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Synthesis of Monoazaphenoxazine Derivatives *via* Buchwald-Hartwig Tandem Amination Protocol

FLORENCE UCHENNA EZE* and UCHECHUKWU CHRIS OKORO

Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Nigeria

*Corresponding author: E-mail: florence.ali@unn.edu.ng

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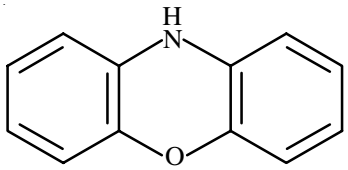
Synthesis of monoazaphenoxazine *viz.*, 3-chloro-1-azaphenoxazine (**7**) and some of its functionalized anilino derivatives (**7a-e**) *via* Buchwald-Hartwig amination methodology is reported. The intermediate 3-chloro-1-azaphenoxazine (**7**), was obtained by base-catalyzed condensation reaction between 2-aminophenol (**8**) and 2,3,5-trichloropyridine (**9**). Further reaction of compound **7** with various substituted anilines (**10**) *via* Tandem catalysis gave the anilino derivatives (**7a-e**). Structures of the synthesized compounds were assigned by spectroscopic methods.

Keywords: Aminophenol, Aniline, Phenoxazine, Tandem catalysis.

INTRODUCTION

Phenoxazines are pharmaceutically important class of tricyclic nitrogen-oxygen hetetrocycles[1]. The synthesis of phenoxazine derivatives and isolation of natural phenoxazines[2] have been a subject of continuing interest over the years owing to the wide range of applications of these compounds[3]. Among the applications of phenoxazine are in the fields of medicine, industry and agriculture. The pharmacological activities range from antitumor[4], anticancer[5], antituberculosis[6], antibacterial[7], antiepileptic[8] to central nervous system (CNS) depressants[9], sedatives, herbicides, tranquilizers, spasmolytic and parasiticidal agents[10].

Interest in the pharmacological activities of phenoxazine prompted the synthesis of scaffolds of phenoxazine and their aza analogues. The parent ring phenoxazine (**1**) was first synthesized by Bernthsen[11].



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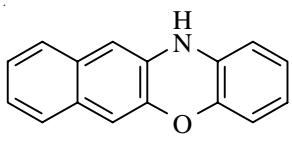
A number of structural modification has been carried out since the discovery of the parent ring phenoxazine (**1**) to enhance their pharmacological activities, minimize undesirable effects[12] and open new areas of applications. Such molecular modifications have yielded derivatives as **2, 3, 4, 5** and **6**.



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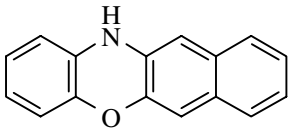

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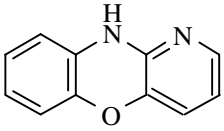

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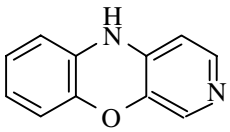

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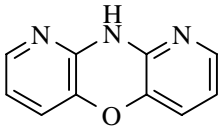

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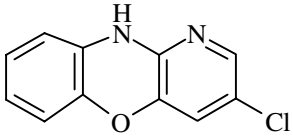

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Although the literature contains quite a lot of information on phenoxazine derivatives especially the 10-*N*-substituted analogues, there are few reports of C-substituted side chain derivatives especially the C-N analogue which has constituted a major challenge. At present there is practically no report of side chain amino derivatives of phenoxazine *via* metal catalyzed tandem reactions. We now report the synthesis of 3-substituted amino derivatives of 1-azaphenoxazine (**7**) *via* palladium catalyzed cross-coupling reaction.

EXPERIMENTAL

All reactions were carried out under an atmosphere of nitrogen. Melting points were determined with Fischer John's melting point apparatus and are uncorrected. UV and visible spectra were recorded in ethanol on a Unicon UV-2500PC spectrophotometer using matched 1 cm quartz cells; absorption are measured in nanometer (nm). IR spectra were recorded on 8400s Fourier transform infrared (FTIR) spectrophotometer and are reported in wave numbers (cm^{-1}). UV-visible and IR analysis were done at National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna state, Nigeria. Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) were determined using Jeol 400 MHz at Strathclyde University, Scotland. Chemical shifts are reported in (δ) scale. All reagents were purchased from Sigma-Aldrich and used without further purification.

