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Rapid Access Hetero-Amino Derivatives of Angular Phenoxazine Dye

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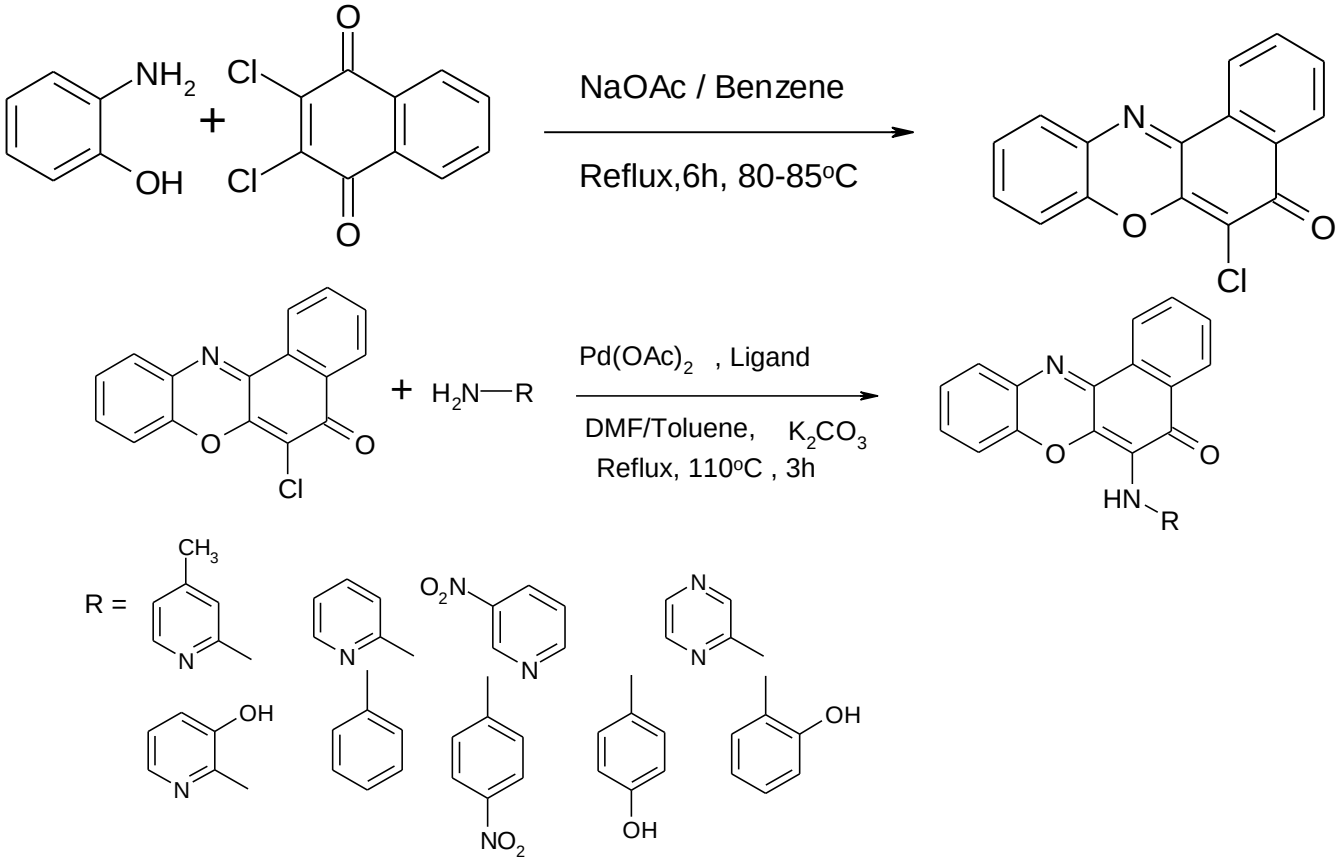
ABSTRACT

The synthesis of nine hetero-amino derivatives of the angular phenoxazine, 6-chlorobenzo[a]phenoxazin-5-one is reported. New hetero-amino derivatives of 6-chlorobenzo[a]phenoxazin-5-one dye were obtained via palladium catalyzed Buchwald-Hartwig cross coupling reactions. This was achieved by first synthesizing the intermediate, 6-chlorobenzo[a]phenoxazin-5-one by anhydrous base-catalyzed condensation reaction between 2-aminophenol and 2,3-dichloro-1,4-naphthoquinone. Palladium acetate catalyzed Buchwald-Hartwig cross coupling of the intermediate with various readily available amines via water mediated catalyst preactivation procedure in a mixture of 1:1 mixture of toluene and N,N-dimethylformamide as solvent and 1,4-bis(2-hydroxy -3,5-di-tert-butylbenzyl)piperazine ligand at a temperature of 110°C yielded the previously unknown highly coloured amino derivatives in good yields. Structural assignments were established by spectroscopic techniques (UV, IR, 1H and ^{13}C NMR).

