Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(8):54-59

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

One-pot synthesis of naphtho[2,1-e][1,3]oxazin-2-ones and naphtho[1,2e][1,3][oxazin-3-ones and their transformation into novel condensed heterocyclic systems

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ABSTRACT

A series of 4-aryl-3,4-dihydronaphtho-[2,1-e]oxazin-2-ones and another series of 1-aryl-2,3-dihydronaphtho[1,2-e][1,3]oxazin-3-ones have been synthesised using the one pot three component coupling of α-naphthol/β-naphthol, urea and variedly substituted aldehydes and potash alum under solvent free conditions. These naphthoxazinone derivatives were further reacted with various aliphatic and aromatic amines to yield the varied condensed heterocyclic systems.

Key words: α-naphthol, β-naphthol, aryl/hetryl aldehydes, naphthoxazinone and potash alum.

INTRODUCTION

Quinazolines and Oxazinones are important pharmacophoric scaffolds with a wide range of biological activities[1]. Quinazolines possess immense biological properties including the anti-inflammatory[2], analgesic[3], antimycobacterial[4] and antihelmentic[5]. Metolonazone and quinathazone contain quinazoline core and are increasingly being used as diuretics in medicine[6]. Benzimidazole condensed quinazolines derivatives are increasingly being used as hypertensive agents[7]. Oxazinones posssess antibacterial[8], antifungal and anti-HIV[9] properties. Some are known to be anti-inflammatory in nature[10]. Pyrimidines have a wide range of biological and medicinal applications including antiprotozoal[11], antihypertensive[12], antihistaminic[13], antibacterial[14] and antihelminthic[15]. 5-Thiouracil exhibits antineoplastic properties[16]. A large number of 2,4-diaminopyridines act as inhibitors of enzyme dihydrofolate reductase[17]. Pyrimidine derivatives of sulpha drugs namely sulphadiazines are readily used in the treatment of urinary tract infections[18]. Heterocycles bearing pyrimidine moiety are also found to posssess antituberculosis, antimalarial and cardiovascular properties[19]. Pharmacologically active pyrimidine derivatives such as prazin, quinethazone, folic acid are increasingly being used in medicine[20]. Azocine nucleus is present in a wide variety of natural products [21] and is bestowed with a wide range of biological activities and pharmacological properties including antimalarial, antihypertensive, analgesics[22]. These are also used as nasal-decongestors[23].

A number of methods are known in literature [24-25] for the synthesis of aromatic oxazinones but most of them involve harsh conditions and use of toxic reagents. Only a few methods are reported in literature for generation of substituted azocines [26-27] and most of them furnish low yields and are for not useful synthesising fused azocines. In our ongoing efforts towards the synthesis of heterocyclic moieties, naphthoxazinone derivatives have been synthesised in the present study by one-pot three component coupling of α- and β-naphthol with appropriate aromatic/hetryl aldehyde and urea using catalytic amount of potash alum.

EXPERIMENTAL SECTION

General Experimental: The melting points were determined in open capillary tubes on Perfit melting point apparatus and are uncorrected. The purity of the products was checked on TLC plates coated with BDH silica gel-G. Visualization of spots was effected by exposure to iodine vapours and Draggendroff reagent. The I.R spectra were recorded on Perkin-Elmer FTIR spectrophotometer (ν_{max} in cm^{-1}). **^{1}H** and **^{13}CNMR** Spectra were recorded on Bruker Ac-400 (400& 100 MHz respectively). EIMS were recorded on Bruker Micro mass VG-7070 mass spectrometer. Elemental analysis was performed on Leco CHNS 932 analyser.

