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Synthesis of New Derivatives of 1-Azaphenothiazine *via* Buchwald-Hartwig Amination Methodology

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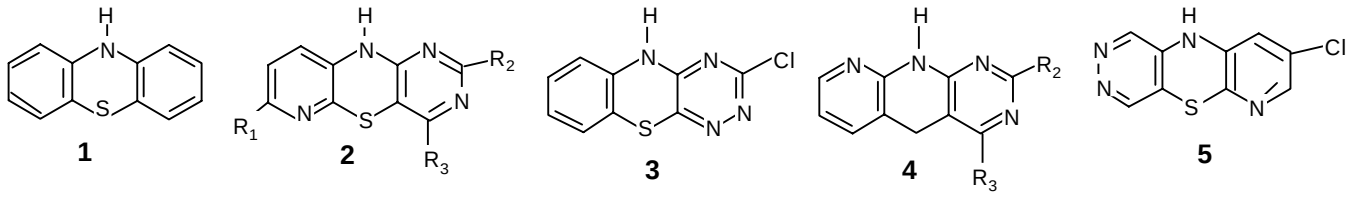
Synthesis of new derivatives of 1-azaphenothiazine (**10a-d**) *via* tandem amination methodology is reported. This was achieved by the reaction of 2-aminothiophenol (**6**) with 2,3,5-trichloropyridine (**7**) in aqueous basic medium to yield 3-chloro-1-azaphenothiazine (**8**) as a greenish yellow solid. Compound **8** was then subjected to palladium catalyzed Buchwald-Hartwig coupling reaction with substituted amines (**9a-d**), by refluxing using palladium acetate [$Pd(OAc)_2$] as palladium source catalyst, potassium carbonate as base, 1,4-*bis*(2-hydroxy-3,5-di*tert*-butylbenzyl)piperazine as ligand and *tert*-butanol (*t*-BuOH) as solvent at 110 °C to yield 3-anilino-1-azaphenothiazine derivatives (**10a-d**) in good to excellent yield. The compounds were characterised using UV, FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

Keywords: 1-Azaphenothiazine, Buchwald-Hartwig, Amination reaction, 2,3,5-Trichloropyridine, Cross coupling.

INTRODUCTION

Phenothiazine (**1**) also called dibenzothiazine or thiodiphenylamine is a yellow crystalline compound soluble in hot acetic acid, benzene and ether. It is a three ring structure compound in which two benzene rings are joined by sulphur and nitrogen atom at nonadjacent positions. It is obtained by fusing diphenylamine with sulphur[1]. Phenothiazine belongs to an important class of heterocyclic compounds known for their pharmaceutical properties. It is the active component in sedatives, tranquilizer, antituberculotics or bactericides[2]. The basic nitrogen of the ring which donates electrons to the biological receptors by a charge transfer mechanism accounts for the pharmacological activities of phenothiazines there by motivating interest in the synthesis of aza-analogues of phenothiazine[3]. Some of the useful compounds in these series of azaphenothiazines have been obtained by structural modification over the years[4,5]. Phenothiazines and its derivatives have a wide range of application as dyes, industrial oxidants, redox indicator, pesticides, thermal stabilizers, drugs[6-10]. However, recent reports reveal that the Buchwald-Hartwig amination is a chemical reaction used in the synthesis of carbon-nitrogen bonds *via* the palladium-catalyzed cross coupling of amines with aryl halides[11-15]. Also, Buchwald and co-workers developed an efficient protocol for C-N cross-coupling through water-mediated catalyst preactivation which has greatly enhanced the synthesis of azaphenothiazine derivatives[16-20].

All the earlier reports on the aza analogs of phenothiazine were concerned with the chemistry and biological properties of only the monoaza and diazaphenothiazines[21]. Okafor[21] reported the synthesis of the first set of triazaphenothiazine systems, compounds in these series and successfully achieved the preparation of 1,3,6-triazaphenothiazine (**2**) derivatives thereby opening the new chapter on linear phenothiazine chemistry. In addition to the reports on 1,3,6-triazaphenothiazines. Venkataraman[22] also reported the synthesis of another triazaphenothiazine ring system **3**. The third isomeric triazaphenothiazine, 1,3,9-triazaphenothiazine derivatives **4** was reported by Okafor[23] *via* the acid catalyzed condensation of



3-mercapto-2-aminopyridine with 4,5-dihalogenopyrimidine. In tests with mice and rats, these derivatives of 1,3,9-triazaphenothiazine showed CNS depressant activities in doses of 1-4 mg/kg. Wise and Castle[24] reported the replacement of the benzene ring in phenothiazine with pyridazine leading to tetrazaphenothiazines (**5**).