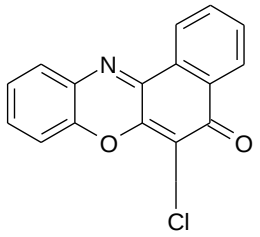
Keywords: Hetero-amino, angular phenoxazine, preactivation, water-mediated, Buchwald-Hartwig, cross coupling.



INTRODUCTION

Following repeated reports on the pharmacological activities of phenoxazine and its derivatives, interest in their synthesis, dyeing properties and biological activities has increased among researchers in synthetic chemistry [1]-[6]. From tests carried out in laboratory animals and in man, it was found that many phenoxazine derivatives show pronounced pharmacological activities as central nervous system (CNS) depressants, sedatives, anti-epileptics, herbicides, tranquilizers, anti-tuberculosis, anti-tumor, antibacterial, spasmolytic, anthelminthic and parasiticidal agents [7]-[10]. Recently Nile red has been used as a fluorescent laser dye because of its high photochemical stability. Phenoxazine dyes are also used as polymerization retardant, photosensitizers, acid base indicators and metal extradants. Detection of biological analytes utilizing fluorescent dyes eliminate the need for

radioactive labels, thereby enhancing safety and diminishing the adverse environmental impact and cost associated with radioactive waste disposal [11]-[17]. Considering the vast applications, exploitation and utilization of angular phenoxazine rings **1**, there is a need to synthesize more derivatives of this compound. Over the years, interest in naturally occurring and synthetic phenoxazine derivatives has triggered the synthesis of new rings, derived from phenoxazine. Although, many derivatives of these compounds have been synthesized, there are few derivatives in which amino groups are attached to the phenoxazine nucleus. In continuation of the search for pharmaco-active compounds in the phenoxazine class, the syntheses of new hetero-amino derivatives of angular phenoxazine dyes were given utmost consideration.



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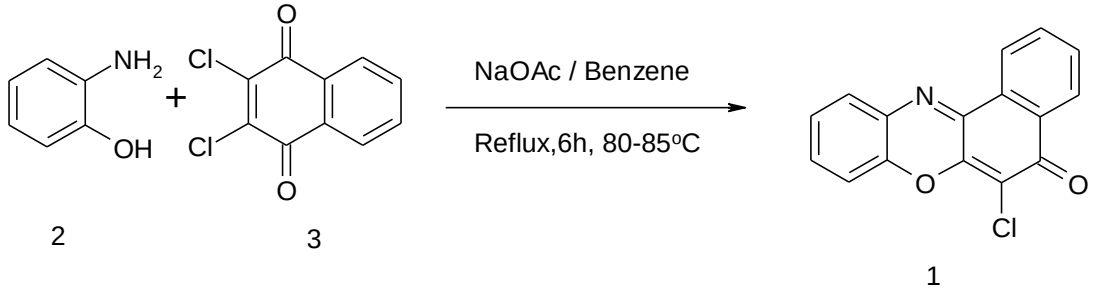
MATERIALS AND METHODS

All reagents are of technical grade. $Pd(OAc)_2$, 2-Aminophenol and 2,3-dichloro-1,4-naphthoquinone were purchased from Sigma-Aldrich. All other reagents used were sourced locally from commercial chemical shops in well sealed containers and were used without further purification. All coupling reactions were carried out under nitrogen atmosphere. Melting points of synthesized compounds were determined using Electrothermal Melting Point Apparatus at the Department of Pharmacy, University of Nigeria, Nsukka, by open tube capillary method and are uncorrected. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and UV-Visible spectroscopy. Ultraviolet and visible spectra were obtained on a UV1 Ultra-Violet Spectrophotometer (manufactured by UNICAM, serial number 061408) using matched 1cm quartz cells. Ethanol was used as solvent. Absorption maximum were given in nanometer (nm) and the figures in parenthesis are the loge

values. Infra-red spectral data were obtained at the National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna State, on FTIR-8400S Fourier Transform Infrared Spectrophotometer using (KBr pellets), and absorptions were given in wavenumbers (cm^{-1}).