3-Chloro-1-azaphenoxazine (7): 3-Chloro-1-azaphenoxazine (**7**) was prepared according to Gulbenk *et al.*[13]. 2-Aminophenol (**8**) (2.0 g, 20 mmol) was placed in a 250 mL three necked flask containing potassium hydroxide (1.0 g, 30 mmol) in water (50 mL). The mixture was warmed until the materials dissolved. 2,3,5-Trichloropyridine (**9**) (3.29 g, 16 mmol) in 1,4-dioxane (50 mL) was added in drops during a period of 15 min. The entire mixture was refluxed with stirring for 4 h. It was poured into a beaker diluted with water to the 500 mL mark and cooled. On filtering, the filtrate was chilled, filtered and the residue air dried and recrystallized from aqueous ethanol to give glistering creamy white plates of compound **7**, Yield: 6.81 g, (62 %); m.p.: 37-38 °C. UV-visible λ_{max} (ethanol): nm 262 (log ε 3.50), 375 (log ε 3.06), 392.5 (log ε 3.03). IR (KBr, ν_{max} cm^{-1}): 3381 (N-H stretch.), 3038 (aromatic C-H), 1544 (C=N stretch.), 1400 (C-H bending), 1031 (C-O-C), 734 (*m*-substituted aromatic ring). ^1H NMR (400 MHz, DMSO-d_6): δ 8.4 (s, 1H), 8.7 (m, 4H) ^{13}C NMR (400 MHz, DMSO-d_6): δ 146.56, 139.03, 130.7, 129.9, 128.09, 127.91, 127.05, 126.54, 125.32, 124.76, 124.02.

General procedure for synthesis of anilino derivatives (7a-e): The anilino derivatives were prepared according to the procedure developed by Buchwald *et al.*[14]. Triphenyl phosphine (0.008 g, 3.0 mmol) and palladium acetate (0.002 g, 1.0 mmol) were placed in a 100 mL three necked flask. Nitrogen gas was introduced for 30 s, water (1 mL) was added and the solution heated for 2 min at 80 °C. The catalyst pre-activation was monitored visually by colour change from yellow to black. Thereafter, compound **7** (0.219 g, 1.0 mmol), potassium carbonate (0.193 g, 1.4 mmol) and 3-substituted anilino derivatives (1.2 mmol) in 2 mL of DMF were added. After 20 min, 2 mL of DMF was added while the passage of nitrogen gas continued for another 30 s. The entire mixture was refluxed with stirring for 2 h at 110 °C under nitrogen atmosphere. The resulting crude product obtained was air dried and recrystallized from aqueous ethyl acetate.

3-Anilino-1-azaphenoxazine (7a): On stirring an activated solution of triphenyl phosphine, palladium acetate and compound **7**, potassium carbonate and aniline **(10a)** in DMF (2 mL) for 2 h at 110 °C, compound **7a** was obtained as a reddish-brown solid, Yield: 0.190 g, (57.6 %), m.p.: 121-122 °C; UV-visible λ_{max} (ethanol): nm 326 (log ε 2.19), 447.50 (log ε 2.33). IR (KBr, ν_{max} cm^{-1}): 3393 and 3305 (N-H stretch.), 1580 cm^{-1} (C=C stretch.), 1407 (C-H bending), 1026 (C-O-C), 695 (*m*-substituted aromatic ring). ^1H NMR (400 MHz, DMSO-d_6): δ 8.5 (s, 1H, NH), 7.6 (m, 4H, Ar-H), 7.5 (m, 5H, Ar-H), 6.5 (s, 1H, Ar-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 145, 132, 129, 127, 125.9, 125.4, 123.7, 123.1, 122, 121.8, 121.5, 121.02, 120.9, 120.2, 117.4, 117.3, 116. Analysis calculated (%) for $C_{17}H_{13}N_3O$: C, 74.18, H, 4.73, N, 15.27. Analysis found (%): C, 74.20, H, 4.58, N, 15.30.

