N_2O5$	3024, Ar(C-H), 3016, COOH, 3264 OH(phenolic), 1642, C=N, 1552, Ar C-C, 1232, C-O, 1528, 1355 NO_2	7.62-8.41(m,9H,Ph) 12.36(s,1H,COOH)
8(e)	2-(4-chlorophenyl)naphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{10}NO_3Cl$	3068, Ar(C-H), 2985, COOH, 1636, C=N, 1544, Ar C-C, 1228, C-O, 758 C-Cl	7.78-8.84(m,9H,Ph) 11.90(s,1H,COOH)
8(f)	2-(4-aminophenyl)naphtho[1,2-d]oxazole-4-carboxylic acid $C_{18}H_{12}N_2O_3$	3326, NH, doublet, 3082, Ar(C-H), 3046, COOH, 1665, C=N, 1528, Ar C-C, 1246, C-O,	4.96 NH_2, doublet 7.54-8.52(m,9H,Ph) 11.76(s,1H,COOH)
10(a)	4-(4-(benzo[d]thiazol-2-yl)naphtho[1,2-d]oxazol-2-yl)benzene $C_{24}H_{14}N_2OS$	2894, Ar(C-H), 1624,1646, C=N, 1572, Ar C-C, 1256, C-O, 762 C-S	7.64-8.92(m,14H,Ph)
10(b)	4-(4-(benzo[d]thiazol-2-yl)naphtho[1,2-d]oxazol-2-yl)-2-hydroxybenzene $C_{24}H_{14}N_2O_2S$	3235 OH, 3005, Ar(C-H), 1618,1636, C=N, 1586, Ar C-C, 1242, C-O, 746 C-S	7.62-8.61(m,13H,Ph) 4.86 (s,1H, OH)
10(c)	4-(4-(benzo[d]thiazol-2-yl)naphtho[1,2-d]oxazol-2-yl)-4-hydroxybenzene $C_{24}H_{14}N_2O_2S$	3266 OH, 2990, Ar(C-H), 1633,1648, C=N, 1593, Ar C-C, 1270, C-O, 754 C-S	7.58-8.64(m,13H,Ph) 4.68 (s,1H, OH)
10(d)	4-(4-(benzo[d]thiazol-2-yl)naphtho[1,2-d]oxazol-2-yl)-3-nitrobenzene $C_{24}H_{13}N_3O_3S$	2926, Ar(C-H), 1622,1656, C=N, 1546, Ar C-C, 1262, C-O, 766 C-S, 1522, 1386 NO_2	7.58-8.64(m,13H,Ph) 4.68 (s,1H, OH)
10(e)	4-(4-(benzo[d]thiazol-2-yl)naphtho[1,2-d]oxazol-2-yl)-4-chlorobenzene $C_{24}H_{13}N_2OSCl$	2982, Ar(C-H), 1632,1650, C=N, 1524, Ar C-C, 1254, C-O, 752 C-S, 784, C-Cl	7.51-8.57(m,13H,Ph)

Table-2

Elemental Analysis, Yield Analysis and Melting Points of Compounds

Compound	Elemental analysis						Yield and (%)	mp (^oC)
	Requires			Found				
	% C	% H	% N	% C	% H	% N		
4	55.95	3.63	7.25	55.82	3.59	7.21	15.84g (82 %)	232-34 ^oC
8a	74.74	3.80	4.84	74.68	3.72	4.79	694 mg (60 %)	186 ^oC (d)
8b	70.81	3.60	4.59	70.64	3.56	4.55	830 mg (68 %)	128-29 ^oC
8c	70.81	3.60	4.59	70.72	3.53	4.54	878 mg (72 %)	152-53 ^oC
8d	64.67	2.99	8.38	64.62	2.96	8.32	720 mg (54 %)	172-174 ^oC(d)
8e	66.76	3.09	4.32	66.71	2.99	4.28	982 mg (76 %)	136-37 ^oC
8f	71.05	3.94	9.21	71.00	3.89	9.19	814 mg (67 %)	116-17 ^oC
10a	76.19	3.70	7.40	76.12	3.65	7.36	506 mg (67 %)	>232 ^oC
10b	79.55	3.86	7.73	79.48	3.82	7.69	536 mg (74 %)	188-90 ^oC(d)
10c	73.09	3.55	7.10	73.02	3.49	7.08	623 mg (79 %)	137-38 ^oC
10d	68.08	3.07	9.92	67.96	3.02	9.87	541 mg (64 %)	167-69 ^oC
10e	69.81	3.15	6.78	69.74	3.12	6.71	577 mg (70 %)	145-46 ^oC(d)
10f	73.28	3.81	10.68	73.16	3.77	10.59	487 mg (62 %)	108-09 ^oC

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