Synthesis and characterization of 2-substituted naphto[1,2-*d*]oxazole derivatives

Rajnish Kumar[1*], Mehadi Imam[1], Manoj Kumar Singh[2], Mithilesh Kumar Singh[1]

1 Department of Chemistry, Patna University, Patna-800005, Bihar, India,

2 R. R. S. D. C. E., Begusarai, Bihar, India.

ABSTRACT :

A series of 2-substituted naphtho[1,2-*d*]oxazole derivatives have been synthesized from 1-amino-2-naphthol hydrochloride as common substrate. For synthesis of 2-methylnaphtho[1,2-*d*]oxazole and 2-phenylnaphtho[1,2-*d*]oxazole we have employed carboxylic acid derivatives, namely acetic anhydride and benzoyl chloride respectively. Other 2-substituted naphto[1,2-*d*]oxazole derivatives have been synthesised from substituted aromatic aldehydes. In spite of evidences of solvent assisted thermal dehydrogenation of dihydroxazole ring, we have employed DDQ for dehydrogenation. All these compounds were characterized by FT-IR, 'HNMR and elemental analysis.

Key word: Naphthoxazole, heterocyclic synthesis, DDQ, Biological properties.

INTRODUCTION:

Benzoxazole and naphthoxazole are a heterocyclic compounds, used in research as a starting material for the synthesis of larger, usually bioactive structures. Many derivatives of benzoxazoles are comercially important. These compounds possess potent biological (Devinder K, et al., 2002) and photochromatic activities. 2-substituted naphthoxazole is a major subunit occurring in natural products (Rodriguez A D, et al., 1999). Orthosubstituted naphthoxazole derivatives show promising inhibitory activity for protein tyrosine phosphatase-1B (PTB-1B) and in vivo antidiabiabetic activity(Kumar A, et al., 2009; Malamas M S, et al., 2000; Malamas M S, et al., 2000;). Benzoxazole and naphthoxazole derivatives possessing antifungal (Ertan T, et al., 2009), anti-inflammatory (Dunwell D W,et al., 1977), antitumour (White A W, et al., 2004) and anti H.I.V.(Novelli F, et al., 1997) activities have been reported. The benzoxazole derivatives are used as fluorescent probes (Xu Y, et al., 2010; Kim TI et al., 2009) and sensors for the detection of different metal ions (Chem W, et al., 2012; Yan L, et al., 2012).

Our present endevour is to prepare 2-substituted naphtho[1,2-*d*]oxazole derivatives from different routes as there are chances of these being biologically active.

EXPERIMENTAL:

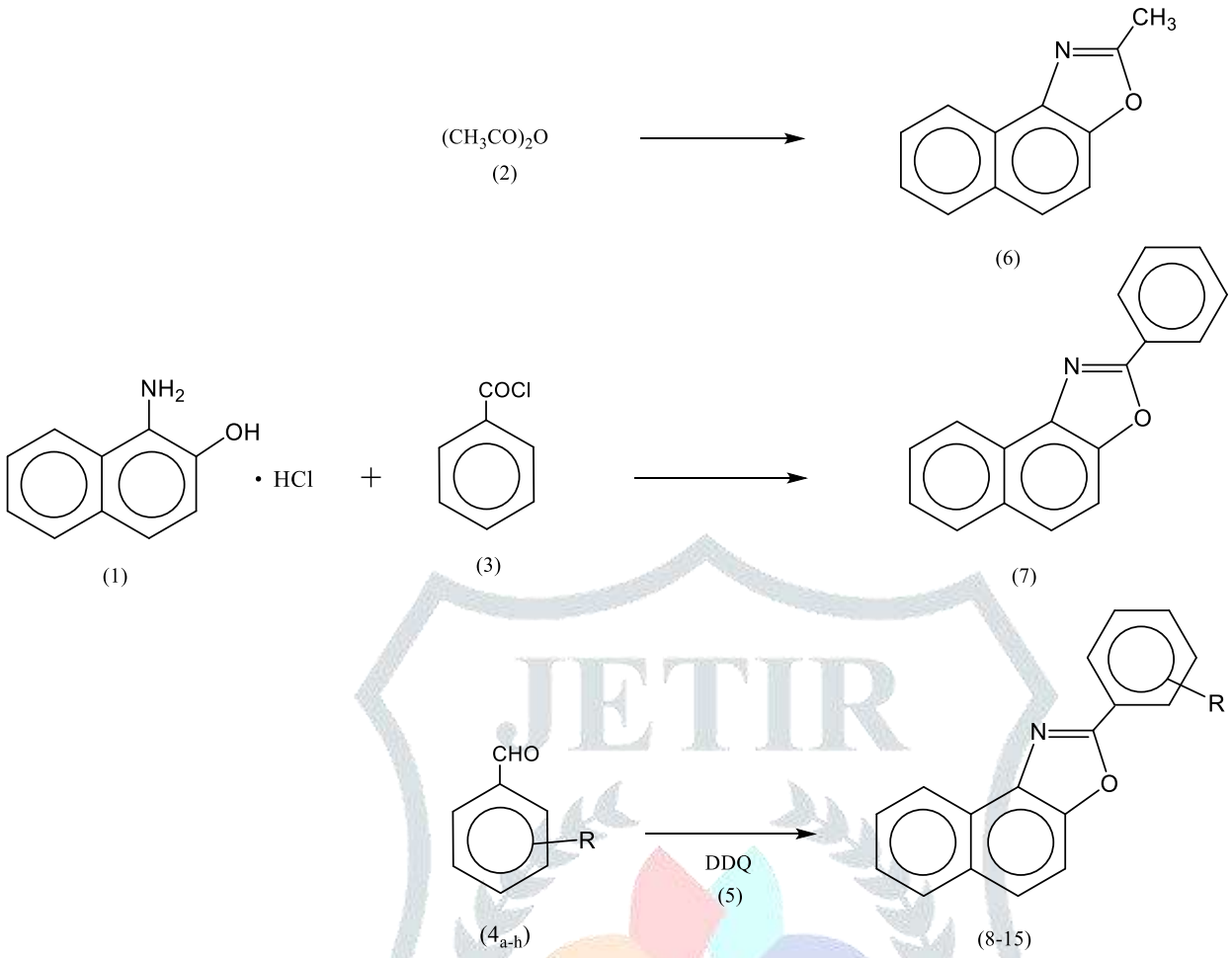
All the chemicals and solvents used in syntheses were obtained from CDH, Sigma Aldrich and Merck chemical companies and used without further purification. Precoated silica gel plates (Kieselgel 60 F254, Merck), were used for TLC and visualised with UV light, (λ_{max} = 254 nm), for monitoring the progress of reactions. Melting points were determined in open capillary tube by using Elico instrument and readings are uncorrected. IR spectrum was recorded in Shimadzu FT-IR spectrophotometer with KBr disc. The results of elemental analysis of C, H and N were obtained for all compounds on a Carlo-Erba EA 1108 elemental analyser. Dry solvents were prepared by using pre heated molecular seives 3 Å or 4 Å whichever applicable. Refluxing was carried out using silicone oil bath and $CaCl_2$ guard tube.

Experimental procedure for the synthesis of 2-Methylnaphtho[1,2-*d*]oxazole (5)

1-amino-2-naphthol hydrochloride (1, 0.98 g, 0.005 mole) added 6 mL of cold hydrochloric acid and stirred. Introduced a solution of 5 g of sodium acetate in 25 ml of water, followed by 5 mL of acetic anhydride (2). Shaken the mixture in cold until the smell of acetic anhydride disappeared. Filtered and the residue washed with cold aqueous ethanol, dried in vacuum. Dry product was refluxed in nitrobenzene for 3 hours maintaining the temperature 180-190°C. Progress of reaction was monitored with TLC (silica gel plates) using EtOAc/Hexane (5:3). Excess solvent was removed by steam distillation and allowed to cool. Crystallization from benzene + ethyl acetate (1:2) in cold afforded pure 2-methylnaphtho[1, 2-*d*]oxazole (5, 0.66 g, 72%).