3-(4-Nitroanilino)-1-azaphenoxazine (7b): On stirring an activated solution of triphenyl phosphine, palladium acetate and compound **7**, potassium carbonate and 4-nitroaniline **(10b)** in DMF (2 mL) for 2 h at 110 °C, compound **7b** was obtained as a greenish-black solid, Yield: 0.277 g, (72.1 %), m.p.: 110-111 °C. UV-visible λ_{max} (ethanol): nm 327 (log ε 2.60), 392 (log ε 2.09), 452 (log ε 2.16). IR (KBr, ν_{max} cm^{-1}): 3490-3340 (N-H stretch.), 3084 (Ar C-H), 1456 (C=C stretch.), 1306 (C-N stretch.), 1090 (C-O-C stretch.), 830-725 (*p*-disubstituted aromatic ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.95 (m, 4H, Ar-H), 7.6 (m, 4H, Ar-H), 6.7 (s, 1H, Ar-H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 156, 136, 132.6, 132.09, 132.02, 129.386, 129.272, 127, 124.9, 124.01, 123.54, 123.21, 122.09, 121.90, 120, 119, 113. Analysis calculated (%) for $C_{17}H_{12}N_4O_3$: C, 63.75, H, 3.75, N, 17.5. Analysis found (%): C, 63.54, H, 4.01, N, 17.30

3-(4-Chloroanilino)-1-azaphenoxazine (7c): On stirring an activated solution of triphenyl phosphine, palladium acetate, compound **7**, potassium carbonate and 4-chloroaniline **(10c)** in DMF (2 mL) for 2 h at 110 °C, compound **7c** was obtained as a brown solid, Yield: 0.219 g, (58.6 %), m.p.: 80-81 °C. UV-visible λ_{max} (ethanol): nm 273 (log ε 3.11), 289.5 (log ε 3.13), 328 (log ε 3.16), 454.50 (log ε 2.13). IR (KBr, ν_{max} cm^{-1}): 3432 and 3318 (N-H stretch.), 3123 (ArC-H), 1599 (C=C stretch.), 1383 (C-N stretch.), 1092 (C-O-C stretch.), 832-715 (*p*-disubstituted aromatic ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.7 (m, 4H, Ar-H) 7.0 (m, 4H, Ar-H), 5.3 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ 149.89, 147.62, 143.67, 138.90, 136.83, 132.97, 132.06, 131.45, 128.78, 128.67, 128.44, 128.15, 125.94, 122.24, 120.23, 118.69, 116.26. Analysis calculated (%) for $C_{17}H_{12}N_3OCl$: C, 65.91, H, 3.88, N, 13.57, Cl, 11.47. Analysis found (%): C, 66.01, H, 3.82, N, 13.54, Cl, 11.50.

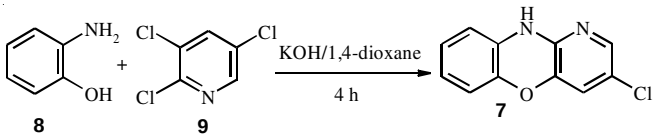
3-(4-Bromoanilino)-1-azaphenoxazine (7d): On stirring an activated solution of triphenyl phosphine, palladium acetate, compound **7**, potassium carbonate and 4-bromoaniline **(10d)** in DMF (2 mL) for 2 h at 110 °C, compound **7d** as a greenish-brown solid, Yield: 0.295 g, (69.4 %), m.p.: 96-97 °C. UV-visible λ_{max} (ethanol): nm 260.5 (log ε 4.33), 290 (log ε 4.17), 375.5 (log ε 3.62), 393.50 (log ε 3.59). IR (KBr, ν_{max} cm^{-1}): 3466 and 3313 (N-H stretch.), 3064 (Ar-H), 1637 (C=C stretch.), 1409 (C-H bending), 1097 (C-O-C stretch.), 825-701 (*p*-disubstituted aromatic ring). ^1H NMR (400 MHz, DMSO-d_6): δ 7.6 (m, 4H), 6.9 (m, 4H), 6.3 (s, 1H, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 149.82, 147.98, 143.66, 136.84, 132.94, 132.06, 131.93, 131.48, 131.38, 131.04, 128.81, 128.58, 128.44, 122.57, 120.31, 115.76, 106.04. Analysis calculated (%) for $C_{17}H_{12}N_3OBr$: C, 57.63, H, 3.39, N, 11.86, Br, 22.60. Analysis found (%): C, 57.60, H, 4.00, N, 11.75, Br, 22.50.