Karpinska *et al*[25] reported the use of phenothiazine as redox indicators in chromatometric determination of $K_4[Fe(CN)_6]$. It has been shown that phenothiazines indictors are superior to conventional indicators (*e.g.*, ferroin, variamin blue). They give sharper end point and act over a wide range of acidity than other conventional indicators.

EXPERIMENTAL

Melting points of the compounds synthesized were determined using electro-thermal melting point apparatus in open capillaries and are uncorrected. Ultraviolet-visible spectra were recorded on a UNICO-UV2102 PC spectrophotometer using matched 1 cm quartz cells. The solvent was ethanol and absorption maxima are given in nanometers (nm); the figures in parenthesis are the log E values. Infrared spectra data was obtained on a Magna FTIR system 750 spectrophotometer (NARICT, Zaria, Kaduna State) using KBr discs and absorptions were given in per-centimeter (cm^{-1}). Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) were determined using varian NMR mercury 200BB spectrophotometer (Obafemi Awolowo University, Ile Ife). Chemical shifts are reported in δ scale (neat). Elemental analysis was carried out to determine the percentage abundance of the elements present. All reagents were purchased from Sigma-Aldrich and used without further purification.

3-Chloro-1-azaphenothiazine (intermediate) (8): 2-Aminothiophenol (2 g, 18 mmol) was placed in the reaction flask containing potassium hydroxide (1.79 g, 44 mmol) in water (50 mL). The mixture was warmed until the material dissolved at about 85 °C. 2,3,5-Trichloro-pyridine (2.97 g, 20 mmol) in DMF (50 mL) was added in drop by drop during a period of 15 min. The entire mixture was refluxed with stirring for 4 h. It was later poured into a beaker, diluted with water to the 500 mL mark and cooled, filtered and the residue recrystallized from ethanol, greenish yellow crystals of 3-chloro-1-azaphenothiazine (**8**) was obtained after suction filtration. Yield: 3.81 g, (99.7 %), m.p. 161-161.5 °C. IR (KBr, ν_{max}, cm^{-1}): 3438 (N-H), 3049 (Ar-H), 1615, 1483, 1417 (C=C of aromatic ring), 1356 (aromatic 3° C-N), 1305 (aromatic 2° C-N), 1093 (C-S-C) 756 (Ar-Cl). UV-visible (ethanol) (log ε): 309.2 nm (2.490), 291 nm (2.464), 360 nm (2.556). ^1H NMR ($CDCl_3$): δ = 8.2 (s, 1H), 7.8 (m, 4H), 7.4 (m, 2H), 6.8 (m, 2H), 4.2 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 147.4, 146.9, 146.4, 135.8, 130.0, 128.6, 126.7, 126.1, 119.1, 118.8, 115.4 Analysis calculated for $C_{11}H_7N_2SCl$: C, 56.30, H, 3.00, N, 11.90, Cl, 15.14, S,13.65. Analysis found: C, 56.40, H, 3.01, N, 11.78, Cl, 15.20, S, 13.61.

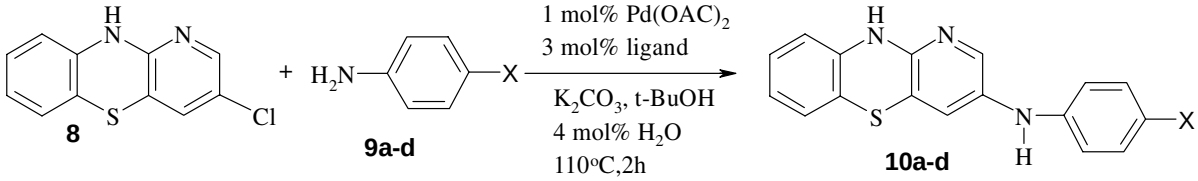
Procedure for Pd-catalyzed coupling of compound 8: Preactivation of palladium acetate catalyst was done by heating $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), water (2 mL), 1,4-*bis*(2-hydroxy-3,5-di*tert*-butybenzyl)piperazine (1.60 g, 0.03 mmol) and *t*-BuOH (2 mL) in a 100 mL three necked flask for 2 min at 80 °C. The activation was monitored visually by colour change until a black catalyst solution was observed. Then the activated catalyst solution was transferred into a 250 mL three necked round bottomed flask containing 3-chloro-1-azaphenothiazine (**8**) (2.34 g, 1 mmol), K_2CO_3 (0.19 g, 1.4 mmol) and substituted aniline **9a-d** (1.2 mmol), equipped with a magnetic stirrer and quick fit thermometer. The solution was heated to 110 °C for 1 min and refluxed for 2 h. A solid product was obtained which on recrystallization with ethyl acetate gave 3-anilino-1-azaphenothiazine derivatives (**10a-d**).

