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Synthesis and Structure of New Anilino Derivatives of Angular Azaphenoxazine Dye by Buchwald-Hartwig Cross Coupling Protocol

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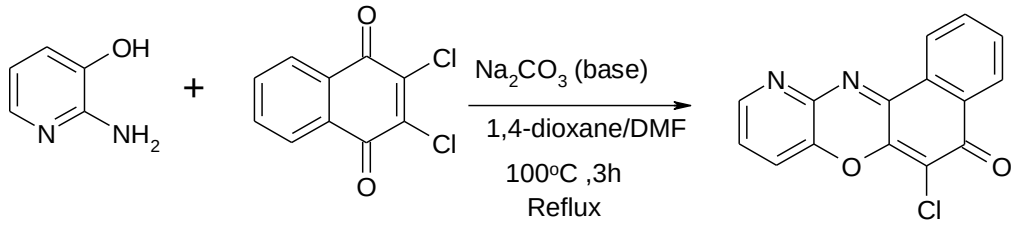
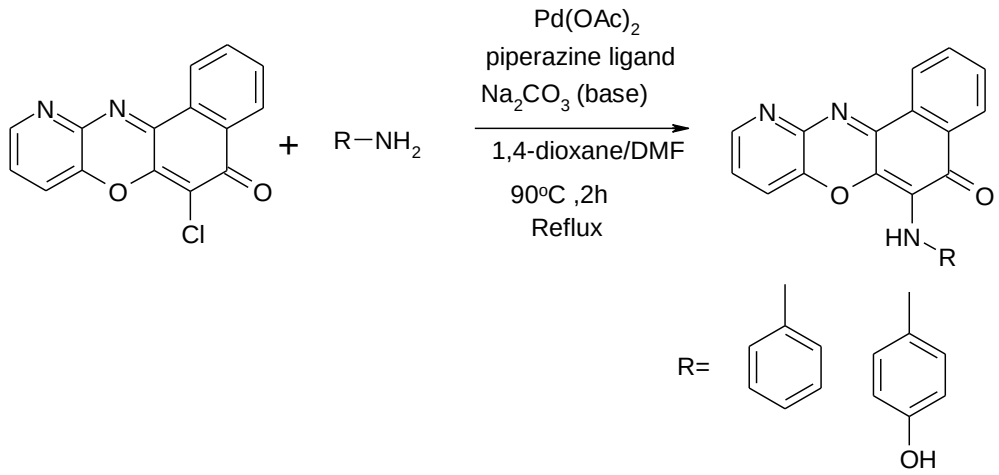
ABSTRACT

New anilino derivatives of angular azaphenoxazine were obtained via Buchwald-Hartwig cross-coupling reaction. This was achieved by first synthesizing the intermediate 6-chlorobenzo[a]-11-azaphenoxazin-5-one by anhydrous base catalyzed condensation reaction between 2-amino-3-pyridinol and 2,3-dichloro-1,4-naphthoquinone. The palladium catalyzed Buchwald-Hartwig cross coupling of this electron rich 6-chlorobenzo[a]-11-azaphenoxazin-5-one with aniline and paranitrophenol, employing $Pd(OAc)_2$, 1,4-bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine ligand and Na_2CO_3 in a 1:1 mixture of 1,4-dioxacyclohexane (1,4-dioxane) and N,N-dimethylformamide as solvent at 90° C, afforded the highly coloured anilino derivatives 6-phenylaminobenzo[a]-11-azaphenoxazin-5-one and 6-(4-hydroxy-phenylamino)-benzo[a]-11-azaphenoxazin-5-one in 50% and 75% yield respectively. Structural assignments were established by spectroscopic (UV,IR, ^1H and ^{13}C NMR).

