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PALLADIUM CATALYZED SYNTHESIS AND FUNCTIONAL GROU MODIFICATION OF 6-ARYL DERIVATIVES OF NON-LINE AZAPHENOTHIAZINONES

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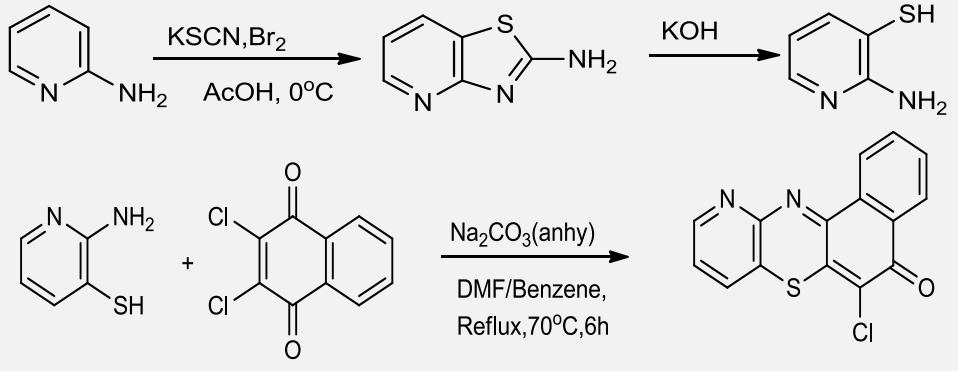
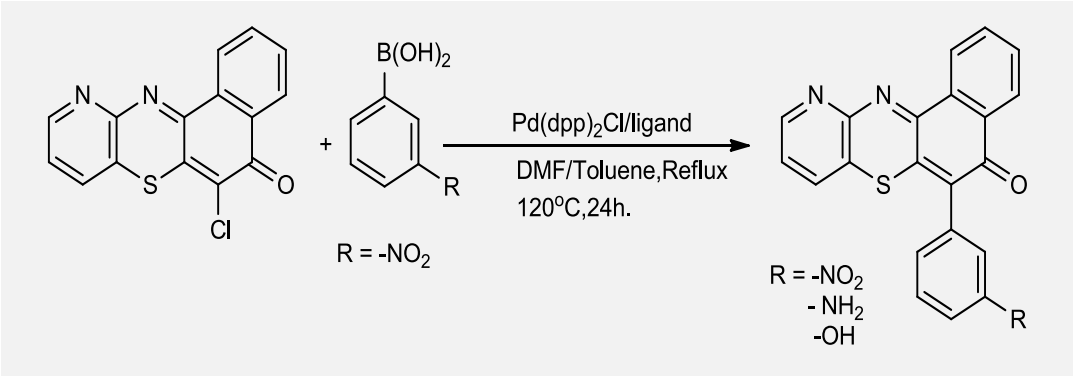
ABSTRACT

This report presents the synthesis of four derivatives of 6-chloro-11-azabenzo[a]phenothiazine-5 one, of the type 15,16,17 and 18 .The starting material, 2-aminopyridine 8 was subjected to thiocynation and subsequently, to hydrolysis to furnish one of the key intermediates, 2 aminopyridine-3-thiol 10 .This was condensed with 2,3-dichloro-1,4-naphthoquinone 11 to yield 6 chloro-11-azabenzo[a]phenothiazinone 5. In the presence of a complex palladium catalyst system, compound 5 was coupled with arylphenylboronic acids, 6 and 7 to give 6-phenyl-11 azabenzo[a]phenothiazine-5-one 15 and 6-(3-nitrophenyl)-11-azabenzo[a]phenothiazine-5-one, 16 respectively. Reduction of the nitro-group in 16, furnished 6-(3-aminophenyl)-11 azabenzo[a]phenothiazine-5-one 17, while the oxidation of the amino-group in compound 17, produced 6-(3-hydroxyphenyl)-11-azabenzo[a]phenothiazine-5-one 18. Treatment of the above compounds 15, 16 ,17 and 18 respectively, with sodium dithionite gave color discharged unstable basis of the types 19, 20, 21 and 22 which could not be isolated, but reverted to the original compounds 15, 16,17 and 18 above immediately they were exposed to air. This property suggests that they can be used as vat dyes. The graphical representation of the schemes is shown below;



