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Synthesis of 1,9-Diazaphenoxazine Carboxamide Derivatives *via* Buchwald-Hartwig Amidation Protocol

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Tandem amidation catalyzed synthesis of linear diazaphenoxazine carboxamide derivatives **(18a-e)** is reported. This was achieved by the reaction of 2-amino-3-hydroxypyridine **(11)** and 2,3,5-trichloropyridine **(12)** in aqueous basic medium to afford 3-chloro-1,9-diazaphenoxazine **(13)** as white solid crystals. Compound **13** was then subjected to Buchwald-Hartwig amidation coupling reaction with various carboxamides **(17a-e)** in the presence of 1,4-*bis*(2-hydroxyl-3,5-di-*tert*-butyl benzyl)piperazine **(16)** as ligand, $Pd(OAc)_2$ as palladium source catalyst, K_2CO_3 as base and 50:50 DMF and toluene as solvent at 110 ºC for 2 h to afford the linear diazaphenoxazine carboxamide derivatives **(18a-e)** in good to excellent yield. The water mediated pre-activation of the catalyst was monitored visually using colour change from yellow to black. The compounds were characterized using UV-visible, FTIR, ^1H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Keywords: Amidation, Carboxamide, Diazaphenoxazine, Buchwald-Hartwig protocol.

INTRODUCTION

Phenoxazine **(1)** is the parent compound of a large number of useful organic dyes which have been extensively studied due to the wide range of application of these compounds as acid-base and redox indicators[1]. The parent ring phenoxazine was first synthesized by Okafor[2]. Following repeated reports on the pharmacological properties of phenoxazine, attention was diverted from their dyeing properties to a study of biological activities. From tests carried out with laboratory animals and man, it was found that many phenoxazine derivatives showed pronounced pharmacological properties as central nervous system depressants, sedatives, antiepileptic, herbicides, tranquilizers, antitumor, antibacterial spasmolytic, anthelminthic and parasiticidal agents[2-4]. Prinz *et al.*[5] reported *N*-benzoylated phenoxazines as inhibitors of tubulin polymerization which implies that the compounds are potential anticancer agent. Nowakowska-Oleksy *et al.*[6] reported phenoxazine-based conjugates of semiconducting and luminescent properties. Raju *et al.*[7] reported the facile synthesis of phenoxazines *via* ring opening of benzoxepines. Thome *et al.*[8] reported the transition-metal-free synthesis of *N*-substituted phenoxazines from *N*-acetylated aryloxy anilides. Reddy[9] reported an improved process for the synthesis of phenoxazine with anti-diabetic properties. Jose and Burgess[10] reported the synthesis of benzophenoxazine-based fluorescent dyes for labeling biomolecules. Hayashi *et al.*[11] reported phenoxazine derivatives that could suppress infections caused by herpes simplex virus type-1 and herpes simplex virus type-2. Shimamoto *et al.*[12] reported novel phenoxazine derivatives with *in vitro* and *in vivo* antitumor effect on human leukemia cell lines. Iwata *et al.*[13] reported phenoxazine derivatives of ability to suppress proliferation of poliovirus and porcine parvovirus. Idries and Abeed[14] synthesized 10*H*-substituted phenoxazine-3-yl-6-pyrimidin-2-phenylthiol/ol/amine/thiol pyrroles using 2-[4-hydroxybenz-1-(propene-1-one)] pyrrole. Frade *et al.*[15] reported benzo[a]phenoxazine heterocycles with antimicrobial activity. Persson[16] reported the synthesis of non-conjugate potential-stepping phenothiazine and phenoxazine based polymer hole-transport material for dye-sensitized solar cells. Kohli *et al.*[17] reported 5-(2-aryl-4-oxo-1,3-thiazolidine)-2-(phenoxazinylmethyl)-1,3,4-thiadiazole derivatives with antitubercular activity. Early improvement on the structure of phenoxazine involved changes in the side chain and the 10-alkylamino group. However, nowadays interest is being showed on the modifications on the phenoxazine ring itself through replacement of one benzo groups with furan, pyrrole, pyridine or pyrazine ring as the case may be. The modification could also involve expansion of the oxazine ring leading to oxazepines and oxazocines.