Keywords: Anilino, angular, anhydrous, azaphenoxazine, Buchwald-Hartwig, cross-coupling



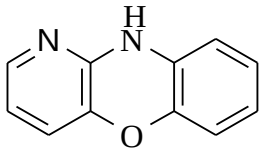


INTRODUCTION

The synthesis of azaphenoxazine 1 and its derivatives [1]-[4] have been one of the most explored fields in the last years in search for more effective and therapeutically safer drugs for the management and cure of many diseases [5]-[8]. One of the commonest strategies in this area of drug design has been the formation of C-N bonds via Buchwald-Hartwig cross-coupling protocol. Buchwald-Hartwig cross-coupling reaction is used in the formation of C-N and C-O bonds. Buchwald-Hartwig cross coupling is the direct palladium-catalyzed C-N and C-O bond formation between aryl halides or trifluoromethanesulphonates and amines (1° and 2° aliphatic or aromatic amines, imides, sulphonamides, sulphoximines) or between aryl halide or triflates and alcohols (aliphatic alcohols and phenols) in the presence of a stoichiometric amount of base.[9].

Phenoxazines are pharmaceutically important class of tricyclic nitrogen-oxygen hetetrocycles. The synthesis of phenoxazine derivatives and isolation of natural phenoxazines have been a subject of continuing interest over the years owing to the wide range of applications of these compounds. Notable applications of phenoxazine are in the fields of medicine, industry and agriculture. The pharmacological activities range

from antitumor, anticancer, antituberculosis, antibacterial, antiepileptic to central nervous system (CNS) depressants, sedatives, herbicides, tranquilizers, spasmolytic and parasiticidal agents [5]-[8]. Although many derivatives have been synthesized, there are few derivatives in which anilino groups are attached to the azaphenoxazine nucleus. In continuation of the search for pharmaco-active compounds in the azaphenoxazine class, we have embarked on the synthesis of new anilino derivatives of angular azaphenoxazine dye using Buchward-Hartwig cross coupling reaction.



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MATERIALS AND METHODS

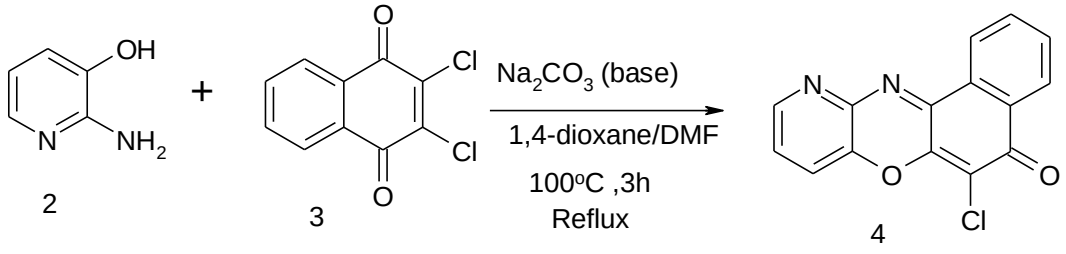
2-Amino-3-pyridinol and 2,3-dichloro-1,4-naphthoquinone were purchased from Kermel. Aniline, paranitrophenol and palladium acetate were purchased from Lobachem and were used as purchased. Melting points of synthesized compounds were determined using Gallen Kamp melting point apparatus produced in England with register design 889339. Melting points were determined by open capillary tube method at the Centre for Energy Research, University of Nigeria Nsukka and are uncorrected. All compounds were characterized by UV-visible spectroscopy and infra-red spectroscopy. Ultra violet and visible spectra were obtained on a shimadzu UV-1800 series spectrophotometer using a matched 1cm quartz cell. N, N-dimethylformamide was employed as solvent. Samples for UV were prepared in mass to volume (0.01g:10mL).

Absorption maximum values were given in nanometers (nm) and the figures in parenthesis are the log e values. Infra red spectra data were obtained on FTIR Shimadzu, model IR Affinity 1 spectrophotometer using potassium bromide (KBr) pellets. Absorptions were given in wavenumbers (cm^{-1}). Nuclear magnetic resonance (^{1}H- NMR and ^{13}C-

NMR) were determined using Jeol 400 MHz at Strathclyde University, Scothland. Chemical shifts were reported in (δ) scale. All reagents were of technical grade. The purity of samples was determined by TLC. Samples that showed traces of impurities were further purified by column chromatography on silica gel by employing toluene and acetone as solvent for elution. Eluents were concentrated using a solvent extractor and were air dried.