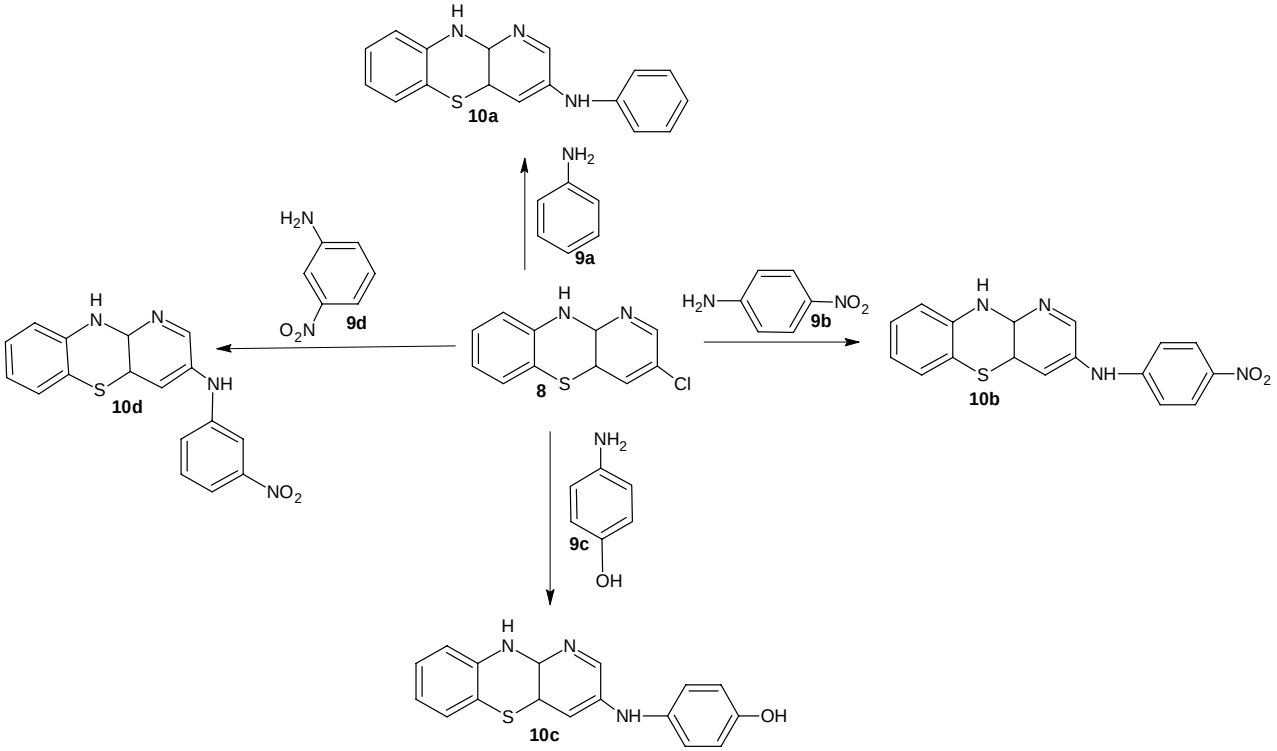
3-Anilino-1-azaphenothiazine (10a): On stirring an activated solution of piperazine, palladium acetate, compound **8**, potassium carbonate and aniline (**10a**) in *t*-BuOH (2 mL) for 2 h at 110 °C, compound **10a** was obtained as a dark tan solid, Yield: 0.26 g (95 %), IR (KBr, ν_{max}, cm^{-1}): 3437, 3305 (2 NH) 3060, 2843 (Ar-H), 1608, 1467 (C=C aromatic), 1368 (aromatic 3° C-N), 1307 (aromatic 2° C-N) 1135, 1034 (C-S-C) 808 (substitution in benzene ring). UV-visible (ethanol) (log ε): 237 nm (2.375), 261.8 nm (2.418), 307 nm (2.487), 409.8 nm (2.613) ^1H NMR ($CDCl_3$): δ = 8.4 (m, 5H), 7.9 (s, 1H), 7.5 (m, 4H), 6.8 (m, 2H), 4.4 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 147.4, 146.7, 141.9, 137.5, 136.0, 134.1, 130.0, 129.3, 126.1, 119.1, 118.8, 118.5, 115.1, 112.7. Analysis calculated for $C_{17}H_{13}N_3S$: C,70.10, H, 4.47, N, 14.43, S, 11.00. Analysis found: C, 69.89, H, 4.50, N, 14.48, S, 11.13.