† Corresponding author



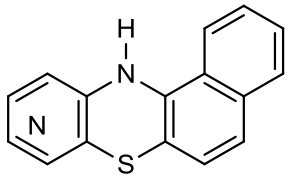
Keywords: 2-Aminopyridine, Thiocyanation, Hydrolysis, Catalyst, Palladium, Arylboronic acids, Condensation.

Contribution/ Originality

This study contributes in the existing literature that phenothiazine derivatives can be produced from simple commercially available starting materials. Also the use of transition metal catalyst systems is an efficient method that can be used in the synthesis of compounds of industrial importance.

1. INTRODUCTION

Phenothiazine and its derivatives have very wide applications in agricultural, pharmaceutical, paints, photographic, printing, textile and petroleum industries [1-7]. Interest in their studies has been sustained and thousands of derivatives have been synthesized and reported. However, the search for more useful derivatives of this group of heterocyclic compounds is ongoing, especially the non-linear-aza-analogues of the type 1 which have superior industrial and medicinal applications than the linear and the non-aza-angular analogues of the type **2** and **3** [8]; [9].



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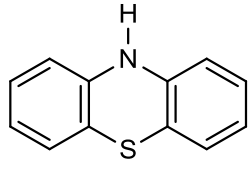

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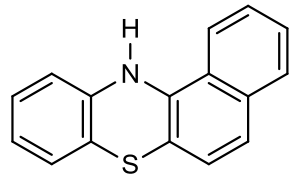

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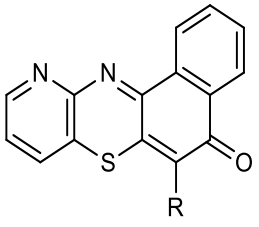
Recently, transition metal catalyst systems have been employed in the synthesis of phenothiazine and phenoxazine derivatives, thus; Anoh and co-workers [10] reported on nickel-catalyzed cross coupling of 6-chloro-8-azabenzo[a]phenoxazine-5-one. The use of nickel-catalyst in the synthesis of 6-aryl-phenothiazinones was also investigated by by Ijeoma A.O and co-workers [11]. In another development, E.A. Onoabedje and co-workers [12] reported on the use of nickel-catalyzed Grignard reagent synthesis of phenothiazines derivatives of pharmaceutical interest. In this write-up, we have described the use of palladium catalyzed synthesis of new aryl-phenothiazine derivatives using 6-chloro-11-azabenzo[a]phenothiazine-5-one **5** and phenylboronic **6** acids and 3-nitrophenylboronic **7**. Also described in this work is the transformation of the nitro-group functionality in **7** to the corresponding amino and hydroxyl

functionalities, to give 6-(3-aminoaryl)-11-lazabenzo[a]phenothiazine-5-one 17 and 6-(3-hydroxyaryl)-11-azabenzo[a]phenothiazine-5-one 18 derivatives of 6-aryl-11-azabenzo[a]phenothiazine-5-one of the type 4 respectively. This work is a continuation of our investigation on the use of palladium metal catalyst system and different aryl boronic acid in the synthesis of phenothiazine derivatives as shown in some of our previous works [13]; [14]; [15].