Procedure for the synthesis of 4-Aryl-3,4 –dihydronaptho[2,1-e][1,3]-oxazin-2-ones (4) and 1-Aryl-1,2-dihydro-naphtho[1,2-e][1,3]oxazin-3-one (4$^/$) :
A mixture of α-naphthol (1 mmol), aromatic/hetryl aldehyde and urea was finely mixed by grinding thoroughly. The reaction was placed in a screw-capped vial and heated without any solvent at 170^0C in the presence of catalytic amount of potash alum (0.1mmol). After cooling the reaction mixture was washed with water, separated by filtration, dried and then recrystallised from AcOEt-Hexane (1:2) to afford the pure product **4a** in good yield. The compounds **4$^/$a** was prepared by a similar procedure by using β-naphthol instead of α-naphthol and under slightly different conditions of time and temperature.

Procedure for the synthesis of compounds 7-Aryl/hetryl-7,8-dihydrobenzimidazo[1,2-a]benzo[h]quinazoline. 5a-d
A mixture of **4a** and ortho-phenylene diammine (1:1mmol) was refluxed in absolute alcohol for 2-4 hrs in presence of catalytic amount of $ZnCl_2$ (0.1mmol). After cooling the reaction mixture was filtered, residue washed with water and recrystallised from ethanol to afford the pure product **5a** in good yield. Compounds **5b-d** were obtained following the similar procedure.

Procedure for the synthesis of compounds 7-Aryl/hetryl-7,8-dihydrobenzimidazo[1,2-a]benzo[h]quinazolines. 6a-d
A mixture of **4a** and 1,3-diaminopropane (1:1mmol)was refluxed in absolute alcohol for 3-4 hrs in presence of catalytic amount of $ZnCl_2$(0.1mmol). After cooling the reaction mixture was filtered, residue washed with water and recrystallised from ethanol to afford the pure product **6a** in good yield. Compounds **6b-d** were obtained following the similar procedure.

Procedure for the synthesis of compounds 11-Aryl/hetryl-2,3,11,12-tetrahydrobenzo[f]imidazo[1,2-a]quinazoline. 7a-d
A mixture of **4$^/$a** and ethylene diammine (1:1mmol) was refluxed in absolute alcohol for 1-2 hrs in presence of catalytic amount of $ZnCl_2$ (0.1mmol). After cooling the reaction mixture was filtered, residue washed with water and recrystallised from methanol to afford the pure product **7a** in good yield. Compounds **7b-d** were obtained following the similar procedure.

Procedure for the synthesis of 5-Aryl/hetryl-6,7-dihydro-5*H*-naphtho[1,2-g]pyrido[1,2-a][1,3,5]triazocin-7-one. 8a-d
A mixture of **4$^/$a** and 2-aminopyridine(1:1mmol) was refluxed in absolute alcohol for 3-4 hrs in presence of catalytic amount of $ZnCl_2$(0.1mmol). After cooling the reaction mixture was filtered, residue washed with water and recrystallised from methanol to afford the pure product **8a** in good yield. Compounds **8b-d** were obtained following the similar procedure.

Spectral data of some representative compounds.
4-(p-Methylphenyl)-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazin-2-one (4a). IR(KBr,υ,cm^{-1}): 3247 (NH), 1724 (C=O), 1376(C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 8.78 (s, 1H, NH, D_2O exchangeable), 8.05 (d, 1H, J= 7.8 Hz), 7.82 (d, 1H, J= 7.8 Hz), 7.69-7.20 (m, 8H, ArH's), 5.98 (s, 1H, 4CH), 2.23 (s, 3H, CH_3). **^{13}CNMR (DMSO-d_6)**: δ 157.7, 143.5, 139.8, 135.9, 132.7, 129.8, 129.4, 128.5, 128.2, 127.4, 126.4, 126.1, 125.9, 123.5, 122.1, 120.2, 118, 51.4, 24.3.**EIMS** m/z= 290 (M^++H).