3-(4-Nitroanilino)-1-azaphenothiazine (10b): On stirring an activated solution of piperazine ligand, palladium acetate, compound **8**, potassium carbonate and aniline (**10b**) in *t*-BuOH (2 mL) for 2 h at 110 °C, compound **10b** was obtained as a grey solid Yield 2.59 g (96 %), m.p. 97-98 °C. IR (KBr, ν_{max}, cm^{-1}): 3428, 3318 (2N-H), 3074, 2942 (Ar-H), 1613, 1506, 1417 (C=C aromatic) 1337 (Ar-NO_2), 1307 (aromatic 2° C-N), 1126, 1080, 1042 (C-N-C), 837 (substitution in benzene ring). UV-visible (ethanol) (log ε): 210.4 nm (2.323), 246 nm (2.391), 310 nm (2.491), 370.4 nm (2.569), 497.8 nm (2.70). ^1H NMR ($CDCl_3$): δ = 8.1 (m, 4H), 7.3 (m, 4H), 6.7 (m, 2H), 4.1 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 152.8, 147.4, 141.9, 138.4, 137.5, 136.0, 134.1, 130.0, 126.1, 124.4, 119.1, 118.8, 116.0, 115.4, 112.7. Analysis calculated for $C_{17}H_{12}N_4O_2S$: C, 60.71, H, 3.57, N, 16.67, S, 9.52. Analysis found: C, 60.80, H, 3.61, N, 16.60, S, 9.49.

3-(4-Hydroxyanilino)-1-azaphenothiazine (10c): On stirring an activated solution of piperazine, palladium acetate, compound **8**, potassium carbonate and aniline (**10c**) in *t*-BuOH (2 mL) for 2 h at 110 °C, compound **10c** was obtained as a resin. Yield: 0.26 g (95 %), m.p. 117-118 °C. IR (KBr, ν_{max}, cm^{-1}): 3432 (N-H), 3305 (O-H), 3070, 2930 (Ar-H), 1615, 1469 (C=C aromatic), 1357 (aromatic 3° C-N), 1301 (aromatic 2° C-N), 1210, 1090 (C-S) 959 (benzene substitution). UV-visible (ethanol), (log ε): 237.4 nm (2.375), 307.4 nm (2.488), 378 nm (2.577), 496.2 nm (2.692). ^1H NMR ($CDCl_3$): δ = 8.3 (m, 4H), 7.9 (s, 1H), 7.4 (m, 4H), 6.8 (m, 2H), 5.0 (s, 1H), 4.2 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 147.4, 147.3, 141.9, 139.3, 137.5, 136.0, 134.1, 130.0, 126.1, 119.1, 118.8, 116.5, 115.4, 112.7. Analysis calculated for $C_{17}H_{12}N_3SO$: C, 66.67, H, 3.92, N, 13.73, S,10.46. Analysis found: C, 66.70, H, 3.80, N, 13.81, S, 10.50.

3-(3-Nitroanilino)-1-azaphenothiazine (10d): On stirring an activated solution of piperazine ligand, palladium acetate





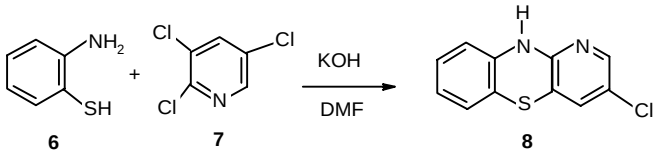
Scheme-II: Synthesis of anilino derivatives (**10a-d**)

and compound **8**, potassium carbonate and aniline (**10d**) in *t*-BuOH (2 mL) for 2 h at 110 °C, compound **10d** was obtained as a grey solid. Yield: 2.75 g, (95 %), m.p. 88-89 °C. IR (KBr, ν_{max}, cm^{-1}): 3476, 3357 (2N-H), 3054 (Ar-H), 1612, 1456, 1424 (C=C aromatic), 1340 (aromatic 3° C-N), 1307 (aromatic 2° C-N), 1164, 1103, 1043 (C-N-C), 951 (substitution in benzene). UV-visible (ethanol), (log ε): 212 nm (2.326), 248.2 nm (2.395), 307 nm (2.487), 360 nm (2.556). ^{1}H NMR ($CDCl_3$): δ = 8.2 (s, 1H), 7.4 (m, 4H), 6.8 (m, 2H), 4.0 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 149.2, 147.6, 147.1, 141.9, 137.5, 136.0, 134.1, 130.2, 130.0, 126.1, 119.1, 118.8, 115.4, 113.6, 112.7, 110.2. Analysis calculated for $C_{17}H_{12}N_4O_2S$: C, 60.71, H, 3.57, N, 16.67, S, 9.52. Analysis found: C, 60.79, H, 3.49, N, 16.64, S, 9.48.

