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Original Research Paper

Synthesis of Functionalized Aryl Derivatives of 1,11-Diazabenzo[a]phenoxazin-5-one and 1-Azadibenzo[a,j]phenoxazin-5-one via Pd-Catalyzed Mizoroki-Heck Reaction

Chemistry

KEYWORDS: 1,11-Diazabenzo[a]phenoxazin-5-one, 1-Azadibenzo[a,j]phenoxazin-5-one, Mizoroki-Heck Reaction, 7-Chloroquinoline-5,8-dione, 1-Amino-2-naphthol hydrochloride.

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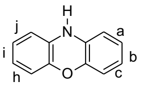
ABSTRACT

The synthesis of functionalized angular phenoxazines and related benzo[a,j] analogues was thoroughly explored. This was achieved by initial preparation of the two intermediates used for the Heck coupling from two key precursors. The first precursor was obtained by multistage conversion of 8-hydroxyquinoline to 7-chloroquinoline-5,8-quinone. The second was obtained by diazotization of aniline and coupling with 2-napththol followed by reduction of the resulting product to yield 1-amino-2-naphthol hydrochloride. The two intermediates, 1,11-diazabenzo[a]phenoxazin-5-one and 1-azadibenzo[a,j]phenoxazin-5-one were afforded by reacting 7-chloroquinoline-5,8-quinone with 2-amino-3-hydroxypyridine and 1-amino-2-naphtol hydrochloride respectively in anhydrous basic medium. Thereafter, each intermediate was coupled with 4-iodophenol, 2-iodobenzoic acid and 4-iodonitrobenzene, refluxing for 4 h at 60 oC using Pd(dppb)Cl2, 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine, K2CO3 and methanol as the catalyst, ligand, base and solvent correspondingly to yield the derivatives (20a-c) and (21a-c) respectively. Structures of the synthesized compounds were established by spectroscopic methods (UV-VIS, FTIR, 1H-NMR, 13C-NMR mass spectroscopy).

Introduction

Phenoxazine **1** is a dibenzo analogue of 1,4-oxazine which exists as 10*H*-tautermer. It is leaf-like crystal which is soluble in ether, benzene and mineral acids; and almost insoluble in water. Its solution shows purple or purplish-red fluorescence. It is a three ring structure compound in which two benzene rings are joined by oxygen and nitrogen atom at non-adjacent positions. The benzophenoxazines have also been prepared and characterized. The reaction of *o*-aminophenol with 2,3-dichloro-1,4-naphthoquinone was pioneered by VanAllen and Reynolds[1]. The chemistry of phenoxazine and its derivatives has been extensively studied because of their versatile utility in industry, agriculture and medicine. In industries, They have been applied as organic dyes for dye-sensitized solar cells [2-4], acid-base and redox indicators, polymerization retardants, metal extractant [5] and chromophoric compound in host guest artificial protonic antenna system[6]. It has been reported that polymers/oligomers containing a phenoxazine unit could be promising conducting and fluorescent materials.[7, 8] A report of the applications of the phenoxazines and their angular derivatives cannot be deemed complete without a portray of their medicinal properties. They are bioactive heterocyclic compounds with spectrum of biological activities ranging from anti-tumour [9-11], anti-proliferative [12-14], anti-viral [15], anti-malaria [16], anti-microbial [17], anti-tubarcular, anti-cataract [5] to anti-bacteria [18]. For example, the phenoxazine derivative, 2-amino-4,4 -dihydro-4 ,7-dimethyl-3*H*-phenoxazine-3-one (**2**) prepared by the reaction of 2-amino-5-methylphenol with bovine haemolysates was reported by Shimmamoto et *al.* [11] to inhibit proliferation and induce apoptosis in the human leukemia cell lines K562, HL-60 and HAL-01 in dose-dependent manner. However, Iwala *et al* [15] and Shimizu *et al.*[19] showed that compound (**2**) is handy in inhibition of multiplication of poliovirus in Vero cells between 0.25-2 g with maximal activity at 1 g, and exhibition of antimicrobial activity against non-tubercular mycobacteria respectively. 2-Amino-3*H*-phenoxazin-3-one was reported by Kohno *et al.* [20] to have anti-inflamatory and immunoregulatory properties thereby providing a promising therapeutic strategy for the treatment of T cell-mediated inflammatory autoimmune disease as well as bacteria-induced-chronic inflammatory disease. Some phenoxazine structural scaffolds are used as valuable pharmacophores for potent tubulin polymerization inhibitors [14]. Naturally occurring phenoxazines are also known. They are found as the central core of a number of natural chemical compounds such as the antibiotic actinomycin D **2** isolated from soil bacteria of the genus Streptomyces,20 dactinomycin **3** known as a chromopepptide antibiotic isolated from *S. parvulus* which was tried with great success in the treatment of Wilm's tumour, the ommochrome xanthomatin **4** found in different anthropods and is responsible for coloration in the wings, cuticles and eyes of insects, and the orcein extracted from several species of ,lichen commonly known as "orchella weeds", found in various parts of the world . Orcein is a reddish-brown dye, orchil is a purple-blue dye. Orcein is used as a stain in microscopy to visualize , chromosomes[22] elastic xfibers, [23] Hepatitis B surface antigens, [24] and copper-associated proteins.[25]