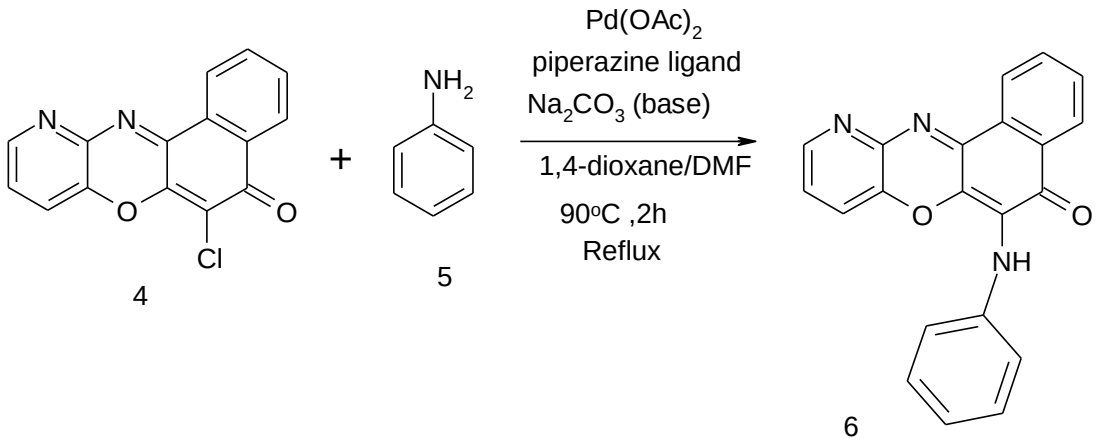
Synthesis of 6-chlorobenzo[a]-11-azaphenoxazin-5-one 4

1,4-dioxane (70mL) was transferred into a two-necked quick fit flask. 2-amino-3-pyridinol **2** (2g, 18.18mmol) was dissolved in the 1,4-dioxane (70 mL), followed by the addition of anhydrous sodiumtrioxocarbonate (IV) [Na_2CO_3] (1g, 9.43mmol), and the mixture was warmed to boiling temperature in the flask. Then 2,3-dichloro-1,4-naphthoquinone **3** (4.128g, 18.18mmol) was added and the mixture was refluxed at 100°C with continuous stirring using a magnetic stirrer on a water bath for 3 hours. The reaction mixture was allowed to cool and then added to a beaker containing crushed ice. The crystals formed were air dried on the filter paper. The product was recrystallized from N,N-dimethylformamide in an efficient fume cupboard to obtain a yellow orange solid **4** [**scheme 1**]. The yield was 4.21g [90%] [melting point 208-209°C] [Literature 207-208°C] [10]. The quality of the recrystallized product was confirmed was by thin layer chromatography. Melting point result was compatible with that reported on literatures [10].