4-(3,4-Dimethoxyphenyl)-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazin-2-one (4b).IR(KBr,υ,cm^{-1}): 3237 (NH), 1719 (C=O), 1345(C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 8.75 (s, 1H, NH, D_2O exchangeable),7.5-7.9(m, 6H, ArH's), 6.3-6.7(m, 3H), 3.75(s,6H, OCH_3), **^{13}CNMR (DMSO-d_6)** δ 157.7, 143.5, 139.8, 135.9, 132.7, 129.8, 129.4, 128.5, 128.2, 127.4, 126.4, 126.1, 125.9, 123.5, 122.1, 120.2, 118, 56,3, 56.2, 51.4, 24.3.**EIMS** m/z= 336(M^++H).

4-(3-Indolyl)-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazin-2-one (4c). IR (KBr, υ, cm^{-1}): 3250 (NH) ,1723 (C=O), 1375 (C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 9.82 (s, 1H, NH, D_2O exchangeable), 8.89 (s, 1H, NH, D_2O

exchangeable), 8.12 (d, 1H, J= 7.8 Hz), 7.92 (d, 1H, J= 7.8 Hz), 7.85-7.69 (m, 8H, ArH's), 6.18 (s, 1H, CH of pyrrole ring), 5.98 (s, 1H, 4CH). **^{13}CNMR (DMSO-d_6)**: δ 157.8, 143.5, 136.5, 135.2, 132.9, 129.0, 127.5, 126.2, 126.0, 125.9, 125.5, 122.2, 121.0, 120.5, 120.2, 119.5, 118.2, 111.5, 101.8, 53.5.**EIMS**, m/z= 316 (M^++ H).

Table-1 Physical and Analytical data of the compounds

Compound	Ar	Mp's (^oC)	Yield (%)	Mol. formulae	Calcd. formula% Obsd. Formula%		
					C	H	N
4a / 4′a	4-methylphenyl	215 / 167	81 / 79	$C_{19}H_{15}NO_2$	78.87 78.53 78.52	5.23 5.05 5.01	4.84 4.62 4.68
4b / 4′b	3,4-dimethoxyphenyl	223 /185	79 / 77	$C_{20}H_{17}NO_4$	71.63 71.51 71.52	5.11 5.08 5.03	4.18 4.02 4.06
4c / 4′c	3-indolyl	227 /192	77 / 74	$C_{20}H_{14}N_2O_2$	76.42 76.31 76.33	4.49 4.35 4.45	8.91 8.76 8.77
4d / 4′d	2-furyl	190 /221	72 / 69	$C_{16}H_{11}NO_3$	72.45 72.34 72.32	4.18 4.14 4.12	5.28 5.21 5.27
5a	4-methylphenyl	220	72	$C_{25}H_{19}N_3$	83.08 82	5.30 5.21	11.83 11.71
5b	3,4-dimethoxyphenyl	243	75	$C_{26}H_{21}N_3O_2$	76.64 76.41	5.19 5.08	10.31 10.25
5c	3-indolyl	248	68	$C_{26}H_{18}N_4$	80.81 80.62	4.69 4.67	14.50 14.47
5d	2-furyl	230	66	$C_{22}H_{15}N_3O$	78.32 78.21	4.48 4.42	12.46 12.32
6a	4-methylphenyl	190	70	$C_{22}H_{21}N_3$	80.70 80.67	6.46 6.41	12.83 12.82
6b	3,4-dimethoxypphenyl	197	69	$C_{23}H_{23}N_3O_2$	73.97 73.95	6.21 6.15	11.25 11.19
6c	3-indolyl	225	69	$C_{23}H_{20}N_4$	78.38 78.14	5.72 5.71	15.90 15.82
6d	2-furyl	196	64	$C_{19}H_{17}N_3O$	75.23 75.07	5.65 5.62	13.85 13.74
7[a]	4-methylphenyl	195	66	$C_{21}H_{19}N_3$	80.48 80.37	6.11 6.08	13.41 13.39
7b	3,4-dimethoxyphenyl	198	63	$C_{22}H_{21}N_3O_2$	73.52 73.39	5.89 5.87	11.69 11.70
7c	3-indolyl	201	65	$C_{22}H_{18}N_4$	78.08 77.93	5.36 5.29	16.56 16.48
7d	2-furyl	171	62	$C_{18}H_{15}N_3O$	74.72 74.57	5.23 5.15	14.52 14.65
8a	4-methylphenyl	241	71	$C_{24}H_{19}N_3O$	78.88 78.71	5.24 5.18	11.50 11.52
8b	3,4-dimethoxyphenyl	253	66	$C_{25}H_{21}N_3O_3$	72.98 73.04	5.14 5.09	10.21 10.17
8c	3-indolyl	254	64	$C_{25}H_{18}N_4O$	76.91 76.87	4.65 4.63	14.35 14.28
8d	2-furyl	211	60	$C_{21}H_{15}N_3O_2$	73.89 73.70	4.43 4.32	12.31 12.24