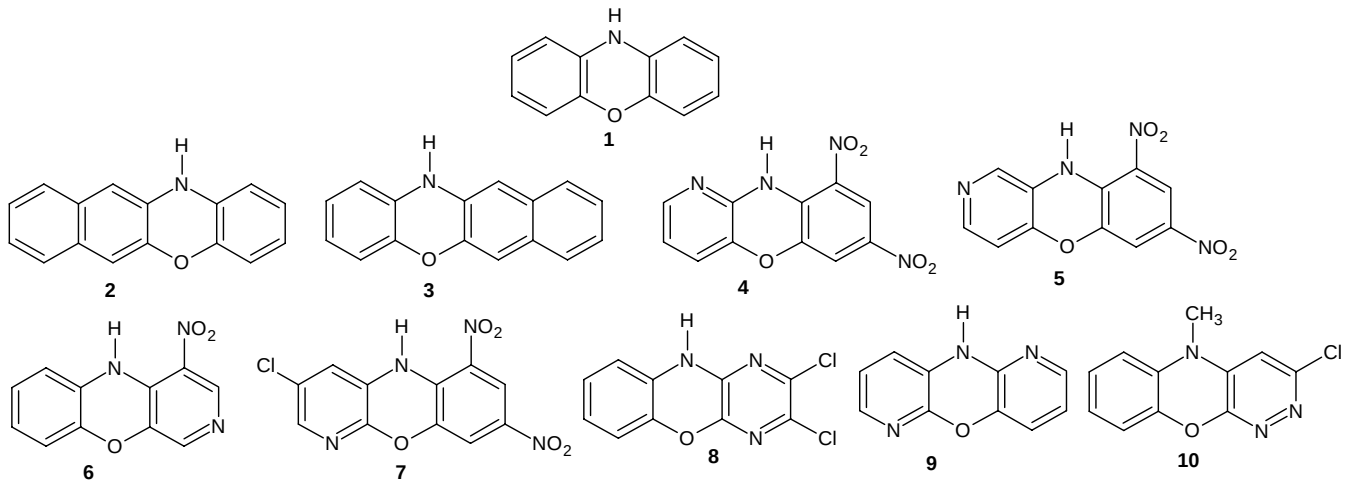
Compounds **2** and **3** are described as "linear phenoxazines" because of the linear arrangement of the ring system[18]. Consequently, polynuclear phenoxazines with a straight arrangement of the ring systems are generally referred to as linear phenoxazines. There structures which incorporates additional annular nitrogen atom(s) known as the aza analogues. Aza analogues which bear one nitrogen atom is called mono aza analogues as shown in structures **4, 5, 6** and **7** above. Compounds **4, 5, 6** and **7** are known as 1-azaphenoxazine, 2-azaphenoxazine, 3-azaphenoxazine and 4-azaphenoxazine, respectively, because of the position of the additional annular nitrogen atom[18]. Further, there are also sometimes where two nitrogen atoms are added in the ring. These are called diazaphenoxazines as shown in compounds **8, 9** and **10** above. Compounds **8, 9** and **10** are called 1,4-diazaphenoxazine, 1,9-diazaphenoxazine and 3,4-diazaphenoxazine respectively, because of the position of the added annular nitrogen (**Scheme-I**). The increasing report of pharmaceutical applications of phenoxazines coupled with the wide report of the biological activities of carboxamides and the need to seek for their synergistic pharmaceutical application informed this research. In the present study, we report the palladium catalyzed Buchwald-Hartwig amidation synthesis of linear diazaphenoxazine carboxamide derivatives.