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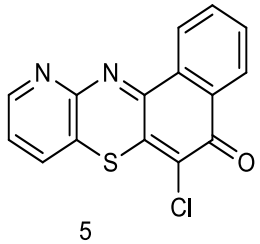

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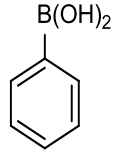

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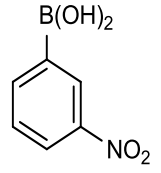

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R = $C_6H_4NO_2$, $C_6H_4NH_2$, C_6H_4OH

2. MATERIALS AND METHODS

Some of the reagents used for this work were purchased from Zayo-Sigma Chemical Industries, while others were sourced locally from commercial chemical shops. All were used without further purification. Melting points of the synthesized compounds were obtained using electro thermal melting point apparatus in open capillaries and are uncorrected. UV–Vis spectra were recorded in DMF on Jenway 6405 spectrophotometer using matched 1cm quartz cells. Absorption maxima are given in nanometer (nm) while the number in parentheses is the Ɛ - values. IR data were obtained on FTIR–8400S, using KBr disc and absorptions are given percentimer (cm^{-1}). (H-NMR and ^{13}C-NMR) were obtained on a JEOL Associate E-400 instrument (chemical shift is reported on δ scale relative to tetramethylsilane (TMS) as an internal standard), while mass spectra were obtained on a Shimadzu QP2010 spectrometer.

Compound **5, 9** and **10** were prepared by using the methods described in the literature [14]; [15].

2.1. 6-Phenyl-11-azabenzo [a]phenothiazin-5-one 15

In a 250ml two-necked-round bottom flask, diphenylphospinobutane palladium chloride ($Pd(dppb)_2Cl$ (catalyst) (0.005mmole) and 1,4-*bis*-(2-hydroxy-3,5-di-*tert*-butylbenzy)piperazine (ligand)(0.005mmole), a mixture of DMF and toluene (10ml) (2:3) were placed and charged for 5minutes by stirring with short magnetic bar without heating. Thereafter, 6-chloro-11-azabenzo[a]phenothiazin-5-one **5** (1.047mmole), phenylboronic acid **6** (0.75mmole), potassium carbonate (1.0mmole) were added and the mixture was refluxed for 24h at 120°C. The reaction was monitored by TLC analysis. At the end of the reaction, the slurry was poured into a glass petri dish and the solvent was evaporated completely while the residue was allowed to dry. The dried residue was treated with water to dissolve the inorganic materials and extracted with acetone to obtain a brownish product. Recrystallization from acetone gave the pure sample of compound 5.Yield (0.34g, 88.2%), melting at 80°C.

Uv-Vis λmax (nm): 322(1.82), 352(1.83). IR (KBr): 3073cm^{-1}(C-H,Ar), 1667cm^{-1}(C=O), 1556cm^{-1}(C=N), 1468cm^{-1}. HNMR (DMSOd$_6$): 8.35(s, 10H), δ8.00 (d, 8H and 9H), δ7.60 (m, 9H, Ar-H). ^{13}C–NMR (DMSO–d) δ177.4 (C=O) δ136.2 (1C, s), δ131.5 (1C, s), δ125.6 (1C, s), δ49.3 (6C, m), 45.9(5C, m), MS:*m/z* (relative intensity): 340(M$^+$ 100%), 312(M$^+$–CO) 10%, 308(M$^+$-S) 25%, 263(M$^+$–C$_6$H$_5$)35%.

2.2. 6-(3-Nitrophenyl)-11-azabenzo[a]phenothiazin-5-one 16

In a 250ml two-necked round bottom flask, diphenylphosphinobutane palladium chloride, Pd(dppb)$_2$Cl (0.005mmol) 1,4-*bis*-(2-hydroxy-3,5-di-*tert*-butylbenzyl)piperazine (0.005mmol) and a mixture of DMF and toluene (10ml) (2:3) were placed and stirred for 5minutes using a short magnetic bar without heating. Thereafter, compound ***5*** (1.047mmol), 3-nitrophenylboronic acid **7** (0.75mmol), and potassium carbonate (0.11mmol) were added and the mixture was refluxed for 24h. The course of the reaction was monitored with TLC analysis. At the end of the reaction, the mixture was poured into a glass petri dish while the solvent was completely evaporated and the residue was allowed to air dry. The dried residue was treated with water (10ml) to dissolve the inorganic materials and then extracted with acetone (10ml) to obtain a reddish product which was recrystallized from acetone to yield compound 16, melting at 157-158^{o}C (0.39g, 76.9%).