^{1}H NMR and ^{13}C-NMR were determined at Strathclyde University, Scotland, using Jeol 400MHz instrument. All ^{1}H NMR experiments are reported in d units, [parts per million (ppm)] relative to the signals for Tetramethylsilane (TMS). All ^{13}C NMR are recorded in d units, [parts per million (ppm)]. 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 ethyl acetate and n-hexane as solvent for elution. Eluents were concentrated using a solvent extractor and air dried.

Procedure for the Synthesis of 6-Chlorobenzo[a]phenoxazin-5-one
Benzene (100mL) was transferred into a three necked quickfit flask. 2-Aminophenol (4g, 37mmol) **1** was dissolved in the benzene (100 mL) followed by the addition of anhydrous sodium acetate (8.2g, 37mmol), and the mixture was warmed to boiling temperature in the flask. Then 2, 3-dichloro-1,4-naphthoquinone (8.2g, 37 mmol) **2** was added and the mixture refluxed at 80°C with continuous stirring using a magnetic stirrer on a water bath for 6 hours. The reaction mixture was allowed to cool and then added to a beaker containing crushed ice. The precipitate formed was air dried on the filter paper. The product was recrystallised from a heterogeneous mixture of ethanol-water 2:1 to obtain a yellow solid **3** which was obtained in 95% yield, (m.p. 199-201°C) (202-203°C)[94]. The quality of the recrystallised product was confirmed using the thin layer chromatography and melting point



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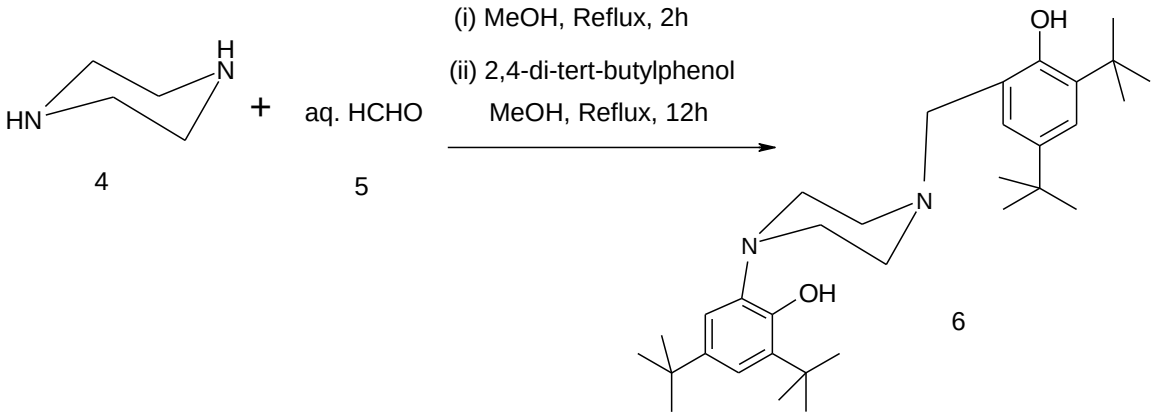
Scheme 1 Synthesis of 6-chlorobenzo[a]phenoxazin-5-one

Synthesis of 1, 4-bis (2-hydroxy-3, 5-di-*tert*-butylbenzyl/piperazine

A mixture of piperazine (2.2g, 25.54mmol) **4** and 40% aqueous paraformaldehyde solution (4g, 56.88mmol) **5** was dissolved in methanol (40 mL) and heated to reflux for 2 hours at a temperature of 65°C to obtain a white solution. The solution was then cooled. To the cooled solution was added 2, 4-di-*tert*-butylphenol (10.3g, 50.41mmol) in methanol (60mL). The resulting solution was refluxed at 65°C with continuous stirring using a magnetic stirrer for further 12 hours on a water bath to obtain the titled product. The solution was cooled to room temperature. Recrystallization of the product was done from toluene to obtain the pure ligand 1,4-bis(hydroxyl-3,4-di-tert-butylbenzyl)piperazine **6** as a white crystal of melting point 260°C (Literature: above 250° C) [18-20].