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. Melting points were determined with a Fischer Johns melting point apparatus and are uncorrected. UV/visible spectra were recorded in ethanol on a Unicon UV-2500PC spectrophotometer using matched 1 cm quartz cells, absorptions were 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 spectral analysis were done at the National Research Institute for Chemical Technology (NARICT), Zaria, Kaduna State, Nigeria. Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were obtained using a Jeol 400 MHz spectrometer at Strathclyde University, Scotland. Chemical shifts are reported in (δ) scale. The elemental analysis was done on a Heraeus CHN-O rapid analyzer. All reagents used were of technical grade. 2-Amino-3-hydroxypyridine, 2,3,5-trichloropyridine, $Pd(OAc)_2$, piperazine, formaldehyde, 2,4-di-*tert*-butyl phenol were purchased from Sigma. Potassium hydroxide, acetamide, benzamide, 4-nitrobezamide, phthalamide, formamide, potassium carbonate, 1,4-dioxane, methanol and ethanol were purchased from Aldrich in sure-seal bottles and were used without further purifications.

3-Chloro-1,9-diazaphenoxazine (13): This compound was prepared using the procedure reported by Huang *et al.*[19]. Into a 250 mL two necked flask which was equipped with magnetic stirrer was added potassium hydroxide (3 g, 53.6 mmol) dissolved in distilled water (50 mL). 2-Amino-3-hydroxypyridine (**11**) (4 g, 36.4 mmol) was added to the flask and heated until it dissolved. Then 2,3,5-trichloropyridine (**12**) (3.2 g, 18.88 mmol) in 1,4- dioxane (50 mL) was added drop by drop for 15 min. The entire mixture was refluxed for 4 h at 80 ºC. It was poured into a beaker and allowed to cool. Then it was filtered and the residue air dried and recrystallized with aqueous ethanol as white solid crystals of 3-chloro-1,9-diazaphenoxazine (**13**) (4.4 g, 72 %) with a melting point of 48 ºC. UV-visible (ethanol) λ_{max}: 204 (log ε 3.01), 211.5 (log ε 3.02), 222.5 (log ε 3.05) nm. IR (KBr, ν_{max}, cm^{-1}): 3394 (N-H stret), 1650 (C=C), 1429 (C=N stretch), 1053 (C-O), 761 (substituted aromatic ring). ^1H NMR (400 MHz, DMSO): δ 8.6 (1H, s, NH), 8.4 (1H, s, ArH), 7.6 (3H, m, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 132.23, 130.01, 127.59, 127.01, 125.96, 125.20, 124.10, 120.45, 118.20, 115.90

1,4-*Bis*(2-hydroxyl-3,5-di-*tert*-butyl benzyl)piperazine (16): The ligand, 1,4-*bis*(2-hydroxyl-3,5-di-*tert*-butyl benzyl)piperazine (**16**) was prepared using the method of Mohanty *et al.*[20] with little modification. A mixture of piperazine (**14**) (2.2 g, 25.54 mmol) and 5.3 mL of 40 % aqueous formaldehyde solution (75.36 mmol) dissolved in methanol (40 mL) was heated to reflux for 2 h to obtain a clear solution. The clear solution was allowed to cool. Then 2,4-di-*tert*-butyl phenol (**15**) (10.3 g, 50.4 mmol) solution in methanol was added to the clear solution and refluxed for a further 12 h. The resulting product was cooled to room temperature and filtered to obtain 1,4-*bis*(2-hydroxyl-3,5-di-*tert*-butyl benzyl)piperazine (**16**) ligand as white crystalline solid which melts above 260 ºC (lit. above 250 ºC).