UV/Vis λmax (nm): 322 (1.81), 323(1.82), 325(1.83), IR (KBr), 3090cm-^{1} (C-H Ar), 1671cm^1 (C=O), 1536cm^{-1} (C=N) 1341cm^{-1}, 1120cm^{-1},769cm^{-1}. H-NMR DMSO-d$_6$:δ 8.25(s,10-H),δ 8.10(d,8-H and 9-H),δ7.99(m 4Hs Ar),δ 7.90(s,1-H ortho subst. of the phenyl ring) δ 7.70(s,3Hs of the phenyl ring). ^{13}C–NMR (DMSO–d) δ177.4 (C=O) δ136.2 (1C, s), δ131.5 (1C, s), δ125.6 (1C, s), δ49.3 (6C, m), 45.9(4C, m), 38.6(C-NO$_2$); MS:*m/z* (relative intensity) 385(M$^+$ 100%), 357(M$^+$-CO)18%, 353 (M$^+$–S)22%, 320 (M$^+$-C$_6$H$_4$O$_2$N)27%, 340(M-NO$_2$)12%

2.3. 6-(3-Aminophenyl)-11-azabenzo[a]phenothiazin-5-one 17

Iron powder (0.0714mol), distilled water (20.0ml), 5% aqueous HCl (5.0ml) and 6(3-nitrophenyl)-11-azabenzo[a]phenothiazin-5-one 16 (0.6329mmol) were placed in a 250ml reaction flask, equipped with a magnetic stirrer and a reflux condenser. The mixture was refluxed for 45minutes while heating on a water bath. At the end of the reaction time, the flask was cooled in an ice-salt bath and its content was neutralized with aqueous NaOH. The mixture was treated with crushed ice, poured into a Buchner funnel and filtered under suction. The residue was allowed to dry and recrystallized from acetone to furnish compound 17, melting at 145-146^{o}C (0.20g, 81.9%). UV/Vis λmax (nm): 320(1.81), 325(1.82), 327(1.84), IR(KBr), 3400cm^1(NH$_2$) 3090cm-^{1} (C-H Ar), 1671cm^1 (C=O), 1536cm^{-1} (C=N) 1344cm^{-1}, 1123cm^{-1},756cm^{-1}. H-NMR DMSO-d$_6$: δ 8.15(s,10-H),δ 8.00(d,8-H and 9-H),δ7.89(m 4Hs Ar),δ 7.80(s,1-H ortho subst. of the phenyl ring) δ 7.69(s,3Hs of the phenyl ring), δ 4.95(N-H). ^{13}C–NMR (DMSO–d) δ177.4 (C=O) δ136.2 (1C, s), δ131.5 (1C, s), δ125.6 (1C, s), δ49.3 (6C, m), 45.9(4C, m), 39.5(C-NH$_2$); MS:*m/z* (relative intensity) 355(M$^+$100%), 327(M$^+$-CO)20%, 323 (M$^+$–S)24%, 263 (M$^+$-C$_6$H$_4$NH$_2$)29%, 319(M-NH$_2$)15%.