3-(4-Hydroxyanilino)-1-azaphenoxazine (7e): On stirring an activated solution of triphenyl phosphine, palladium acetate, compound **7**, potassium carbonate and 4-hydroxyaniline **(10e)** in DMF (2 mL) for 2 h at 110 °C, compound **7e** was obtained

as a dirty-green solid, Yield: 0.211 g, (60.4 %), m.p.: 113-114 °C. UV-visible λ_{max} (ethanol): 281 nm (log ε 3.31). IR (KBr, ν_{max} cm^{-1}): 3447 (N-H), 3338 (OH stretch.), 3048 (aromatic C-H), 1614 (C=C aromatic ring), 1410 (C-H bending), 1007 (C-O-C), 826-692 (*p*-disubstituted aromatic ring). ^{1}H NMR (400 MHz, DMSO): δ 7.6 (m, 4H), 7.2 (m, 4H, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 154, 132.102, 132.002, 129.109, 129.288, 128.43, 128.01, 126.76, 125.90, 125.31, 123.76, 123.06, 122.84, 122.04, 120. Analysis calculated (%) for $C_{17}H_{13}N_3O_2$: C, 70.10, H, 4.47, N, 14.43. Analysis found (%): C, 70.00, H, 4.50, N, 13.98.

RESULTS AND DISCUSSION

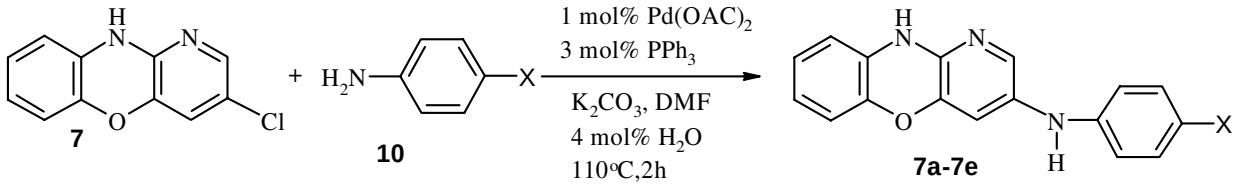
Palladium catalyzed synthesis of monoazaphenoxazine; 3-chloro-1-azaphenoxazine (**7**) and some of its functionalized anilino derivatives (**7a-e**) using 2-aminophenol (**8**), 2,3,5-trichloropyridine (**9**) and 4-substituted aniline (**10a-e**) as starting material is reported. As shown in **Scheme-I**, the reaction of 2-aminophenol (**8**) and 2,3,5-trichloropyridine (**9**) as reported by Gulbenk *et al.*[13] gave 3-chloro-1-azaphenoxazine (**7**). Accordingly, the anilino derivatives were synthesized by condensation of compound **7** with 4-substituted anilines as reported in **Scheme-II**.