Scheme-I: Examples of phenoxazine derivatives

Synthesis of linear diazaphenoxazine carboxamides (18a-e): These compounds were prepared using the procedure developed by Anderson and co-workers[21]. 1,4-*Bis*(2-hydroxyl-3,5-di-*tert*-butyl benzyl)piperazine (**16**) (0.016 g, 0.003 mmol) and palladium acetate (0.002 g, 0.001 mmol) were placed in a 100 mL two necked flask. Nitrogen gas was introduced for 30 s, 2 mL of water was added and the mixture heated for 2 min at 80 ºC. The catalyst pre-activation was monitored visually using colour change from yellow to black. Then 3-chloro-1,9-diazaphenoxazine (**13**) (0.208 g, 1.0 mmol), potassium carbonate (0.193 g, 1.4 mmol) and substituted carboxamide derivatives (**17a-e**) (1.2 mmol) in DMF (2 mL) were mixed with toluene (2 mL) and evacuated with nitrogen gas for another 30 s. The entire mixture was heated under reflux with stirring for 2 h at 110 ºC in an oil bath under nitrogen atmosphere. The crude product obtained was cooled at room temperature, air dried and recrystallized from aqueous ethyl acetate.

3-Formamido-1,9-diazaphenoxazine (18a): 3-Formamido-1,9-diazaphenoxazine (**18a**) was obtained as an ash solid, yield 0.168 g (78.7 %), mp 200 ºC. UV-visible (ethanol) λ_{max}: 280.5 nm (log ε 2.36). IR (KBr, ν_{max}, cm^{-1}): 3855 and 3741(2 N-H stret), 1685 (C=O stret), 1534 (C=N stret); ^{1}HNMR (DMSO): δ 8.12 (1H, s, Ar-H), 7.2 (3H, m, Ar-H), 5.2 (1H, s, b, NH), 3.5 (1H, s, C-H). ^{13}C NMR (DMSO): δ 170.10, 147.20, 142.60, 138.50, 136.39, 130.68, 127.68, 127.10, 125.90, 124.76, 123.29. Analysis of $C_{11}H_8N_4O_2$ (% calcd./found): C: 57.89/58.01, H: 3.53/3.48, N: 24.55/24.50.

3-Phthalamido-1,9-diazaphenoxazine (18b): 3-Phthalamido-1,9-diazaphenoxazine (**18b**) was obtained as an ash solid, yield 0.209 g, (54.6 %), mp 247 ºC. UV-visible (ethanol) λ_{max}: 282.5 nm (log ε 2.91). IR (KBr, ν_{max}, cm^{-1}): 3393 and 3297 (2 N- H stret), 3137 (ArC- H), 1690 (C=O), 1449 (C=N stret), 1008 (C-O stret), 845-722 (substituted aromatic ring). ^{1}H NMR (400 MHz, DMSO): δ 5.25 (1H, s, 1H, NH), 7.0–6.6 (2H, m, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 170.01, 169.90, 150.45, 149.60, 146.01, 145.67, 145.10, 146.01, 145.98, 145.24, 140.21, 130.00, 128.09, 126.10, 125.05, 124.90, 124.10 and 119.10. Analysis of $C_{18}H_{10}N_4O_3$ (% calcd./found): C: 65.45/65.35, H: 3.05/3.10, N: 16.96/17.01.

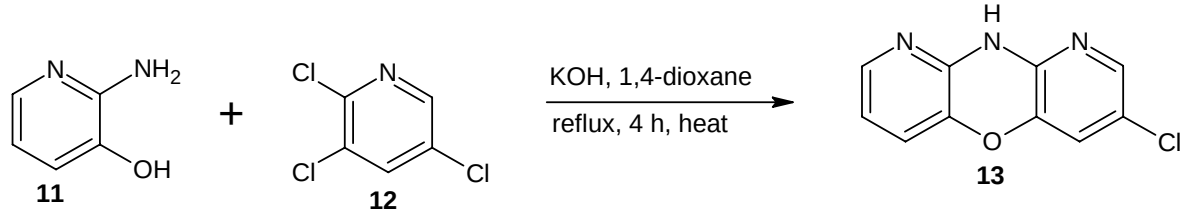
3-(4-Nitrobenzamido)-1,9-diazaphenoxazine (18c): 3-(4-Nitrobenzamido)-1,9-diazaphenoxazine (**18c**) was obtained as an ash solid, yield 0.357 g, (87.8 %), mp 310 ºC. UV-visible (ethanol) λ_{max}: 280.5 nm (log ε 2.91). IR (KBr, ν_{max}, cm^{-1}): 3741and 3855 (2 N-H stret), 1664 (C=O), 1535 (C=N stret). ^{1}H NMR (400 MHz, DMSO): δ 8.6 (1H, s, NH), 8.4 (1H, s, Ar-H), 7.64 (4H, m, Ar-H), 7.46 (3H, m, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 168.23, 164.40, 150.05, 143.90, 143.45, 142.76, 142.03, 138.69, 138.10, 136.49, 135.89, 135.12, 134.32, 130.24, 126.45, 122.23 and 119.94. Analysis of $C_{17}H_{11}N_5O_4$ (% calcd./found): C: 58.45/58.50, H: 3.17/3.15, N: 20.05/20.01.