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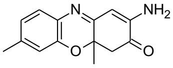

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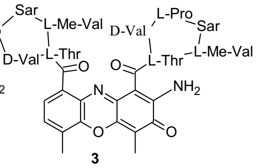

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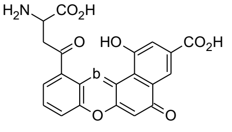

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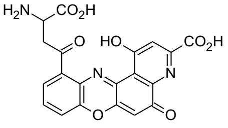

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Extensive structural modifications of **1** and its derivatives are still in progress in an attempt to obtain new derivatives having more desirable properties. Although several synthetic routes to linear and angular phenoxazines have been reported, methods are often not applicable for the preparation of a wide variety of their derivatives with excellent yields and good pharmacological activity. Moreover, because of the current indespensibility of benzophenoxazine rings as valuable molecular motif for the development of chemotherapeutic agents with high pharmacokinetic profile, it becomes imperative to investigate elegant and facile reaction protocols to synthesized possibl,e derivatives with variety of functionalities.

Experimental section

Melting points were determined on an electro-thermal melting point apparatus in open capillaries and were uncorrected. UV/VIS was measured on a JENWAY 6405 UV/VIS spectrophotometer using matched 1 cm quartz cells. Absorption maxima were given in nanometers (nm); absorptivity values in parenthesis. IR (KBr pellets) was recorded on FTIR-8400S Fourier Transform Infrared spectrophotometer and absorption was given in per centimeter (cm^{-1}) (NARICT, ZARIA). ^{1}H-NMR and ^{13}C-NMR were measured on a Varian NMR 400 MHz spectrometer (STRACTHCLYDE UNIVERSITY, SCOTLAND). GC-MS analysis was recorded on GC-MS-QP2010PLUS SHIMADZU, JAPAN.

8-Hydroxy-5-nitrosoquinoline hydrochloride, 7

8-Hydroxyquinoline (59.0 g, 400 mol) **6** and distilled water (200 mL) were placed in a 1 litre beaker. Concentrated hydrochloric acid (75 mL) and ice (20.0 g) were also added to the reaction mixture. Sodium nitrite (30.0 g) was made into solution using water (100ml). The solution of sodium nitrite was added gradually into the mixture with vigorous stirring at 0-4 °C for 1 h in an ice-salt bath. The mixture was allowed to stand overnight at 0 °C then the product was collected by suction, washed with cold water and air dried to afford a yellow solid **7**; yield 66.0 g, 78 %; m.p. (dec.) 181°C (lit. 180)[26].

8-Hydroxy-5-nitroquinoline, 8

The compound was prepared according to the report of Petrow and Sturgeon concentrated nitric acid (108 mL) and water (72 mL) were placed in a 1 litre beaker and allowed to cool to 17 °C in an ice-salt bath. Finely divided **7** (36.0 g, 200 mmol) was added with vigorous stirring for 1 h and 15 min while the temperature was maintained at 17 °C. As the stirring progressed, there was evolution of nitrogen dioxide while the nitrosoquinoline was converted to the insoluble 8-hydroxy-5-nitroquinoline nitrate. After 1h and 15 min has elapsed; the mixture was diluted with equal volume of water, cooled to 0°C and made alkaline with cold concentrated potassium hydroxide solution (pH 13). The red potassium salt was decomposed on neutralization with acetic acid, filtered by suction, washed with water and air dried. The yellow compound was re-crystallized from ethanol to give a bright yellow crystal of **8**; yield 30.0 g, 73 %; m.p. 178 °C (lit 180 °C) [26].