1-(p-Methylphenyl)-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazin-3-one (4′a) IR (KBr, υ, cm^{-1}):3225 (NH), 1710 (C=O), 13617 (C-O)cm^{-1} 830(C-H); **^{1}HNMR (DMSO-d_6)**: δ 8.79 (s, 1H, NH, D_2O exchangeable),7.1-7.8(10 H, m Ar-H),6.15(1H,d CH), 2.24(3H, s CH_3). **^{13}CNMR (DMSO-d_6)**: δ 157.8, 143.5, 136.4, 135.1, 132.9, 129.1, 127.5, 126.2, 126.0, 125.9, 125.5, 122.4, 121.0, 120.5, 120.2, 119.6, 118.2, 111.5, 101.8, 53,22.**EIMS**, m/z= 291 (M^++ H).

1-(3,4-Dimethoxyphenyl)-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazin-3-one (4′b). IR (KBr, υ, cm^{-1}): 3248 (NH), 1705 (C=O), 1365 (C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 8.75 (s, 1H, NH, D_2O exchangeable), 7.90-7.12 (m, 9H, ArH's), 5.25 (s, 1H, 1CH), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3). **^{13}CNMR (DMSO-d_6)**: δ 158.6, 157.5, 151.7, 136.4, 133.8, 130.0, 128.8, 128.5, 128.0, 126.8, 123.2, 122.5, 121.5, 121.3, 118.7, 115.9, 113.0, 49.8, 43.5, 56.2. **EIMS**, m/z= 336 (M^++H).

1-(2-Furyl)-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazin-3-one (4′d). IR (KBr, υ, cm^{-1}): 3247 (NH), 1705 (C=O), 1362 (C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 8.78 (s, 1H, NH, D_2O exchangeable), 7.85-7.30 (m, 6H, ArH's), 6.95-

6.18 (m, 3H, ArH's), 5.08 (s, 1H, 1CH). **^{13}CNMR (DMSO-d_6)**: δ 157.5, 151.7, 151.1, 141.5, 133.8, 128.8, 128.5, 128.0, 126.8, 123.2, 122.5, 118.7, 115.9, 110.0, 105.9, 43.5.**EIMS** m/z= 266 (M^++H).

7-(p-Methylphenyl)-7,8-dihydrobenzimidazo[1,2-a]benzo[h]quinazoline (5a). . IR (KBr, υ, cm^{-1}): 3245 (NH), 1725 (C=O), 1372 (C-O)cm^{-1} ; **^{1}HNMR (DMSO-d_6)**: δ 8.01 (d, 1H, J= 7.8 Hz), 7.92 (d, 1H, J= 7.8 Hz), 7.76-7.20 (m, 12H, ArH's), 5.65 (s, 1H, NH, D_2O exchangeable), 4.12 (s, 1H, 7CH), 2.35 (s, 3H, CH_3). **^{13}CNMR (DMSO-d_6)**: δ 141.8, 138.9, 135.7, 135.4, 135.0, 134.9, 132.4, 130.5, 129.8, 129.6, 129.4, 129.0, 127.8, 127.5, 127.4, 127.2, 126.7, 126.3, 125.2, 123.5, 123.0, 115.5, 115.0, 52.6, 24.6. **EIMS**, m/z= 362 (M^++H).