Scheme 1: Synthesis of 6-chlorobenzo[a]-11-azaphenoxazin-5-one

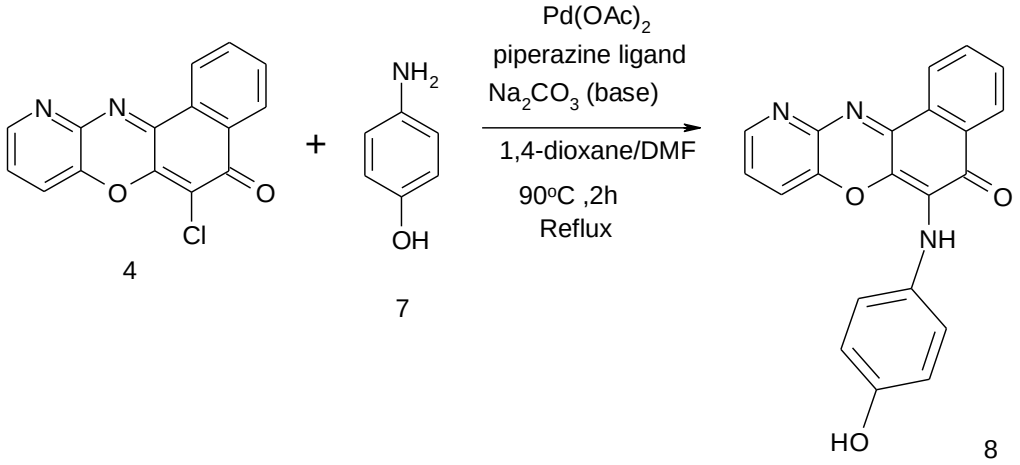
The two-necked flask was air dried and flushed with nitrogen gas. The catalyst (palladium acetate) $Pd(OAc)_2$ (0.002g, 0.01mmole) was dissolved in distilled water (1mL) to reduce the Pd(II) to pd(0) in the two necked flask. 1,4-Bis(2-hydroxyl-3,5-di-tertiary-butylbenzyl) piperazine ligand (1g, 11.63mmole) and 1,4-dioxane (1mL) was then added to the content of the two-necked flask. The content of the two-necked flask was heated for 1 minute at 80°C after which the mixture was allowed to cool. This is the water mediated preactivation of the Pd(II) to Pd(0) [11]. The flask was flushed again with nitrogen gas. Then a mixture of 6-chlorobenzo[a]-11-azaphenoxazin-5-one **4** (1g, 3.87mmole), aniline **5** (0.112g,1.2 mmole) and $NaCO_3$ (0.5g, 4.7mmole) dissolved in a 1:1 mixture of 1,4-dioxane and N,N-dimethylformamide (4mL:4mL) was added to the content of the mixture in the two-necked flask. The content of the two-necked flask was refluxed with continuous stirring using a magnetic stirrer at 90°C with for 2 hours on a water bath. The reaction mixture was allowed to cool and was then added to a beaker containing crushed ice. The crystals formed were filtered and air dried on the filter paper. The product was recrystallised from N,N-dimethylformamide in an efficient fume cupboard to obtain a reddish-brown solid **6** [**scheme 2**] . The yield was 67% [melting point was 140-144°C]



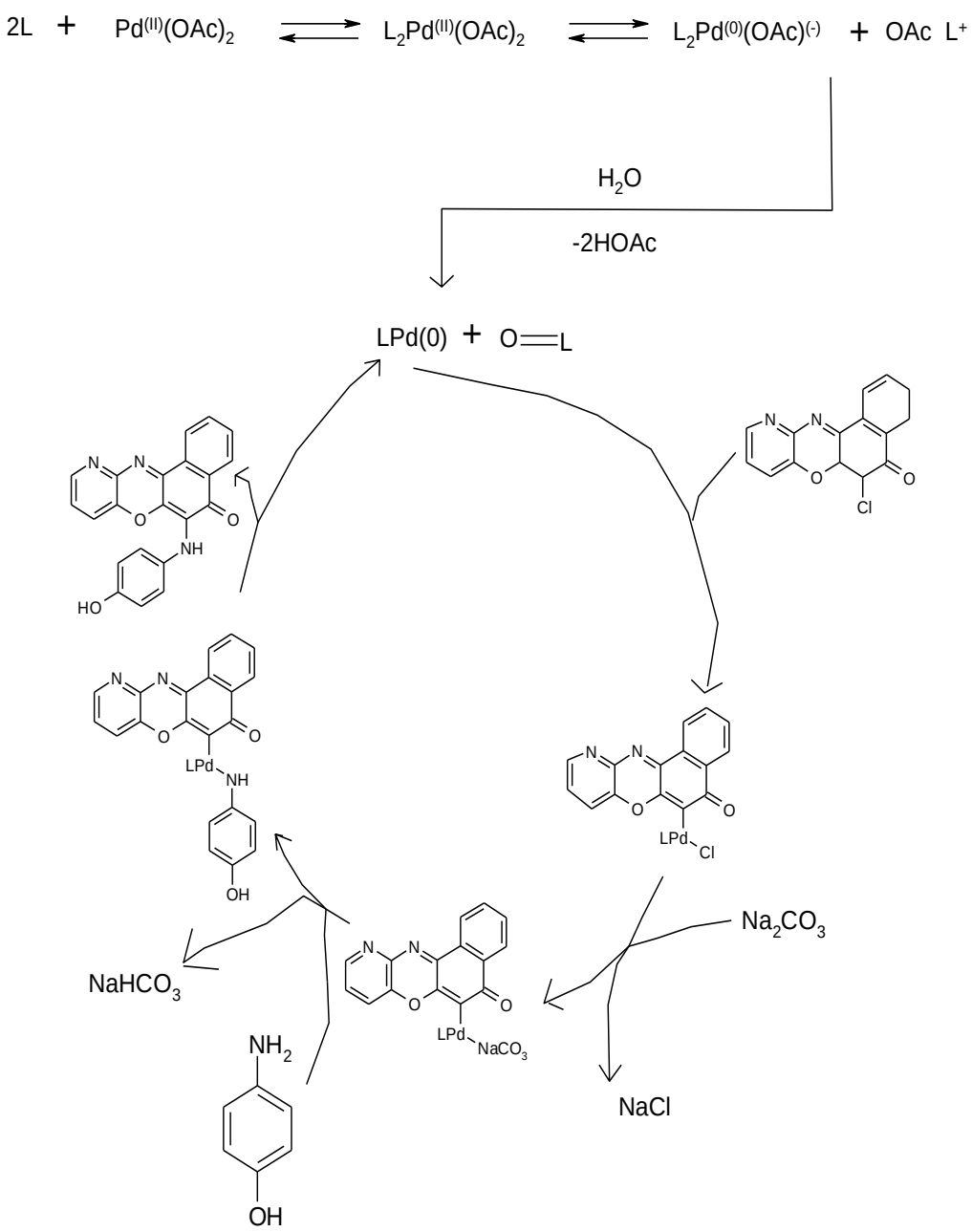
Scheme 2: Synthesis of 6-phenylaminobenzo[a]-11-azaphenoxazin-5-one