7-Chloro-8-hydroxy-5-nitroquinoline, 9

Chlorination of **8** was accomplished by the procedure described by Pratt and Drake [27]. The **8** (10.0 g, 53 mmol) was suspended in water (I L) in a beaker (2 L). Potassium hydrochloride (54 mL, 1M) was added and the mixture was stirred as sodium hypochlorite (72 mL, 5 % excess) was added in portion over 1.5 h. As the addition progressed, the starting material dissolved and soon the orange salt of **9** began to precipitate. After the addition of sodium hypochlorite, the mixture was further stirred for 2 h, neutralized with acetic acid and stirred to permit complete conversion of the precipitate to the free quinolinol. It was filtered by suction, washed with water, air dried, re-crystallized from ethyl acetate, to give a bright orange compound **9**; yield 9.8 g, 83 %; m.p 238 °C (lit. 239-240.5 °C) [28].

5-Amino-7-chloro-8-hydroquinoline, 10

The compound was prepared as previously described by Pratt and Drake.[27] Compound **9** (11.2g, 100 mmol) was ground in a mortar with potassium hydroxide solution (110 mL, 1M) to ensure complete reduction of the insoluble potassium salt. The mixture was transferred to a RB flask (500 mL) equipped with a magnetic stirrer. Water (280 mL) was added and the mixture was heated to 50 °C with vigorous stirring in a water bath. Solution of KOH (70 mL) was added then the temperature was raised to 80 °C and maintained there for 10 mins while a rapid stream of nitrogen was passed into the flask. After 10 mins, more sodium dithionite (10 g) was added while the passage of nitrogen gas continued for 10 mins. The resulting suspension was cooled in ice under nitrogen gas and the precipitate was filtered off by suction, washed with cold water containing a trace of dithionite and dried rapidly in oven to give **10** a golden yellow solid**;** yield 15.0 g, 77 %; m.p. 171°C (lit. 172-173°C)[26].

7-Chloroquinoline-5,8-dione, 11

Compound **10** (12.0 g, 100 mmol) was suspended in water (300 mL) in a beaker (1 L) with a magnetic stir bar in an ice-salt bath. Sulphuric acid (18 mL, 6 M) was added to dissolve the amine. The solution was cooled to 2 °C with vigorous stirring and the salt precipitated out in a finely divided form. An ice cold solution made up of 10 % solution of potassium dichromate (103 mL) and sulphuric acid (17 mL, 6 M) was stirred and cooled in an ice-salt bath for 15 mins. The precipitated salt was filtered off in a cold Buckner funnel containing trace of ice, washed with cold water and air dried. A light tan yellow solid was obtained and re-crystallized with DMF to give **11** as a fine light tan yellow solid; yield 12.1 g, 79 %; m.p. 176 °C (lit. 173.5-174.5 °C)[26]. UV-visible $_{max}$ (DMA) ((log): 320.8 (2.5062), 360 (2.5563), 388.8 (2.5897), 408.2 nm (2.6108).

1-Phenylazo-2-naphthol, 14

Aniline **12** (4.9 mL, 54 mmol) was dissolved in concentrated hydrochloric acid (16 mL) of water in a small beaker and was placed in an ice–bath until the solution cooled to 0 °C. Sodium nitrite (4.0 g, 58 mmol) was dissolved in H_2O (20 mL) and was cooled in an ice bath to 0°C. The cold solution of $NaNO_2$ was added in portions at 0-5 °C into the cold solution of aniline hydrochloride. When the last portion was added, the solution was shaken for 4 mins and a drop of the solution diluted with three drops of water was tested using starch iodide paper to give immediate blue colour on the paper. 2-naphthol **13** (78.0 g, 54 mmol) was dissolved in NaOH (45 mL, 10 %) solution in a beaker (250 mL) and cooled in a salt-bath to 0 °C with the help of ice chips (25.0 g). the cold naphthol solution was stirred vigorously with slow addition of the cold diazonium salt solution. A red colour develops as the red crystals of **14** separates out after the addition of the diazonium salt solution, the mixture was allowed to stand in the bath for 30 mins with occasional stirring, the product filtered using gentle suction and dried between filter papers. One fourth of the crude product, weight 22.0 g, was re-crystallized from acetic acid, washed with ethanol and dried between filter paper to afford the pure product melting at 129°C (lit. 13 °C)[26].