Experimental procedure for the synthesis of 2-Phenylnaphtho[1,2-*d*]oxazole (7)

1-amino-2-naphthol hydrochloride (1, 0.98 g, 0.005 mole) was taken in Sodium hydroxide solution, stirred at room temperature. Benzoyl chloride (3, 1.05 g, 0.0075 mole) was added drop wise with constant shaking, venting and cooling until the odour of benzoyl chloride had disappeared. Filtered the residue, washed with cold ether and dried in vacuum. Dry product (1.02 g, 78%) was taken in chlorobenzene and refluxed on oil bath at 110 –130^o C for 2.5 hours. Excess solvent was removed by distillation in vacuum and crude was allowed to cool at room temperature. Crystallization from methyl ethyl ketone afforded 2-phenylnaphtho[1,2-*d*]oxazole (6, 0.82g, 67%).



8, R= *O*-OH.C_6H_4

9, R= *m*-OH.C_6H_4

10, R= *O*-Cl.C_6H_4

11, R= *p*-Cl.C_6H_4

12, R= *O*, *p*-Cl_2.C_6H_3

13, R= *O*-NO_2.C_6H_4

14, R= *m*-NO_2.C_6H_4

15, R= *p*-NO_2.C_6H_4

Scheme 1. Synthesis of 2-substituted naphto[1,2-*d*]oxazole derivatives (6-15)

General experimental procedure for the synthesis of 2-(substituted phenyl)naphtho[1,2-*d*]oxazole derivatives (8-15)

1-amino-2-naphthol hydrochloride (1, 0.98g, 0.005 mole) and corresponding aromatic substituted aldehyde (4, 0.005 mole) were refluxed in DMF at 140 –155^o C up to the completion of reaction (10-15 h). Progress of reaction was monitored with TLC using EtOAc/Hexane. Reaction mixture was cooled at room temperature. DDQ (5, 1.13g, 0.005 mole) added in reaction mixture and temperature was maintained at 145 –155^o C for 2-3 hours. The reaction mixture was cooled and solvent evaporated under vacuum. Crud was washed with water and recrystallized to afford corresponding compounds (8-15) in 54-73% yield.

Report of FT-IR spectral data

Compound No.	Description	Frequency: ν(cm^{-1})
6	2-methylnaphtho[1,2-*d*]oxazole	2960, 2860 (-CH_3 stretching), 3050 (Aromatic –CH stretching), 1600, 1585 (Aromatic C=C stretching), 1550 (Aromatic C=N stretching), 1150 (C-C stretching)
7	2-phenylnaphtho[1,2-*d*]oxazole	3040,(Aromatic -CH stretching), 1615 (C=C ring stretching), 1576 (C=N stretching), 1216, 1126 (C-O stretching), 1160 (C-C stretching)
8	2-(Naphtho[1,2-*d*]oxazol-2-yl)phenol	3364,3351(-OH stretching), 3045 (Aromatic –CH stretching), 1626 (C=C ring stretching), 1574 (C=N ring stretching), 1215,1126 (C-O stretching)
9	3-(Naphtho[1,2-*d*]oxazol-2-yl)phenol	3375, 3355(-OH stretching), 3055 (Aromatic –CH stretching), 1628,1563 (C=C, C=N ring stretching), 1213,1134 (C-O stretching)
10	2-(2-chlorophenyl)naphtho[1,2-*d*]oxazole	3047(Aromatic -CH stretching), 1625,1575 (C=C, C=N ring stretching), 1214,1120 (C-O stretching), 730 (-CCl stretching)
11	2-(4-chlorophenyl)naphtho[1,2-*d*]oxazole	3056 (Aromatic -CH stretching), 1629,1560 (C=C, C=N ring stretching), 1215,1135 (C-O stretching), 732 (-CCl stretching)
12	2-(2,4-Dichlorophenyl)naphtho[1,2-*d*]oxazole	3040 (Aromatic -CH stretching), 1615,1571 (C=C, C=N ring stretching), 1216,1122 (C-O stretching), 726 (-CCl stretching)