Synthesis of 6-(4-hydroxylphenylamino)benzo[a]-11-azaphenoxazin-5-one

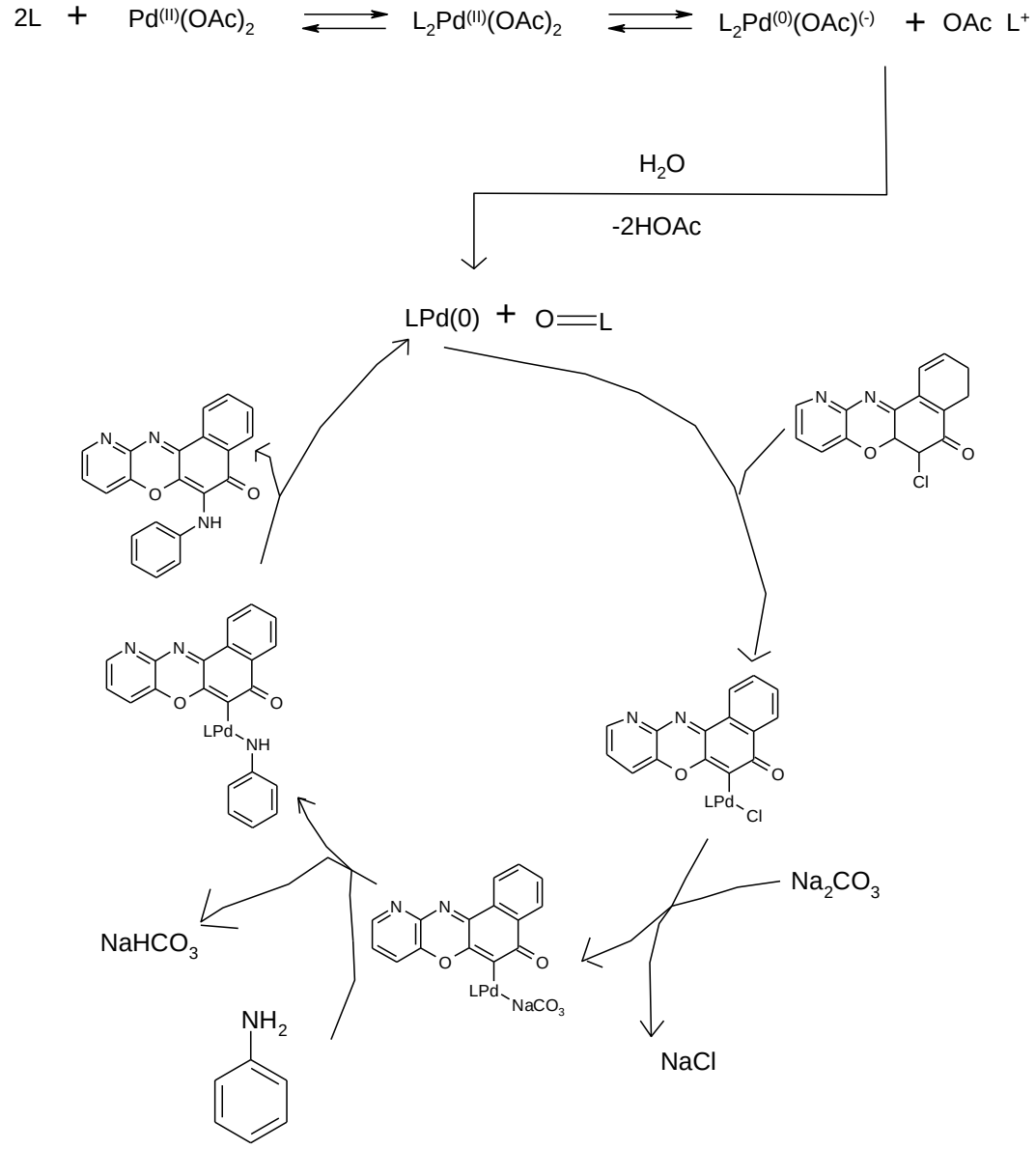
The two-necked flask was air dried and flushed with nitrogen gas. The catalyst (palladium acetate) $Pd(OAc)_2$ (0.002g, 0.01mmole) was dissolved in distilled water (1mL) to reduce the Pd(II) to Pd(0) in the two necked flask [11]. 1,4-Bis(2-hydroxyl-3,5-di-tertiary-butylbenzyl) piperazine ligand (1g, 11.63mmole) and 1,4-dioxane (1mL) was then added to the content of the two-necked flask. The content of the two-necked flask was heated for 1 minute at 80°C after which the mixture was allowed to cool. Then the two necked flask was flushed again with nitrogen gas. Then a mixture of 6-chlorobenzo[a]-11-azaphenoxazin-5-one **4** (1.5g, 5.803mmole), 4-aminophenol **7** (0.422g, 3.869 mmole) and $NaCO_3$ (0.5g, 4.72mmole) dissolved in a 1:1 mixture of 1,4-dioxane and N,N-dimethylformamide (5mL:5mL) was added to the content of the mixture in the two-necked flask. The content of the two-necked flask was refluxed with continuous stirring using a magnetic stirrer at 90°C for 2 hours on a water bath. The reaction mixture was allowed to cool and was then added to a beaker containing crushed ice. The crystals formed were filtered and air dried on the filter paper. The product was recrystallised from N, N-dimethylformamide in an efficient fume cupboard to obtain a dark-red solid **8** [**scheme 3**]. The yield was 1.12g (75% [melting point was 141-146°C]



Scheme 3: Synthesis 6-(4-hydroxyl-phenylamino)benzo[a]-11-azaphenoxazin-5-one



Catalytic cycle for the synthesis of 6(4-hydroxyl-phenylamino)-benzo[a]-11-azaphenoxazin-5-one



Catalytic cycle
for the synthesis of 6-phenylaminobenzo[a]-11-azaphenoxazin-5-one