1-Amino-2-naphthol hydrochloride, 15

The crude 1-phenylazo-2-naphthol **14** (16.5 g, 67 mmol) was placed in a round bottomed flask (350 mL), provided with a reflux condenser containing industrial spirit (100 mL) and boiled until most of fk the azo compound has dissolved. Tin (II) chloride (20.0 g, 105 mmol) was dissolved in concentrated hydrochloric acid (60 mL) and heated until a clear solution was obtained. The clear solution was added to the flask and all the azo compounds dissolved rapidly and then refluxed for 30 mins at which point the solution acquired a pale brown colour. After 30 mins, the solution was decanted into a beaker and allowed to stand in an ice-bath. **15** separated as fine grayish-white crystals. It was filtered, washed with 1:4 dilute HCl and dried in a dessicator. It was re-crystallized from minimum volume of hot water with few drops of Tin (II) chloride solution in an equal weight of HCl to reduce atmospheric oxidation. The clear solution was cooled in an ice-bath, filtered by suction, dried and stored in a dessicator to afford **15**; yield 9.0 g, 74.5 %[26].

4-Iodophenol, 18

Compound **18** was prepared according Williamson's description. 4-aminophenol **16** (3.4 g, 30 mmol) was placed in a round bottom flask (100 mL), water (25 mL) and concentrated hydrochloric acid (6 mL) was added and heated until solid dissolved. It was cooled in ice-salt bath to 0 °C while a rapid stream of nitrogen was added to displace the air. At 0 °C, sodium nitrite (1.8 g, 26 mmol) in water (6 mL) was added slowly. After 5 mins, potassium iodide (4.25 g) in water (6 mL) was added gradually and there was separation of black complex. The mixture was allowed to stand under nitrogen without cooling for 5 mins, and then it was warmed to 40 °C. At that point, a vigorous reaction ensued (gas evolution and separation of tan solid) after 10 mins reaction; the mixture was heated over a steam bath for 10 mins, cooled in ice with the addition of a pinch of sodium bisulphate to destroy any iodine present. A black mass **18** was collected, washed with water and then recrystalised with ethanol; yield 3.6 g ,52 %; m.p.

92 °C (lit. 91 °C)[26].

1, 11-Diazabenzo[a]phenoxazin-5-one, 20

2-amino-3-hydroxypyridine **19** (0.55 g, 5 mmol), Na_2CO_3 (0.53 g, 50 mol), DMF (4 mL) with benzene (40 mL) were put in a round bottom flask (100 mL) fitted with a reflux condenser. It was heated at 70-75 °C with vigorous stirring for 45 mins. 7-chloroquinoline-5,8-quinone **11** (0.93 g, 5 mmol) in DMF (2 mL) was added to the mixture to give a brown solution which became dark brown as the reaction progressed and after 2.5 h, there was no more colour change until the 8 h. The reaction was monitored using TLC plates. After the 8 h, the reaction was stopped and exposed to dryness then the product **20** was extracted using acetone. Weight 0.76 g, 61 %. A brown compound melting at 290 °C was obtained. Uv/vis $_{max}$ (acetone) ((Log): 219.8 (2.6709), 346.4 (2.5395), 411.2 (2.6140), 468.8 nm (2.6709); ^{1}H-NMR ($DMSO_{d6}$) ppm: 9.42-9.40 (1H, d), 9.22 (2H, d), 8.61 (1H, m), 7.40-7.39 (2H, m), 5.43 (1H, s); ^{13}C-NMR ($DMSO_{d6}$) ppm: 182.1, 164.6, 159.6, 154.9, 154.5, 150.3, 139.5, 141.7, 139.5, 133.9, 133.4, 126.8, 106.5.

1-Azadibenzo[a,j]phenoxazin-5-one, 21

In a round bottom flask (100 mL) fitted with a reflux condenser, 1-amino-2-naphtholhydrochloride **15** (0.4 g, 2 mmol), sodium carbonate (0.2 g, 21 mmol), DMF (3 mL) and benzene (40 mL) were placed and heated for 45 mins with vigorous stirring at 60-75 °C. 7-Chloroquinoline-5,8-quinone **11** (0.5 g, 2 mmol) in DMF 2 mL was added while the heating and stirring continued. The reaction was monitored with TLC plates. There was colour change from initial brown colour to an intense brown colour which persisted until the end of the reaction after eight hours. The mixture was allowed to dry in air and then the product 1-azadibenzo[a,j]phenoxazin-5-one was extracted using acetone as a dark brown compound melting at 204 °C. Weight (0.62 g, 76 %) UV/vis max (acetone) (Log): 287.2 (0.308), 444.4 (2.6477), 497.8 nm (2.6970); ^{1}HNMR (DMSO-d_6) ppm: 9.20 (1H, d), 8.78 (1H, d), 7.94-7.34 (2H, t), 7.89 (2H, m), 7.53 (2H, m), 6.97 (1H, d), 5.09 (1H,s).