3-Benzamido-1,9-diazaphenoxazine (18d): 3-Benzamido-1,9-diazaphenoxazine (**18d**) was obtained as a reddish-brown solid, yield 0.242 g, (68.5 %), mp 129 ºC. UV-visible (ethanol) λ_{max}: 307.50 nm (log ε 2.32). IR (KBr, ν_{max}, cm^{-1}): 3740 and 3365 (2 N-H stret), 3178 (ArC-H), 1646 (C=O), 1400 (C=N stret), 1021 (C-O stret), 785 and 665 (substituted aromatic ring). ^{1}H NMR (400 MHz, DMSO): δ 8.5 (5H, m, Ar-H), 8.0 (1H, s, b, NH), 7.3 (3H, m, Ar-H), 7.1 (1H, s, Ar-H). ^{13}C NMR (400 MHz, DMSO): δ 160.01, 146.64, 146.07, 142.34, 140.92, 135.76, 132.44, 128.09, 126.99, 126.23, 125.87, 125.03, 122.93, 122.13, 121.90, 120.58, 119.89. Analysis of $C_{17}H_{12}N_4O_2$ (% calcd./found): C: 67.10/67.11, H: 3.97/4.01, N: 18.41/18.35.

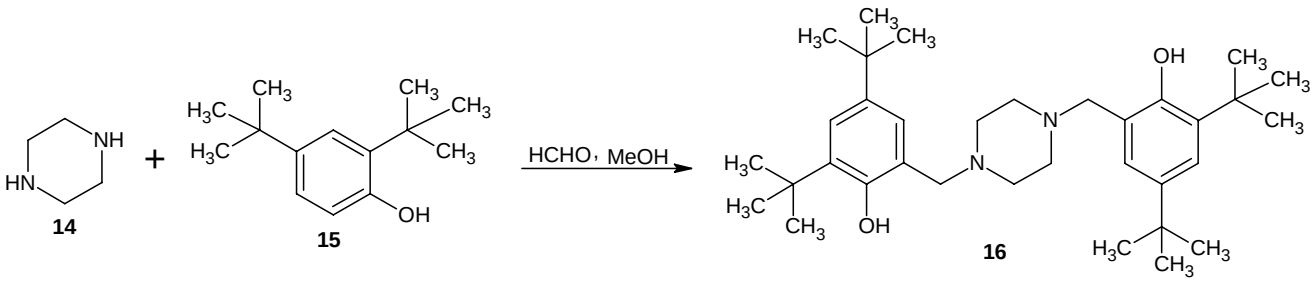
3-Acetamido-1,9-diazaphenoxazine (18e): 3-Acetamido-1,9-diazaphenoxazine (**18e**) was obtained as a yellow solid, yield 0.222 g, (79.6 %), mp 310 ºC. UV-visible (ethanol) λ_{max}: 218 (log ε 3.04), 225 (log ε 3.05), 232.5 (log ε 3.06), 283.5 (log ε 2.78) nm. IR (KBr, ν_{max}, cm^{-1}): 3736 and 3394 (2 N-H stret), 1655 (C=O stret), 1452 (C=N stret), 1058 (C-O stret), 773 (substituted aromatic ring). ^{1}H NMR (400 MHz, DMSO): δ 8.2 (3H, m, Ar-H), 8.0 (1H, s, b, NH), 7.6 (1H, s, Ar-H), 2.5 (3H, s, CH_3). ^{13}C NMR (400 MHz, DMSO): δ 159.76, 145.23, 142.98, 136.45, 135.99, 135.10, 130.24, 128.81, 126.91, 123.12, 120.35, 50.23. Analysis of $C_{12}H_{10}N_4O_2$ (% calcd./found): C: 59.50/59.60, H: 4.16/4.10, N: 23.13/23.10.