RESULTS AND DISCUSSION

The palladium catalyzed synthesis of 1-azaphenothiazine; 3-chloro-1-azaphenothiazine **8** and some of its functionalized anilino derivatives (**10a-d**) using 2-aminothiophenol (**6**), 2,3,5-trichloropyridine **7** and substituted aniline (**9a-d**) as starting material is reported.

As shown in **Scheme-I**, the reaction of 2-aminothiophenol **6** and 2,3,5-trichloropyridine **7** gave 3-chloro-1-azaphenothiazine **8**. Accordingly, the anilino derivatives were synthesized by condensation of compound **8** with 4-substituted anilines (**9a-d**) as reported in **Scheme-II**.



Scheme-I: Synthesis of 3-chloro-1-azaphenothiazine (**8**)

Conclusion

The synthesis of 3-chloro-1-azaphenothiazine (**8**) and its transformation to the various substituted anilino derivatives (**10a-d**) *via* Buchwald-Hartwig tandem amination protocol has been achieved successfully. The assigned structures were supported by spectral and elemental analysis.

REFERENCES

1. S.P. Massie, *Chem. Rev*., **54**, 797 (1954).
2. N.L. Smith, *J. Org. Chem*., **16**, 415 (1951).
3. U.C. Okoro, *Indian J. Chem*., **29B**, 117 (1990).
4. C.O. Okafor, *Int. J. Sulphur Chem*., **6**, 237 (1971).
5. C.O. Okafor, *J. Heterocycl. Chem*., **18**, 405 (1981).
6. A.N. Gritsenko, Z.I. Ermakova, T.Y. Mozhaeva, V.S. Troitskay and S.V. Zhuravlev, *Chem. Abstr*., **83**, 9942 (1975).
7. V.A. Petrow and E.L. Rewald, *J. Chem. Soc*., **40**, 591 (1945).
8. C.O. Okafor, I.O. Uche and L.E.S. Akpanisi, *J. Heterocycl. Chem*., **18**, 1589 (1981).
9. C.O. Okafor, M.L. Steenberg and J.P. Buckley, *Eur. J. Med. Chem*., **3**, 249 (1976).
10. C.O. Okafor, *J. Org. Chem*., **40**, 2753 (1975).
11. D.S. Surry and S.L. Buchwald, *Chem. Sci*., **2**, 27 (2010).
12. J.F. Hartwig, *Angew. Chem. Int. Ed*., **37**, 2046 (1998).
13. J.P. Wolfe, S. Wagaw, J.F. Marcoux and S.L. Buchwald, *Acc. Chem. Res*., **31**, 805 (1998).
14. B. Schlummer and U. Scholz, *Adv. Synth. Catal*., **346**, 1599 (2004).
15. L. Jiang and S.L. Buchwald, in eds.: A. de Meijere and F. Diederich, Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH: Weinheim, Germany, p. 23 (1998).
16. B.P. Fors, P. Krattiger, E. Strieter and S.L. Buchwald, *Org. Lett*., **10**, 3505 (2008).
17. B.P. Fors and S.L. Buchwald, *J. Am. Chem. Soc*., **132**, 15914 (2010).
18. B.P. Fors, D.A. Watson, M.R. Biscoe and S.L. Buchwald, *J. Am. Chem. Soc*., **130**, 13552 (2008).
19. D. Zim and S.L. Buchwald, *Org. Lett*., **5**, 2413 (2003).
20. G.D. Vo and J.F. Hartwig, *J. Am. Chem. Soc*., **131**, 11049 (2009).
21. C.O. Okafor, *J. Org. Chem*., **38**, 4386 (1973).
22. K. Venkataraman, *Chem. Synth. Dyes*, **11**,791 (1952).
23. C.O. Okafor, *J. Org. Chem*., **40**, 2753 (1975).
24. D.S. Wise Jr. and R.N. Castle, *J. Heterocycl. Chem*., **11**, 1001 (1974).
25. J. Karpinska, B. Starczewska and H. Puzanowska-Tarasiewicz, *Anal. Sci*., **12**, 161 (1996).