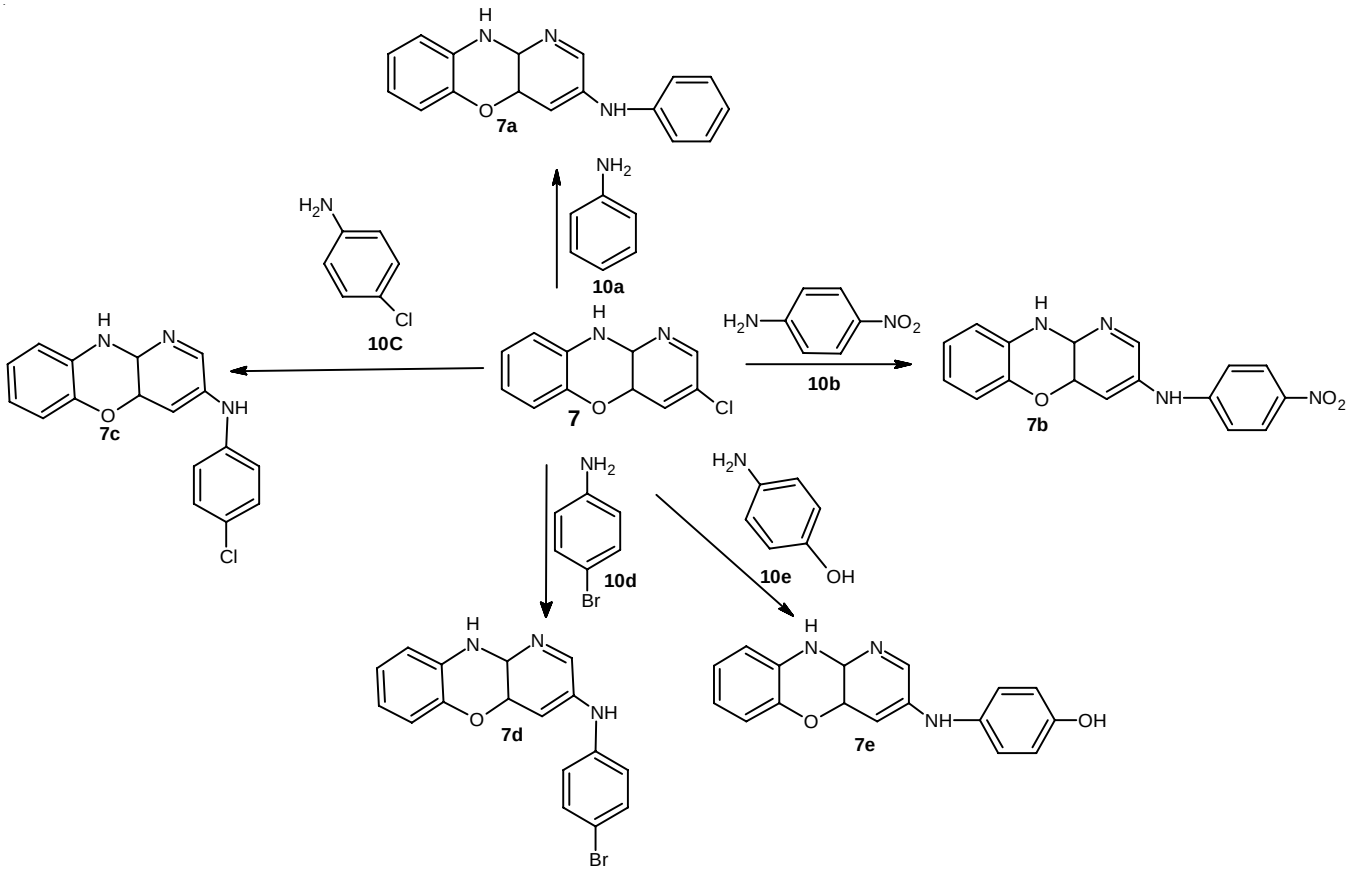
Scheme-I: Synthesis of 3-chloro-1-azaphenoxazine (**7**)

Conclusion

The synthesis of 3-chloro-1-azaphenoxazine (**7**) and its transformation to various 3-substituted anilino derivatives *via* Buchwald-Hartwig tandem amination protocol has been achieved successfully. The assigned structures were supported by spectral analysis.



X = **7a**: H, **7b**: NO_2, **7c**: Cl, **7d**: Br and **7e**: OH



Scheme-II: synthesis of anilino derivatives (**7a-e**)

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