6-(p-Methylphenyl)-2,3,5,6-tetrahydro-1*H*-benzo[h]pyrimido[1,2-a]quinazoline (6a).
^{1}HNMR (DMSO-d_6): δ 7.95 (d, 1H, J= 7.8 Hz), 7.71 (d, 1H, J= 7.8 Hz), 7.58-7.23 (m, 8H, ArH's), 5.85 (s, 1H, NH, D_2O exchangeable), 4.08 (s, 1H, 6CH), 3.08 (t, 2H, CH_2), 2.85 (t, 2H, CH_2), 2.38 (qn, 2H, CH_2), 2.35 (s, 3H, CH_3). **^{13}CNMR (DMSO-d_6)**: δ 165.7, 140.7, 135.9, 135.4, 132.8, 129.8, 129.5, 129.1, 128.8, 128.5, 126.1, 124.7, 124.6, 123.2, 120.5, 118.7, 118.0, 44.3, 42.4, 40.2, 24.3, 19.8. **EIMS**, m/z= 328 (M^++H).

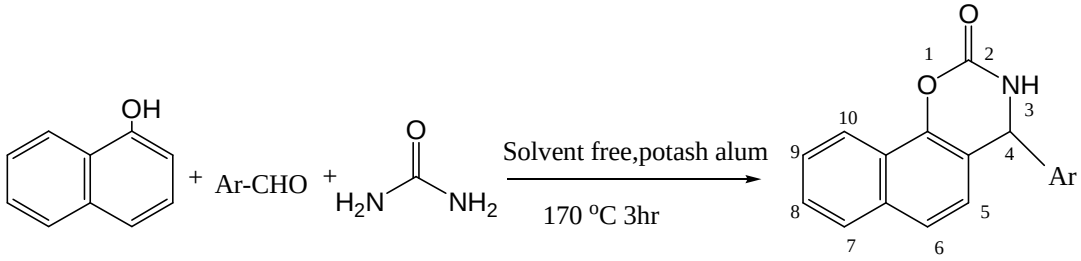
11-(2-Furyl)-2,3,11,12-tetrahydrobenzo[f]imidazo[1,2-a]quinazoline (7d). ^{1}HNMR (DMSO-d_6): δ 7.86-7.28 (m, 6H, ArH's), 6.98-6.28 (m, 3H, ArH's), 5.82 (s, 1H, NH, D_2O exchangeable), 4.08 (s, 1H, 11CH), 3.07 (t, 2H, CH_2), 2.82 (t, 2H, CH_2). **^{13}CNMR (DMSO-d_6)**: δ 151.1, 141.5, 138.5, 134.8, 133.5, 133.0, 130.4, 128.7, 127.9, 126.5, 125.8, 125.4, 124.7, 124.0, 115.9, 110.0, 105.5, 50.8.**EIMS**,m/z= 290 (M^++H).

5-(3-Indolyl)-6,7-dihydro-5*H*-naphtho[1,2-g]pyrido[1,2-a][1,3,5]triazocin-7-one (8c). ^{1}HNMR (DMSO-d_6): δ 11.21 (s, 1H, NH), 9.81 (s, 1H, NH, D_2O exchangeable), 7.92-6.85 (m, 14H, ArH's), 6.18 (s, 1H, CH of pyrrole ring), 5.08 (s, 1H, 5CH). **^{13}CNMR (DMSO-d_6)**: δ 168.4, 147.0, 140.8, 135.9, 135.1, 132.3, 128.5, 128.0, 127.8, 126.0, 125.4, 124.9, 124.5, 124.0, 122.4, 120.4, 119.8, 119.0, 118.7, 118.0, 111.4, 109.5, 101.5, 75.8, 47.8.**EIMS**, m/z= 391 (M^++H).