13	2-(2-Nitrophenyl)naphtho[1,2-*d*]oxazole	1530, 1325 (-NO_2 stretching), 3041 (Aromatic -CH stretching),1621,1572 (C=C, C=N ring stretching), 1210,1125 (C-O stretching)
14	2-(3-Nitrophenyl)naphtho[1,2-*d*]oxazole	3045 (Aromatic -CH stretching),1628,1577 (C=C, C=N ring stretching), 1215,1130 (C-O stretching), 1533, 1327 (-NO_2 stretching)
15	2-(4-Nitrophenyl)naphtho[1,2-*d*]oxazole	1537, 1330 (-NO_2 stretching), 3043 (Aromatic -CH stretching),1625,1575 (C=C, C=N ring stretching), 1211,1127 (C-O stretching)

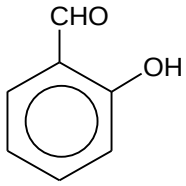
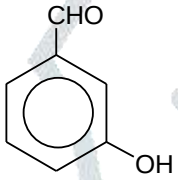
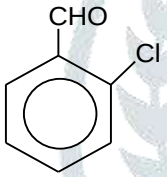
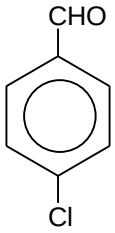
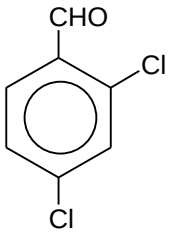
RESULT AND DISCUSSION :

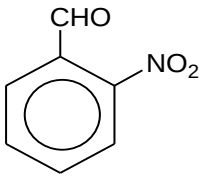
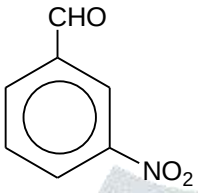
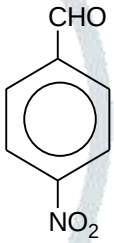
In the light of above mentioned synthesis approaches and our several experimental trails, we divided our synthetic scheme for substituted naphtho[1,2-*d*]oxazole into two categories using 1-amino-2-naphthol hydrochloride as common substrate. For synthesis of 2-methylnaphtho[1,2-*d*]oxazole (6) and 2-phenylnaphtho[1,2-*d*]oxazole (7) we have employed carboxylic acid derivatives, namely acetic anhydride and benzoyl chloride respectively. Elemental analysis and spectral data indicated the correct synthesis products. ^{1}H NMR spectra of title compound (6) clearly indicates that the presence of methyl group at position -2 in oxazole fragment [δ 2.64 (S, 3H)]. The ^{1}H NMR spectrum of title compound (7) shows the presence of phenyl group at position- 2 of oxazole fragment [δ 8.36 (m, 2H), 7.70 (m, 1H), 7.57 (m, 1H)].

Title compounds (8-15) are being synthesised using a different reaction procedure. 1-amino-2-naphthol hydrochloride is the common starting material as earlier. Now the carboxylic acid derivatives are replaced by substituted aromatic aldehydes. In spite of evidences of solvent assisted thermal dehydrogenation of dihydroxazole ring, we have employed DDQ for dehydrogenation.

Perusal of reaction conditions required for title compounds (8-15) emphasises one very clear cut outcome; that is, the temperature required for condensation and cyclization using different aldehydes is a function of electrophilicity of aldehyde component.

Table- 1: Comparative studies on synthesis of naphtho[1,2-*d*]oxazoles

Title compounds Number	Aldehydes used	Reflux condition for cyclization	Yield (%)
8.		150-55°C , 14 hours	54.6
9.		145-50°C , 11 hours	62.0
10.		140-45°C, 14 hours	67.8
11.		150-55°C , 12 hours	59.8
12.		140-45°C , 15 hours	61.3

13.		140-45°C , 11 hours	73.3
14.		140-45°C , 12 hours	66.7
15.		150-55°C , 10 hours	72.5

CONCLUSION :

We have synthesized a series of substituted naphtho[1,2-*d*]oxazole derivatives from modified routes. These synthesized compounds may show good biologically active compounds.

All synthesized compounds were confirmed by FT-IR elemental analysis.

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