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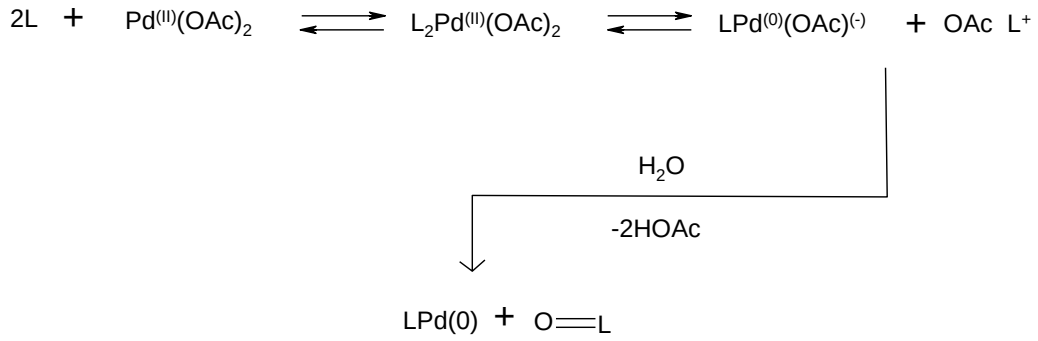
SCHEME 2 Synthesis of 1, 4-bis (hydroxyl-3, 4-di-tert-butylbenzyl)piperazine

General procedure for the synthesis of amino derivatives of 1

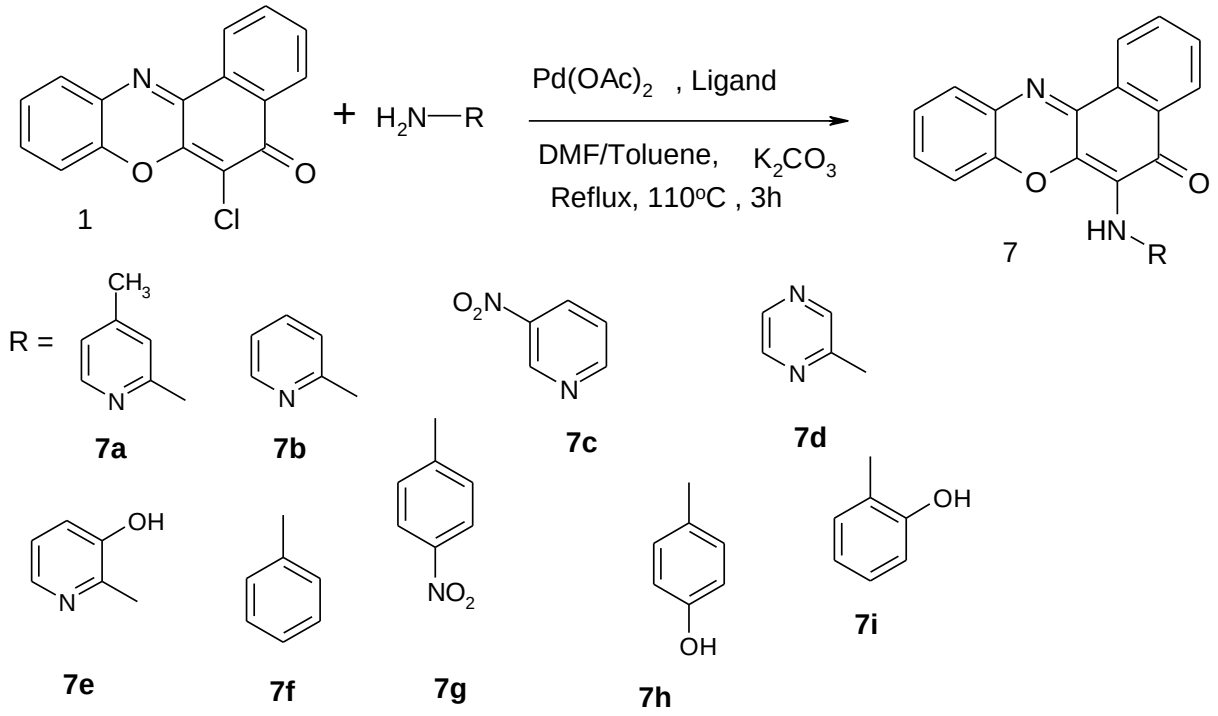
The flask was dried and flushed with nitrogen. The catalyst, $Pd(OAc)_2$ (0.002g, 0.01mmol) was dissolved in distilled water (1 mL) to reduce the Pd(II) to Pd(0) . 1,4-Bis(2-hydroxy-3,5-di-tert-butylbenzyl)piperazine (0.003g, 0.03 mmol) was added followed by the addition of 1, 4-dioxane (1 mL) and heated for 1minute at 80°C after which the mixture was allowed to cool. This is the water mediated preactivation of the catalyst [18-19].