RESULTS AND DISCUSSION

In the present study we have have synthesised the 4–aryl-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazin-2-ones **4a-d** and 1–aryl-2,3-dihydro-1*H*-naphtho[1,2-e][1,3]oxazin-3-ones **4′a-d**. Grinding thoroughly a mixture of α-naphthol **1**, appropriate aromatic/ heteryl aldehyde **2a-d** and urea in the mole ratio of 1:1:1 followed by refluxing of the molten mass at 170 °C for 3 hr in the presence of a catalytic amount of potash alumwithout using any solvent afforded the products **4a-d** in good yield as shown in **Scheme 1**. Using β-naphthol and other related substrates the naphthoxazin-3-one derivatives **4′a-d** were obtained also in good yield under solvent free conditions in the presence of a catalytic amount of potash alum at slightly different conditions of temperature and duration i.e., at 160 °C for 1.5 hr as shown in **Scheme-2**. Compounds **4a-d** on heterocyclisation with o-phenylenediamine resulted in the formation of substituted benzimidazo[1,2-a]benzo[h]quinazoline compounds **5a-d.(Scheme-3)** The ^{1}HNMR data of compound **5b** showed a pair of doublets appearing at δ 8.01 and 7.92 due to ortho coupling (J = 7.8 Hz) of five CH and six CH protons. The two multiplets seeming embedded in each other and located probably at δ 7.79-7.30 and δ 7.65-7.20 could reasonably be assigned to the protons of benzene ring fused to the benzimidazole moiety and benzene ring of the quinazoline moiety respectively. The three aromatic protons of 3,4-dimethoxyphenyl group appeared as multiplet at δ 7.85-7.80. A peak at δ 5.70 (exchangeable with D_2O) due to NH proton, a singlet at δ 4.15 indicating the presence of chiral CH proton and two singlets at δ 3.78 and δ 3.72 due to two OCH_3 groups are the other prominent peaks in the ^{1}HNMR spectrum. These assignments characterized the compound **5b** as 7-(3,4-dimethoxyphenyl)-7,8-dihydrobenzimidazo[1,2-a]benzo[h]quinazoline. Further, compounds **4a-d** on heterocyclistion with 1,3-diaminopropane generated compounds **6a-d (Scheme-3)** . Similarly compounds **4′b-d** on heterocyclisation with ethylene diammine produced **7a-d.** Further, compound **4′a** on heterocyclisation with 2-aminopyridine resulted in the formation of the heterocyclic system **8a-d**.**(Scheme-4)**

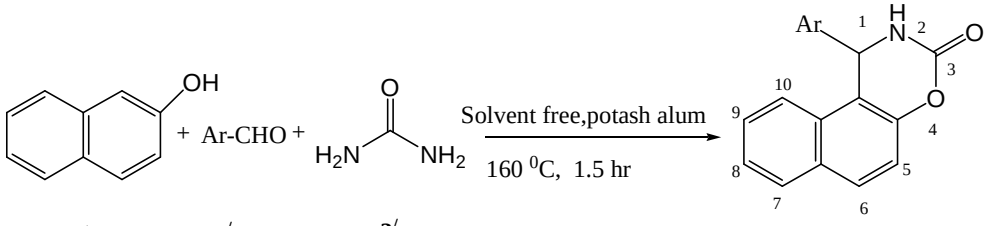
Scheme-1 Preparation of 4- Aryl-3,4 –dihydronaphtho[2,1-e][1,3-oxazin-2-ones(4)



1 **2a-d** **3** **4a-d**

2a, 4a; Ar = 4-methyl phenyl
2b, 4b; Ar = 3,4-dimethoxy phenyl
2c, 4c; Ar = 3-indolyl
2d, 4d; Ar = 2-furyl