2.4. 6-(3-Hydroxyphenyl)-11-azabenzo[a]phenothizin-5-one 18

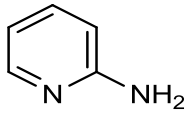
6-(3-Aminophenyl)-11-azabenzo[a]phenothiazin-5-one 17 (0.4202mmol), 3*M* H_2SO_4 (5ml) and distilled water (10ml) were mixed in a 250ml reaction flask placed on a magnetic stirring plate and stirred in an ice bath for 30minutes not allowing the temperature to exceed 10°C. Thereafter, an aqueous solution of sodium nitrite (0.0362mol), was added drop wise at an interval of 2-3 minutes and the mixture was stirred in an ice bath for additional 20 minutes. The content of the flask was treated with distilled water (20ml) and stirred for 5 minutes. At the end of the reaction, the mixture was filtered under suction and the residue was allowed dry and recrystallized from acetone to furnish compound 18, melting at about 160°C (0.10g, 72.9%).UV/Vis λmax (nm): 321(1.82), 324(1.82), 324(1.83), IR(KBr), 3465cm^{1}(OH-stretching) 3093cm-^{1} (C-H Ar), 1672cm^{1} (C=O), 1546cm-^{1} (C=N) 1345cm-^{1}, 1123cm-^{1},856cm-^{1}. H-NMR DMSO-d_6: δ 8.23(s,10-H),δ 8.11(d,8-H and 9-H),δ7.90(m 4Hs Ar),δ 7.60(s,1-H ortho subst. of the phenyl ring) δ 7.40(s,3Hs of the phenyl ring), δ 4.20(O-H) ^{13}C–NMR (DMSO–d) δ174.5 (C=O) δ137.2 (1C, s), δ133.5 (1C, s), δ126.5 (1C, s), 72.3(C-OH), δ40.27 (6C, m), 39.86(4C, m). MS:*m/z* (relative intensity) 356(M^+100%), 328(M^+-CO)18%, 324 (M^+–S)22%, 265 (M^+-C_6H_4OH)27%, 339(M-OH)12%

2.5. Reduction of Compounds 15, 16, 17 And 18

The above compounds (0.02g) each, sodium dithionite (2.0g), acetone (20ml) and few drops of DMSO were put into four different 250ml reaction flasks respectively and refluxed for 30minutes. Thereafter, water (4ml) was added to each of the flasks. The reddish colors of the above compounds changed to light yellow and subsequently to colorless, but when they were filtered, the colorless filtrates became yellowish and afterward changed back to their original reddish colors when they were exposed to air. The products were precipitated with water, isolated to give back the original compounds 15, 16, 17 and 18.

3. RESULTS AND DISCUSSION

2-Aminopyridine **8** was treated with potassium thiocyanate and bromine in acetic acid at 0°C followed by neutralization with concentrated ammonia to give 2-amino-3-thiozole [4,5b] pyridine **9** which was converted to 2-aminopyridine-3-thiol **10** by alkaline hydrolysis [13]; [14]; [15].



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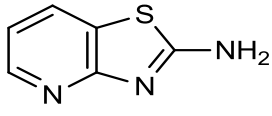

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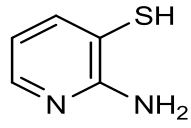

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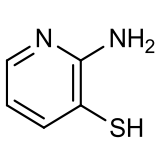
Condensation reaction of compound **10** with 2,3-dichloro-1,4-naphthoquinone **11** in small amount of DMF and benzene gave 6-chloro-11-azabenzo[a]phenothiazine-5-one **5**.



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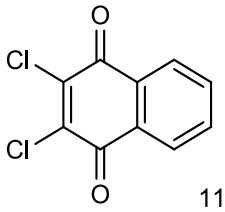

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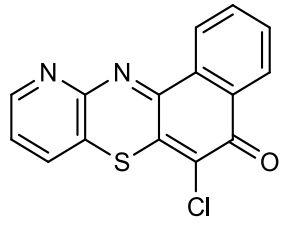