RESULTS AND DISCUSSION

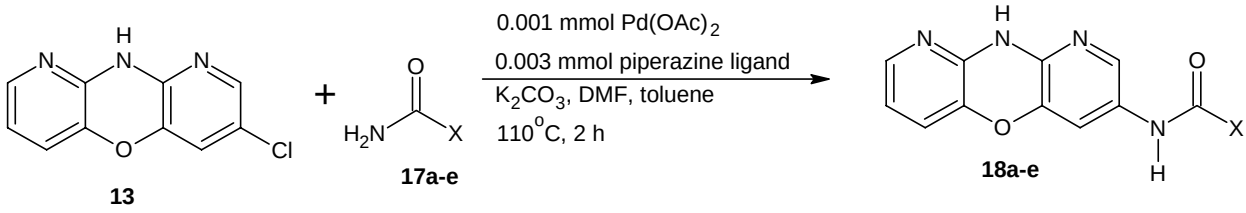
The synthesis of 3-chloro-1,9-diazaphenoxazine (**13**) was achieved by the reaction of 2-amino-3-hydroxypyridine (**11**) with 2,3,5-trichloropyridine (**12**) in 1,4-dioxane in aqueous medium at 80 ºC for 4 h (**Scheme-II**). The ligand 1,4-*bis*(2-hydroxyl-3,5-di-*tert*-butylbenzyl)piperazine (**16**) was prepared by the reaction of piperazine (**14**) and aqueous formaldehyde solution in methanol under reflux for 2 h. The clear solution obtained was then refluxed with 2,4-di-*tert*-butylphenol (**15**) solution in methanol for 12 h to obtain the ligand as a white crystalline solid according to literature (**Scheme-III**)[20]. The water mediated catalyst pre-activation was monitored visually using colour change from yellow to black. The linear diazaphenoxazine carboxamide derivatives (**18a-e**) were synthesized by the reaction of 3-chloro-1,9-diazaphenoxazine (**13**) and substituted carboxamides (**17a-e**) in the presence of activated 1,4-*bis*(2-hydroxyl-3,5-di-*tert*-butylbenzyl) piperazine (**16**), palladium acetate and potassium carbonate under nitrogen in an oil bath at 110 ºC for 2 h using 50:50 DMF and toluene as solvent to obtain the carboxamide derivatives (**Scheme-IV**). The linear diazaphenoxazine carboxamides were obtained in excellent yield (Table-1).