L= Ligand i.e 1,4-bis(2-hydroxy-3,5-di tert-butylbenzyl)piperazine

Scheme 3: Water promoted activation of the $Pd(AOc)_2$

The flask was flushed again with nitrogen. Then a mixture of 6-chlorobenzo[a]phenoxazin-5-one (0.282g, 1.0mmol), 2-amino-4-methylpyridine (or any other amine used respectively) (0.130g, 1.2mmol) and K_2CO_3 (0.194g, 1.4mmol) dissolved in a mixture of dimethylformamide (DMF) and toluene (2mL: 2mL) was added to the content of the flask. The flask was flushed with nitrogen and closed. The content was refluxed at 110°C with continuous stirring using a magnetic stirrer for 3 hours on a paraffin oil bath. Recrystallization was done from a 1:1 heterogeneous mixture of ethyl acetate and water to obtain the titled product as a reddish-brown solid. The quality of the product was determined using TLC.



Scheme 4: equation for the synthesis of products 7a-7i

RESULTS AND DISCUSSION

6-Chlorobenzo[a]phenoxazin-5-one 1

Yellow crystals melting at (199°-201°C) (Lit 202°-203°C)[94]. The yield is 89%. This derivative had **UV-visible** absorption bands at 203 (loge 4.33), 209 (loge 4.33), 884 (loge 1.55), 888nm (loge 1.5) which is consistent with the observed yellow colour. The **IR** spectrum showed bands at 3371-3254 cm^{-1} was due to (NH), 1650-1573 cm^{-1} due to (>C=O), 1588cm^{-1} due to (C=C and C=N stretch), 1371-1288cm^{-1} due to (CH bending), 830 cm^{-1} due to (disubstituted benzene), 739cm^{-1} due to (monosubstituted benzene). **^{1}H NMR (DMSO) d_H** : 6.70-6.63 (m, 4H, Ar-H), 6.57 (triplet, 1H, Ar-H), 6.47 (d, 2H, Ar-H), 6.45 (triplet, 1H, Ar-H) . **^{13}C NMR (DMSO) d_C:** 175.2 (>C=O), 146.7 (Ar-C), 144.7 (Ar-C), 140.7 (Ar-C), 138.3 (Ar-C), 136 (, Ar-C), 132.8(Ar-C), 130.1(Ar-C), 118-115 (>C-N- , >C=C<).

6-(4-Methylpyridin-2-ylamino)benzo[a]-phenoxazin-5-one 7a

Reddish-brown solid melting at 168-170° C. The yield is 85%. It had **UV-visible** absorption bands at 206 (loge 4.33), 214 (loge 4.48), 885 (loge 1.5), 899nm (loge 1.7), The **IR peaks** at 3436-3421 cm^{-1} is due to (NH stretch), 2940-2920 cm^{-1} is due to (CH stretch of aliphatic), 1684-1634 cm^{-1} is due to (>C=O), 1590-1560 cm^{-1} is due to (C=C and C=N stretch), 1380-1360 cm^{-1} is due to (CH deformation), 1293-1014 cm^{-1} is due to (C-O-C), 742 cm^{-1} is due to (monosubstituted benzene). **^{1}H NMR (DMSO) d_H :** 8.53 (s, 1H, Ar-H), 7.89 (d, 1H, Ar-H), 7.798 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 7.67 (m, 4H, Ar-H), 7.54 (triplet, 1H, Ar-H), 6.3-6.25 (triplet, 1H, Ar-H), 5.75 (s,1H, Ar-H), 1.65 (s, 3H, CH_3). **^{13}C NMR (DMSO) d_C:** 160.41 (>C=O), 147.96 (Ar-C), 147.7 (Ar-C), 135.8 (Ar-C), 134.2 (Ar-C), 131.2-130.99 (d, Ar-C), 126(Ar-C), 125.7(Ar-C), 113.94 (>C=N-), 108.6 (>C=C<).

6-(Pyridine-2-ylamino)benzo[a]phenoxazin-5-one 7b

Brown solid melting at 228-229° C. The yield is 74% . It had **UV-visible** absorption bands at 209 (loge 4.41), 207 (loge 4.41), 879 (loge 1.80), 886nm (loge 1.78), **The IR peaks** at 3533-3300 cm^{-1} is due to (NH stretch), 2980-2850 cm^{-1} is due to (CH stretch), 1635-1430 cm^{-1} is due to (>C=O), 1577-1560 cm^{-1} is due to (C=C and C=N stretch), 1284 cm^{-1} is due to (C-O-C), 843 cm^{-1} is due to (monosubstituted benzene). **^{1}H NMR (DMSO) d_H :** 7.91 (d, 1H, Ar-H), 7.89 (d, 1H, Ar-H), 7.79 (triplet, 1H, Ar-H), 7.77 (d, 1H, Ar-H), 7.67-7.55 (m, 4H, Ar-H), 7.54 (triplet, 1H, Ar-H), 6.43 (d, 1H, Ar-H), 5.85 (s,1H, NH). **^{13}C NMR (DMSO) d_C:** 207.34 (>C=O), 134.19 (Ar-C), 130.95 (Ar-C), 126.0 (Ar-C), 125.78 (Ar-C). 112.3 (>C=N-, >C=C<).