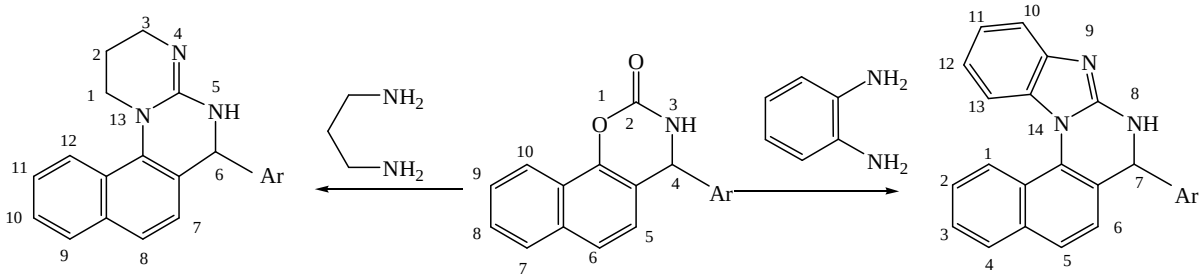
SCHEME-2 Preparation of 1-Aryl-1,2-dihydro-naphtho[1,2-e][1,3]oxazin-3-one (4′)



1′ **2′a-d** **3′** **4′a-d**

2′a, 4a; Ar = 4-methyl phenyl
2′b, 4b; Ar = 3,4-dimethoxy phenyl
2′c, 4c; Ar = 3-indolyl
2′d, 4d; Ar = 2-furyl

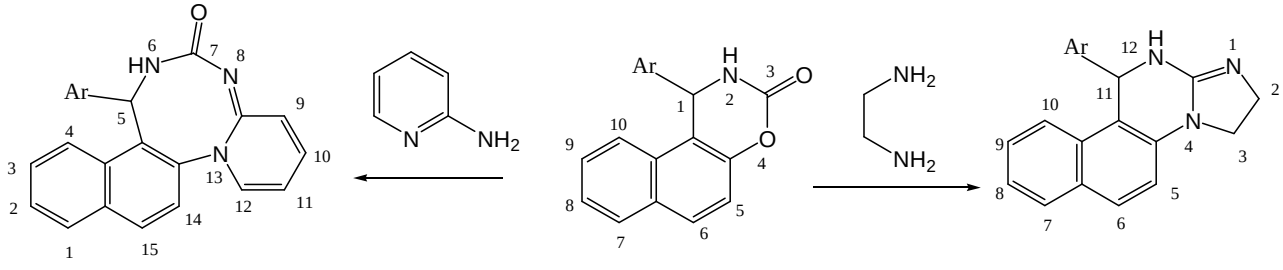
SCHEME-3 Preparation of 7-Aryl/hetryl-7,8-dihydrobenzimidazo[1,2-a]benzo[h]quinazolines (5) and 6-Aryl/hetryl-2,3,5,6-tetrahydro-1*H*-benzo[h]pyrimido[1,2-a]quinazoline (6)



6a-d **4a-d** **5a-d**

4a, Ar=4-Methylphenyl
4b, Ar=3,4-dimethoxy phenyl
4c, Ar=3-indolyl
4d, Ar=2-Furyl

SCHEME-4 Preparation of 11-Aryl/hetryl-2,3,11,12-tetrahydrobenzo[f]imidazo[1,2-a]quinazoline (7) and 5-Aryl/hetryl-6,7-dihydro-5*H*-naphtho[1,2-g]pyrido[1,2-a][1,3,5]triazocin-7-one (8)



8a-d **4′a-d** **7a-d**

4′a/ Ar=4-Methylphenyl
4′b/ Ar=3,4-dimethoxy phenylssss
4′c/ Ar=3-indolyl
4′d,Ar=2-Furyl

CONCLUSION

Summarily we have developed an efficient one pot methodology for the generation of new heterocyclic systems under solvent free conditions using a cheap and efficient catalyst, potash alum.

Acknowledgements
The author is thankful to Department of Chemistry, University of Jammu, for providing laboratory facilities and to UGC for granting NET(J.R.F) fellowship.

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