Preparation of the Ligand, 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine, 25

The compound is prepared according to the method described by Sasmita [28]. A mixture of piperazine **22** (22 g, 25.54 mmol) and 40 % aqueous formaldehyde solution **23** (5.3 mL, 75 mmol) was dissolved in methanol (40 mL) and heated to reflux for 2 h to get a clear solution. To the cooled solution was added 2,4-di-tertbutylphenol **24** (10.3 g, 50 mmol) in methanol (60 mL). The resulting solution was refluxed for further 12 h. The reaction mixture was cooled at room temperature and filtered to get white solid; yield 10 g, 51 %; m.p. 220 °C (lit. 222-224 °C)[28].

General Procedure for the Mizoroki-Heck Reaction

To a two-necked round bottomed flask equipped with a reflux condenser, 1,4-bis(diphenylphosphino)butane palladium(II)chloride (0.003 g, 0.5 mmol) and 1.4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine (0.002 g, 5 μmol) were added and stirred for 5 mins at room temperature in methanol (5 mL). The mixture was heated up to 60 °C and the intermediate (0.005 mol), aryl halide (0.5 mmol), anhydrous K_2CO_3 (0.19 g, 0.14 mmol) were added at once to it. The reaction was refluxed for 4 h in DMF/benzene while being monitored with TLC (Thin Layer Chromatographic) plates. The crude product was air-dried and extracted using acetone and the extract was air-dried..

6-(4-Hydroxyphenyl)-1,11-diazabenzo[a]phenoxazin-5-one, 20a

1,11-Diazabenzo[a]phenoxazine-5-one (0.747 g, 5 mmol) and 4-iodophenol (0.12 g, 0.5 mmol) were used and product was afforded as brown solid. Yield = 0.60 g (59 %); m.p. 110°C UV/visible $_{max}$ 1029.06 (C=CH, Ar-H out of plane bend), 1111.03 (C-O-C str), 1447.62 (C=O), 3348.54-2833.52 cm^{-1} (O-H); MS: m/z (relative intensity) m/z 342[M^+ + 1, 5%] m/z 324 [M^+ - OH, 5 %], m/z 248 [M^+ - C_6H_4, 20 %], m/z 220 [M^+ - CO, 5 %], m/z 177 [M^+ - CH_3CO, 7.5%], m/z 57 [M^+- C_6H_3N, 100 %].

6-(4-Nitrophenyl)-1,11-diazabenzo [a] phenoxazin-5-one, 20b

1,11-diabenzo[a] phenoxazin-5-one (0.747 g, 5 mmol) and 1-iodo-4-nitrobenzene (0.124 g, 0.5 mol) was employed and a reddish-brown solid was obtained; Yield = 0.51 g, 46 %; m.p. 160 °C. UV/vis $_{max}$ (Log): 321.6 (2.5073), 396.6 nm (2.598). IR (KBr) max: 1029.06 (C=CH, Arom. out of plane bend), 1112.00 (C-O-C), 1441.84cm^{-1} (C=O due to ionic resonance); MS: m/z (relative intensity): m/z 370 [M^+ ,3.9 %], m/z 324 [M^+ - NO_2, 3.9 %), m/z 234 [M^+ - C_6H_5,O_2, 6.6 %], m/z 212 [M^+ - NH_2,17 %], m/z 196 [M^+ - $C_9H_3N_2$, 13 %], m/z 57 [M^+ -$C_4H_3N_2$,100 %].