6-(5-Nitropyridin-2-ylamino)benzo[a]- phenoxazin-5-one 7c

Reddish-brown solid melting at 160-161°C. The yield was 45%. It had UV-visible absorption bands at 205 (loge 4.46), 339 (loge 4.46), 849 (loge 1.58), 866nm (loge 1.68), The IR peaks at 3072-3030 is due to (NH stretch), 1680-1619 is due to (>C=O), 1534-1440 cm^{-1} is due to (>CN,

>C=C< stretch), 1552-1530 (NO_2), 1264 is due to (C-O-C), 650-600cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H : 8.83-8.82 (d, 3H, Ar-H), 8.1 (d, 1H, Ar-H), 8.098 (triplet, 2H, Ar-H), 8.07 (d, 1H, Ar-H), 7.52 (d, 2H, Ar-H), 6.48 (triplet, 2H, Ar-H),3.7 (s,1H,NH). ^{13}C NMR (DMSO) d_C: 205.99 (>C=O), 147.86 (Ar-C), 147.53 (Ar-C), 134.9 (Ar-C), 133.1 (Ar-C), 107.7 (>C=C<, >C=N<).

6-(Pyrazin-2-ylamino)benzo[a]phenoxazin-5-one 7d

Orange-brown solid melting at 204-205°C. The yield was 69%. It had UV-visible absorption bands at 210 (loge 4.41), 206 (loge 4.41), 886 (loge 1.78), 886nm (loge 1.78), The IR peaks at 3440-3280cm^{-1} is due to (NH), 1680-1573cm^{-1} is due to (>C=O), 1590-1560cm^{-1} is due to (C=C and C=N stretch), 1391-1370 is due to (CH stretch of aromatic). 733 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H : 7.9 (d, H, Ar-H), 7.89 (d, 1H, Ar-H), 7.79 (d, 2H, Ar-H), 7.77 (triplet, 1H, Ar-H), 7.67 (d, 2H, Ar-H), 7.54 (m, 4H, Ar-H), 6.38 (s,1H,NH). ^{13}C NMR (DMSO) d_C: 167.5 (>C=O), 134.2 (Ar-C), 133.02 (Ar-C), 131.21 (Ar-C), 130.95 (Ar-C), 126.01 (Ar-C), 125.78(>C=C<, >C=N<).

6-(3-Hydroxypyridin-2-ylamino)benzo[a]- phenoxazin-5-one 7e

Purple solid melting at 200-201°C. The yield was 49%. It had UV-visible absorption bands at 224 (loge 4.73), 207 (loge 4.73), 880 (loge 2.06), 888nm (loge 2.03), The IR peaks at 3500-3400cm^{-1} is due to (OH), 3349-3261cm^{-1} is due to (NH stretch), 2940-2920 cm^{-1} is due to (CH stretch of aliphatic), 1700-1620cm^{-1} is due to(C-H broad), 1650-1643 cm^{-1} is due to (>C=O), 1490cm^{-1} is due to (C=C and C=N stretch), 846-727 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H : 9.5 (d, H, Ar-H), 8.99 (d, 1H, Ar-H), 8.49 (triplet, 1H, Ar-H), 8.47 (d, 1H, Ar-H), 8.02-7.96 (m, 4H, Ar-H), 7.82-7.74 (triplet, 2H, Ar-H), 5.53 (s,1H,NH). ^{13}C NMR (DMSO) d_C: 180.54-178.09 (>C=O), 158.2 (Ar-C), 157.4 (Ar-C), 135.08 (Ar-C), 133.7 (Ar-C), 132.4 (Ar-C), 130.4 (Ar-C), 126.75 (Ar-C), 116.5-116.1 (>C=C<, >C=N<).