Scheme-II: Synthesis of 3-chloro-1,9-diazaphenoxazine

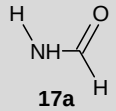
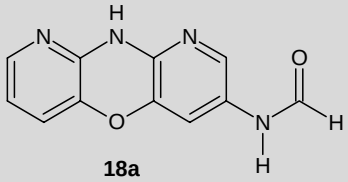
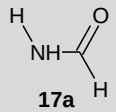
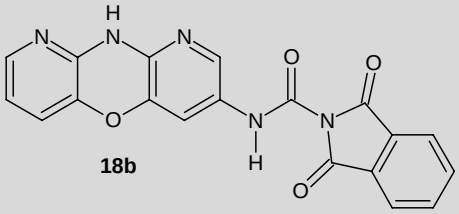
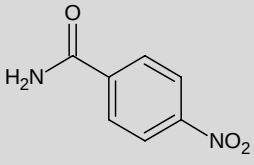
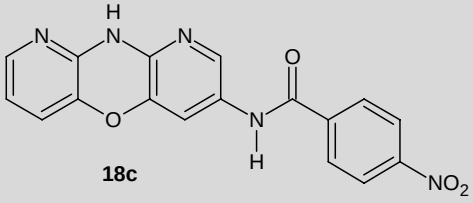
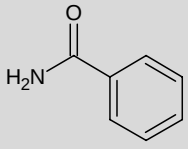
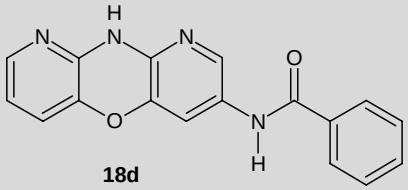
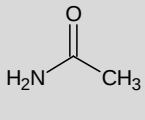
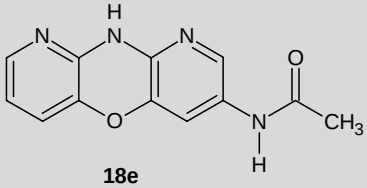


Scheme-III: Synthesis of 1,4-*bis*(2-hydroxy-3,5-di-*tert*-butyl benzyl)piperazine



Scheme-IV: Synthesis of 3-carboxamido-1,9-diazaphenoxazine derivatives

TABLE-1
3-CARBOXAMIDO-1,9-DIAZAPHENOXAZINE DERIVATIVES

Entry	Amide	Linear diazaphenoxazine carboxamide	Colour	Yield (%)
1	 17a	 18a	Ash solid	78.7
2	 17a	 18b	Ash solid	54.6
3	 18c	 18c	Ash solid	87.8
4	 18d	 18d	Reddish-brown	68.5
5	 17e	 18e	Yellow	79.6

In the FTIR spectra, all the compounds gave characteristic vibrational peak at around 1690-1646 cm^{-1} corresponding to the carbonyl stretching bands. The C=N groups was observed around 1535-1400 cm^{-1}, the NH groups was observed around 3736-3297 cm^{-1}, interestingly, all compounds showed two bands within this band indicating the two fundamental bands

for NH. The vibration peaks at around 3178-3137 cm^{-1} corresponding to the aromatic CH stretching bands.

In the ^1H NMR spectra, the aliphatic protons of 3-formamido-1,9-diazaphenoxazine and 3-acetamido-1,9-diazaphenoxazine appeared at δ 3.5 and 2.5 respectively. Other aromatic protons appeared in the expected regions. The ^{13}C NMR of the derivatives in addition to other aromatic peaks expected showed the carbonyl peak around δ 170.10-159.76. Expectedly, the phthalamido derivative **18b** showed two peaks at δ 170.01 and 169.90 corresponding to the two carbonyl groups. The carbons appeared as expected in all the derivatives.

The elemental analysis of the compounds gave a correlated percentage of each element present in the compounds. The UV of all the compounds showed absorption in visible region which corresponds to the increased conjugation in the linear diazaphenoxazine carboxamide derivatives.

Conclusion

The synthesis of 3-carboxamido-1,9-diazaphenoxazine derivatives (**18a-e**) were achieved in two stages. The first stage is the condensation of 2-amino-3-hydroxypyridine **(11)** and 2,3,5-trichloropyridine **(12)** in basic medium to afford 3-chloro-1,9-diazaphenoxazine (**13**). Then the second stage involved Buchwald-Hartwig tandem amidation reaction of compound **13** with substituted carboxamides **(17a-e)** to furnish the carboxamido derivatives of 1,9-diazaphenoxazine (**18a-e**). The structures assigned to the compounds were supported by spectral analysis using UV-visible, FTIR, ^1H NMR and ^{13}C NMR spectroscopy and elemental analysis.

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