6-(4-Caboxyphenyl)-1, 11-diazabenzo[a] phenoxazin-5-one, 20c

1,11-diazabenzo[a]phenoxazine-5-one (0.747 g, 3 mmol) and 2-iodobenzoic acid (0.124 g, 0.5 mmol) were used and the product was obtained as a brown solid;yield 0.81 g, 73 %; m.p. 110 °C. UV/vis $_{max}$ (Log): 321.4 (2.5070), 360 (2.5563), 432.8nm (2.636); IR (KBr) $_{max}$: 1029.06-456.18 cm^{-1} (Ar-H bend out of plane); 1441.84 cm^{-1} (C=O) MS: m/z (relative intensity) m/z 370 [M^+ -1, 5 %] m/z 324 [M^+ - COOH, 5 %], m/z 248 [M^+ - C_6H_4, 14 %], m/z 220 [M^+ - CO, 4 %], m/z 57 [M^+ - CH_3CO, 100 %].

6-(4-Hydroxyphenyl)-1-azadibenzo[a,j]phenoxazin-5-one, 21a

1-Azadibenzo[a,j]phenoxazine (0.894 g, 3 mmol) and 4-iodophenol (0.11 g, 0.5 mmol) were employed and the product afforded as brown solid; yield 0.67 g, 57 %; m.p. 248 °C; UV/visible $_{max}$ (acetone) (Log): 250 (2.5185), 285 (2.4548), 420.0nm (2.623); IR(KBr) $_{max}$: 3340.61 cm^{-1} (O-H), 1443.77 cm^{-1} (C=O), 1112 cm^{-1} (C-O-C) of aromatic system. MS: m/z (relative intensity): m/z 391 [M^+ + 1, 2.5 %], m/z 374 [M^+ -OH, 5 %], m/z 257 [M^+-C_7H_5CO, 15%], m/z 168[M^+-$C_8H_5$6.5%], m/z 149 [M^+-H_2O, 100 %].

6-(4-Nitrophenyl)-1-azadibenzo[a,j]phenoxazin-5-one, 21b

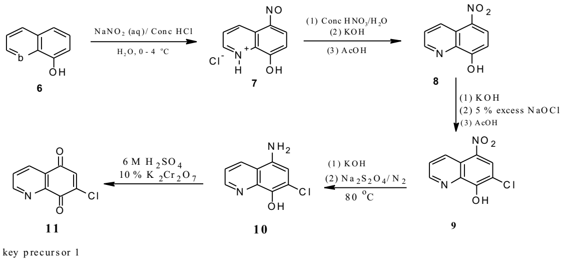
1-Azadibenzo[a,j] phenoxazin-5-one (0.894 g, 3 mmol) and 1-iodo-4-nitrobenzene (0.124 g, 0.5 mol) were utilized and a dark brown product was obtained. Yield = 1.0 g (83 %), m.p. 262 °C. Uv/visible max: 321.2 (Log = 2.506), 409 (Log = 2.6117), 496.2nm (Log = 2.6956); IR (KBr) max: 109.06-448.46 cm^{-1} (C=CH, Ar-H bending out of plane), 1112.00 cm^{-1} (C-O-C), 1447.62 cm^{-1} (C=O), 2941.54-3344.68 cm^{-1} (Ar-H). MS: m/z (relative intensity) m/z 420[M^+ + 1, 14 %], m/z 297 [M^+ - C_6H_4, NO_2, 23 %], m/z 280 [M^+ - OH, 100 %], m/z 251[M^+ - CO, 10 %].

6-(2-Carboxyphenyl)-1-azadibenzo[a,j]phenoxazin-5-one, 21c

1-Azadibenzo[a,j]phenoxazin-5-one (0.894 g, 3 mmol) and 4-iodobenzoic acid (0.124 g, 0.5 mmol) were the product was air dried and extracted using acetone; yield 1.24 g, 99 %; m.p. 200 °C; Uv/visible $_{max}$(Log): 321.6 (2.5073), 360 nm (2.5563); IR (KBr) $_{max}$: 1027.13 (C-H out of plane bend), 1112.00 (C-O-C), 1448.5 (C=C, C=N str.), 1666.55 (C=O), 2942.51 cm^{-1} (Ar-H). MS: m/z (relative intensity) m/z 418[M^+, 10 %], m/z 272 [M^+ - $C_9H_5O_2$, 53 %], m/z 244 [M^+ - CO, 22 %], m/z 115[M^+ - C_6H_4, 15 %], m/z 114[M^+-H, 100 %].