6-Phenylaminobenzo[a]phenoxazin-5-one 7f

Reddish-brown solid melting at 190-191°C. The yield was 84%. It had UV-visible absorption bands at 224 (loge 3.81), 206 (loge 4.53), 880 (loge 2.04), 891nm (loge 1.897), The IR peaks at 3390-3361cm^{-1} is due to (>NH stretch), 1645-1590 cm^{-1} is due to (>C=O), 1380-1360 is due to (CH stretch of aromatic),1590-1560 cm^{-1} is due to (C=C and C=N stretch), 1380cm^{-1} is due to (CH deformation), 836cm^{-1} is due to (disubstituted benzene), 745 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H: 7.72 (d, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 7.69 (triplet, 1H, Ar-H), 7.51-7.497 (m, 4H, Ar-H), 7.38 (d, 1H, Ar-H), 6.84 (m, 4H, Ar-H), 6.3 (s, 1H, NH). ^{13}C NMR (DMSO) d_C: 180.8 (>C=O), 149.45 (Ar-C), 148.82 (Ar-C), 147.95 (Ar-C), 142.49 (Ar-C), 134.30 (Ar-C), 129.39 (Ar-C), 128.5 (Ar-C), 125.85 (Ar-C), 116.5-103.999 (>C=C<, >C=N<).

6-(4-Nitrophenylamino)benzo[a]phen- oxazin-5-one 7g

Dark-red solid melting at 134-135°C. The yield was 70%. It had UV-visible absorption bands at 203 (loge 4.33), 205 (loge 4.53), 879 (loge 1.76), 897nm (loge 1.897), The IR peaks at 3484-3348 cm^{-1} is due to (NH stretch), 1634-1606cm^{-1} is due to (>C=O), 1560-1471 cm^{-1} is due to (C=C and C=N stretch), 1471cm^{-1} is due to (NO_2), 1302-1107 cm^{-1} is due to (CH bending), 1293-1014 cm^{-1} is due to (C-O-C), 836cm^{-1} is due to(disubstituted benzene), 742 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H: 7.95 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 7.69 (d, 2H, Ar-H), 7.53 (triplet, 2H, Ar-H), 6.81 (d, 2H, Ar-H), 6.59 (triplet, 2H, Ar-H), 3.42 (s,1H,NH). ^{13}C NMR (DMSO) d_C: 156.3 (>C=O), 136.16 (Ar-C), 134.18 (Ar-C), 130.95 (Ar-C), 126.95 (Ar-C), 126.02 (Ar-C), 125.79 (Ar-C), 112.95 (>C=C<, >C=N<).

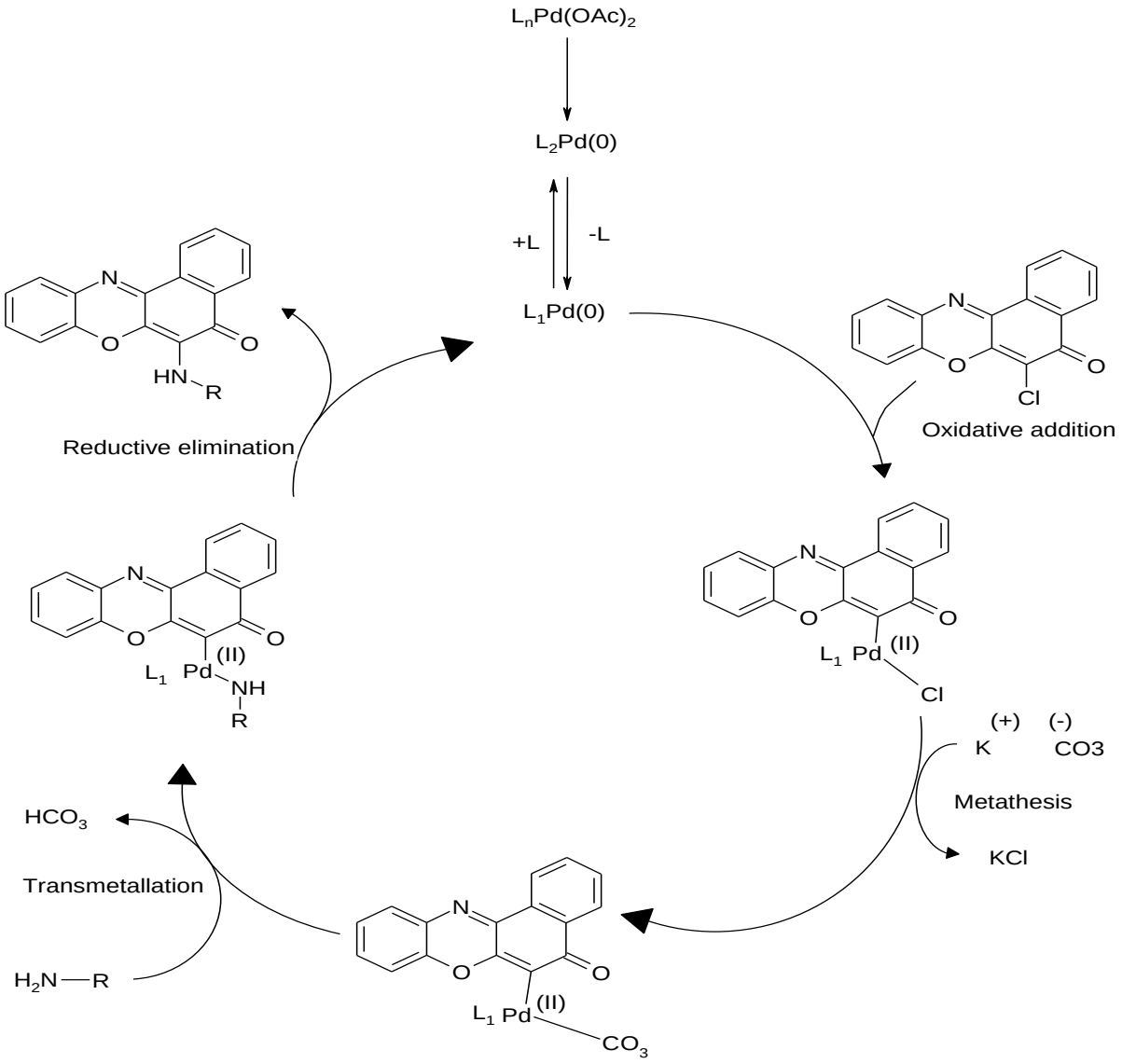
6-(4-Hydroxyphenylamino)benzo[a]phenoxazin-5-one 7h