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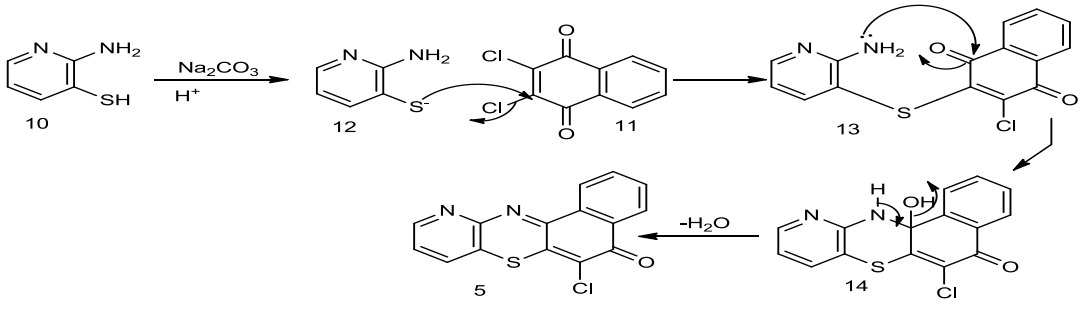
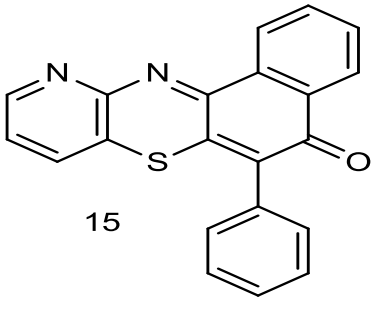
The above non-linear azaphenothiazine-5-one **5** was formed by the nucleophilic attack of the mercaptide ion **12** on C-3 of the 2,3-dichloro-1,4-naphthoquinone **11** leading to the loss of sodium chloride. Condensation of the appropriate naphthoquinone carbonyl with amino group in the pyridine moiety in **13** and loss of a water molecule in **14** led to the isolation of compound **5** as shown below [14]; [15].



When compound 5 was treated with phenylboronic acid 6 and 3-nitrophenylboronic acid 7 in the presence of a palladium catalyst complex , 6-(3-nitrophenyl)-11-azabenzo[a]phenothiazin-5-one 15 and 6-phenyl-11-azabenzo[a]phenothiazin-5-one 16 respectively were produced.



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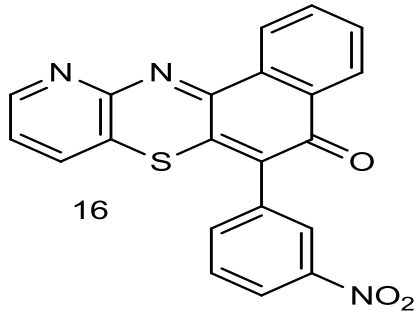

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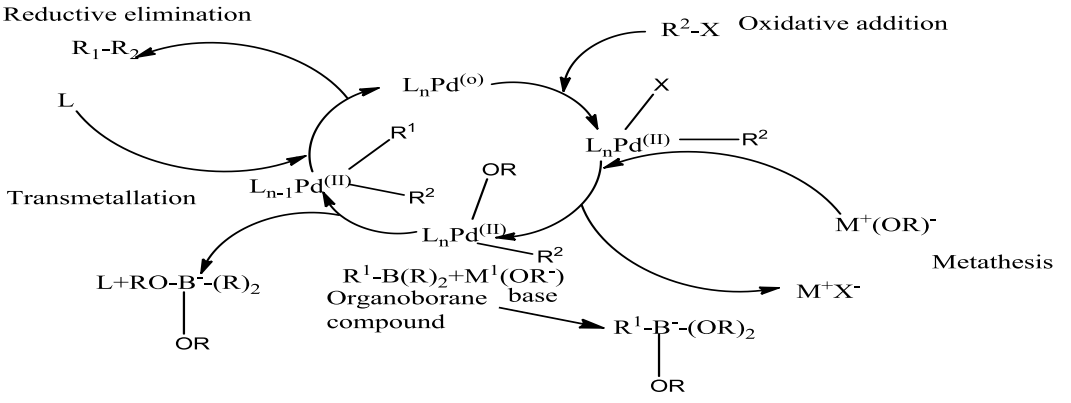
The mechanism of the above process is divided into four stages as shown below [16].