Results and Discussion

The work was achieved by initial synthesis of the two key precursors, **11** and **15**. The first precursor, 7-chloro-5,8-quinolinequinone **11** was obtained by nitrosylation of of 8-hydroxyquinoline **6** followed by oxidation of the nitro derivative to 8-hydroxy-5-nitroquinoline **8**. Compound **8** was successively chlorinated and reduced to afford **9** and **10** respectively. The oxidation of the compound **10** with acidified potassium dichromate (IV) gave the precursor **11** (scheme 1).



Scheme 1

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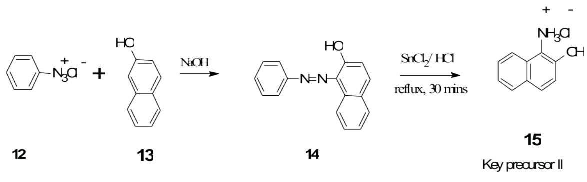
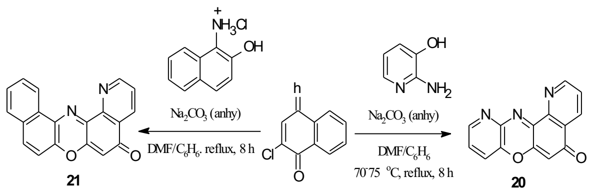
The second precursor, 1-amino-2-naphthol hydrochloride **15** was obtained by diazotization of aniline **12** and coupling with 2-naphthol **13** followed by reduction of the resulting product **14 (scheme 2)**.



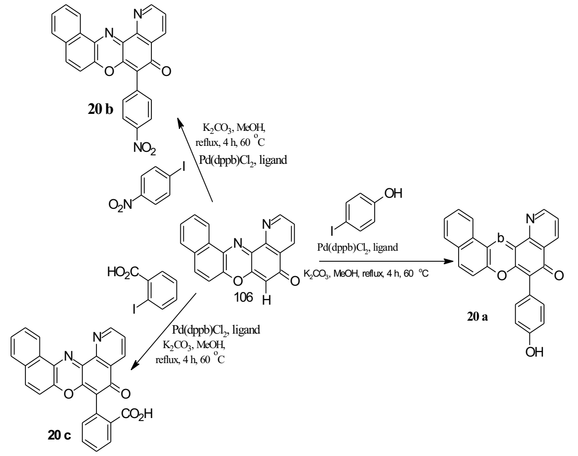
Scheme 2

The compounds **11** and **15** were then used to synthesize the two intermediates, 1,11-diazobenzo[a]phenoxazin-5-one **20** and 1-azabenzo[a]phenoxazin-5-one **21.** The intermediates **20** and **20** were obtained by condensation of the precursor 7-chloroquinoline-5,8-dinone **11** with 2-amino-3-hydroxylpyridine **19** and 1-amino-2-naphtholhydrochloride **15** in anhydrous basic medium respectively (**Scheme 3**).

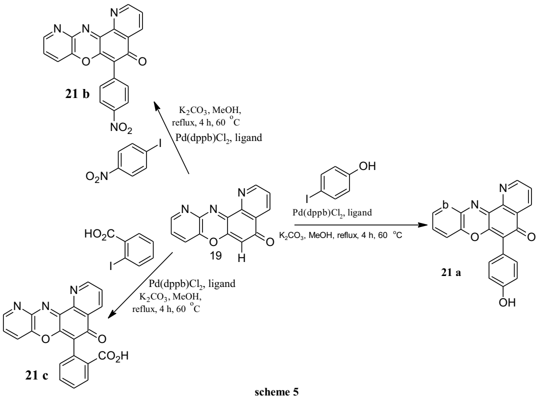


Scheme 3

Thereafter, 1,11-diazabenzo[a]phenoxazin-5one **20** and 1-azadibenzo[a,j]phenoxazin-5-one **21** were arylated, employing Heck protocol with 4-iodophenol, 2-iodobenzoic acid and 1-iodo-4-nitrobenzene as aryl halides to obtain the derivatives **20** (**a-c**) and **21** (**a-c**) using the active palladium (0) in situ prepared according to the method described by Sasmita[28] (**Scheme 4** and **Scheme 5**).



Scheme 4



scheme 5

The structural assignments of the compounds synthesized were consistent with spectroscopic data obtained.

Conclusion

The present study has shown that the palladium-catalyzed Mizoroki-Hartwig cross-coupling reaction offers an excellent route in the preparation of aryl derivatives of angular phenoxazines, **20** and **21**. Hence, the study has opened the window for further research to ascertain the medicinal potentials of these compounds.

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