Dark-brown solid melting at 192-193°C. The yield was 66%. It had UV-visible absorption bands at 204 (loge 4.33), 207 (loge 3.62), 880 (loge 1.695), 891nm (loge 1.66), The IR peaks at 3371-3250 cm^{-1} is due to (OH), 3436-

3254cm^{-1} is due to (NH stretch), 1680-1658 cm^{-1} is due to (>C=O), 1590-1560 cm^{-1} is due to (C=C and C=N stretch), 1371-1288 cm^{-1} is due to (CH bend), 850-830cm^{-1} is due to (p-disubstituted), 742 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H : 8.52 (d, 1H, Ar-H), 8.1 (d, 1H, Ar-H), 7.9 (triplet, 2H, Ar-H), 7.8-7.6 (m, 4H, Ar-H), 7.5-7.4 (m, 4H, Ar-H), 7.2 (d, 2H, Ar-H), 5.8 (s,1H,OH). ^{13}C NMR (DMSO) d_C: 134.4 (Ar-C), 130.77 (Ar-C), 125.85 (Ar-C), 125.46 (Ar-C).

6-(2-Hydroxyphenylamino)benzo[a]phenoxazin-5-one 7i

Black solid melting at 204-205°C. The yield was 89%. It had **UV-visible** absorption bands at 203 (loge 3.42), 220 (loge 4.33), 897 (loge 1.79), 897nm (loge 1.68), The **IR peaks** at 3440-3432 cm^{-1} is due to (NH stretch), 2940-2920 cm^{-1} is due to (CH stretch), 1681-1672 cm^{-1} is due to (>C=O), 1590-1560 cm^{-1} is due to (C=C and C=N stretch), 1000.12is due to (C-OH stretch), 742 cm^{-1} is due to (monosubstituted benzene). ^{1}H NMR (DMSO) d_H: 7.9 (d, 1H, Ar-H), 7.89 (d, 1H, Ar-H), 7.79 (triplet, 2H, Ar-H), 7.77 (d, 2H, Ar-H), 7.67 (triplet, 2H, Ar-H), 7.55 (d, 2H, Ar-H), 7.53 (Ar-C), 6.3 (s,1H,OH). ^{13}C NMR (DMSO) d_C: 167.6 (>C=O), 135.71 (Ar-C), 134.15 (Ar-C), 130.93 (Ar-C), 125.99 (Ar-C), 125.77 (Ar-C).



Scheme 5: Proposed mechanism for $Pd(OAc)_2$ catalyzed Buchwald-Hartwig cross coupling reaction.

CONCLUSIONS

From this work, it had been shown that the Palladium-catalyzed Buchwald-Hartwig cross coupling reaction offers an excellent route in

the preparation of amino-derivatives of angular phenoxazine dyes. This study has opened a window for further studies needed to be conducted on these new compounds to ascertain their medicinal potentials.

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