(a) The oxidative addition of an organic halide to the $Pd^{(o)}$ species to form $Pd^{(11)}$ (organopalladium halide complex) (R–M–X) which is the rate determine step in the catalytic process.

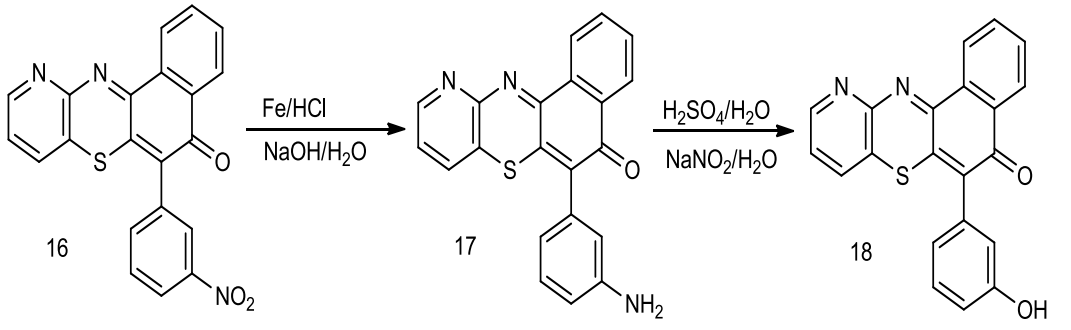
(b) Exchange of the anion attached to the palladium for the anion of the base (metathesis).

(c) Transmetallation between $Pd^{(11)}$and the alkyl borate complex (R–M–R).

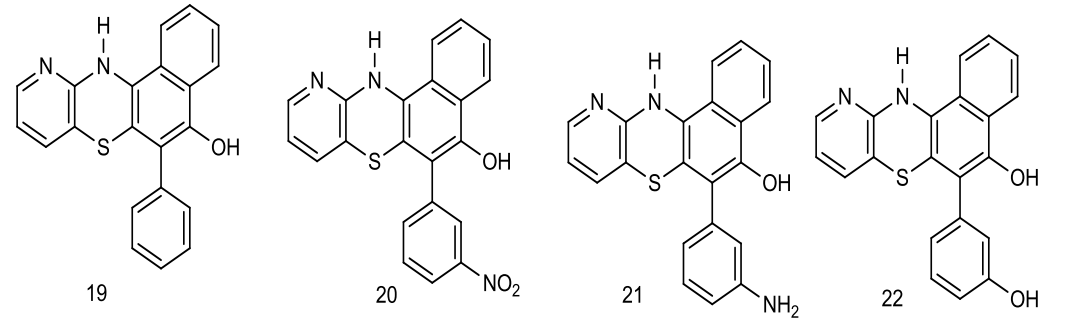
(d) Reductive elimination to form C–C sigma bond and the regeneration of the $Pd^{(0)}$.



The nitro group in the phenyl moiety of the above compound was reduced to an amino group while the amino group was subsequently oxidized to hydroxyl group to give two new additional derivatives of the azaphenothiazinone above respectively as shown below, thus;



Treating the above compounds with sodium dithionite gave color discharged unstable bases of the types 19, 20 and 21 and 22. These could not be isolated, but reverted to compounds 15, 16, 17 and 18 above respectively, immediately they were exposed to air. This property suggests that they can be used as vat dyes [17].



4. CONCLUSION

These newly synthesized compounds were characterized on the basis of UV-Vis, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic analysis and all the assigned structures are in agreement with the spectroscopic data. The molecular formulae of the compounds are $C_{21}H_{12}ON_2S$, 15,

$C_{22}H_{11}O_3N_3S$, 16, $C_{22}H_{13}N_3S$, 17 and $C_{22}H_{12}O_2N_2S$, 18. These compounds are novel and will very useful in petroleum, pharmaceutical, agricultural, textile, paint industries etc.

5. ACKNOWLEDGMENT

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