RESULTS AND DISCUSSION

6-chlorobenzo[a]-11-azaphenoxazin-5-one 4

Yellow-orange crystals melting at 208-209°C [Literature 207-208°C] [10]. The yield is 4.21g (90%). The melting point is close to that reported on literatures. The product showed **UV-visible absorption bands** at 340 (loge = 2.74) and 311.5 (loge = 2.74). the **Infra-red spectrum** showed bands at 3574-3363 cm^{-1} (due to NH stretch), 3078-3265.25 cm^{-1} (due to CH stretch), 2892-2647cm^{-1} (m) (due to secondary amine CH stretch), 2088.02-1690.44cm^{-1} (aromatic ring stretching), 1785.01cm^{-1} (aromatic >CO stretch), 900-700cm^{-1} (Ar-H bands), 885.63 cm^{-1} (Aromatic C-C, C-Cl stretch). ^{1}H NMR (DMSO) d_H : 8.87-8.85(1H,m,aromatic); 8.33-8.31 (1H,m, Ar-H), 7.97-7.94 (1H,m, Ar-H), 7.74-7.72 (2H,m, Ar-H), 7.54-7.42 (3H,m, Ar-H), ^{13}C NMR (DMSO) d_C : 173.9 (carbonyl carbon), 143.8, 138.4,135.2,134.1,133.3,132.0, 131.6, 130.2, 128.3, 126.5, 126.0, 125.3, 125.2, 123.6.

6-phenylamino-benzo[a]-11-azaphenoxazin-one 6

Yellow-orange crystals melting at 208-209°C [Literature 207-208°C]. The yield is (67%). The melting point is close to that reported on literatures. The product showed **UV-visible absorption bands** at 340 (loge = 2.74) and 311.5 (loge = 2.74). The **Infra-red spectrum** showed bands at 3574-3363 cm^{-1} (due to NH stretch), 3078-3265.25 cm^{-1} (due to CH stretch), 2892-2647cm^{-1} (m) (due to secondary amine CH stretch), 2088.02-1690.44cm^{-1} (aromatic ring stretching), 1785.01cm^{-1} (aromatic >CO stretch), 900-700cm^{-1} (Ar-H bands), 885.63 cm^{-1} (Aromatic C-C, C-Cl stretch) . ^{1}H NMR (DMSO) d_H : 8.87-8.85(1H,m,aromatic); 8.33-8.31 (1H,m, Ar-H), 7.97-7.94 (1H,m, Ar-H), 7.74-7.72 (2H,m, Ar-H), 7.54-7.42 (3H,m, Ar-H), ^{13}C NMR (DMSO) d_C : 180.98-173.9 (carbonyl carbon), 151.89, 145.71, 143.8, 138.4,135.2,134.1,133.3,132.66, 131.6, 130.2, 128.3, 126.5, 126.0, 125.3, 123.6.

6-(4-hydroxylphenylamino)benzo[a]-11-azaphenoxazin-5-one 8

Dark-red crystals melting at 141-146°C. The yield is 1.12g (75%). The product showed **UV-visible absorption bands** at 405.5 (loge = 3.15) and 380 (loge = 3.14), 383 (loge = 3.09). The **Infra-red** spectrum showed bands at 3574.12-3481.48 cm^{-1} (due to NH stretch), 3292.34-3045.30 (CH-stretch, several peaks), 2890-2771.24(m) (secondary amine CH stretch), 1756.06 (aromatic >C=O stretch), 1659-1593.94 (NH), 900-700cm^{-1} (Ar-H bands), 885.63 cm^{-1} (Aromatic C-C stretch), 748.60 PHENOL (aromatic OH) at a plane formation. ^{1}H NMR (DMSO) d_H : 8.87-8.85(1H,m,aromatic); 8.33-8.31 (1H,m, Ar-H), 7.97-7.94 (1H,m, Ar-H), 7.74-7.72 (2H,m, Ar-H), 7.54-7.42 (3H,m, Ar-H), ^{13}C NMR (DMSO) d_C : 181.76-173.9 (C=O), 152.56, 143.8, 138.4,135.2,133.3,132.0, 131.6, 130.2, 128.3, 126.5, 126.0, 125.3, 125.2, 123.6, 111.86,110.72

CONCLUSIONS

We have reported the synthesis and structure of new anilino derivatives of angular azaphenoxazine dye by Pd-catalyzed Buchwald-Hartwig cross-coupling protocol. Nitrogen gas is introduced into the two-necked flask to provide an inert environment for the reaction. These syntheses involved oxidative addition, metathesis, Transmetallation and reductive elimination. These anilino derivatives were prepared in good yields. Further research is in progress to explore their pharmacological potential.

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