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Synthesis of 6-Aryl Substituted Derivatives of 6-Bromo-8-Methyl-1, 11-Diazabenzo[A]Phenothiazin-5-One *Via* Palladium Catalyzed Suzuki Coupling Reaction

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ABSTRACT

The synthesis of 6-substituted aryl derivatives of 8-methyl-1,11-diazabenzo[a]phenothiazin-5-one, potential vat dyes is reported. This was achieved by condensation reaction between 2-amino-4-methylpyridine-3-thiol and 6,7-dibromo-5,8-quinolinequinone under anhydrous basic condition to obtain 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one as the parent compound. The 6-aryl derivatives of this parent compound were obtained using Suzuki-Miyaura protocol. The structure of the synthesized compounds was established by spectra and analytical data obtained. These compounds showed great potentials as vat dyes.

Keywords: Synthesis, Phenothiazinones, Suzuki-Miyuara reaction, Vat dye.

INTRODUCTION

Phenothiazine compounds have for long been of interest to chemists as a result of wide range applicability of these compounds. Their uses include as drugs, pesticides, dyes and pigments and antioxidants in petroleum products [1-5]. The parent phenothiazine ring which is dibenzo analogue of 4*H* 1,4-thiazine has undergone a lot of structural modification in order remove some of the undesirable side effects observed from their various uses and also to expand applicability [6]. Suzuki-Miyaura reaction which is the reaction between an organo halide or pseudohalide and arylboronic acid or its ester in the presence of a base and catalyzed by a transition -metal complex is a powerful method for C-C bond formation [7]. A large number of compounds of great importance in medicine and industries have been prepared using this Suzuki coupling [8,9]. Haloazaphenothiazines noted for their usefulness have not received much attention as aryl halide of choice in this cross- coupling [10]. It is the interest in their use as substrate in Suzuki-coupling that promoted the present synthesis of these compounds.

MATERIALS AND METHODS

Melting points of the synthesized compounds were determined by the use of Fischer John's electro-thermal melting point apparatus in open capillaries and were uncorrected. Ultraviolet visible spectra were done on scan Buffer 16 CEUL CE 9050 spectrophotometer using matched 1 cm quartz cells in Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka. The absorption maxima were given in nanometer (nm). Infrared spectra were recorded with FTIR-8400s Fourier Transform Infrared Spectrophotometer in NARICT, Zaria, Nigeria using KBr discs, and the absorption values were given in per centimeter (cm^{-1}). Nuclear Magnetic Resonance (NMR) was determined with Varian NMR-Mercury 200BB spectrometer in Central Science Laboratory Obafemi Awolowo University, Ile-Ife Nigeria. Chemical shift δ is reported in ppm. MS spectra were obtained from GCMS-QP2010 PLUS SHIMADZU, in NARICT, Zaria, Nigeria. Elemental analyses were done on a CE 440 Elemental Analyser at the Central Science Laboratory University of Cairo, Cairo, Egypt. Most of the chemicals were purchased from Aldrich chemical company and were used without further purification. Column chromatography was done using silica gel (mesh 60-80).

Synthesis of 2-Amino-4-methyl-3-thiocyanatopyridine 3

2-amino-4-methypryidine 1 (3.8 g, 0.03 mol) was placed in a 500 cm^3 two-necked flask containing 50% of methanol (50 cm^3). Sodium hydrogen carbonate (8.4 g, 0.1 mol) was added and bromine (10 cm^3) was added from a dropping funnel and stirred for 40 minutes at room temperature. An additional 5.0 g of $NaHCO_3$ was added and the reaction mixture stirred for a period of 2 h and left overnight. The crude product was filtered, washed with water and transferred to a round bottom flask containing 200 cm^3 of hot water stirred until it dissolved, potassium thiocyanate (6.0

g, 0.06 mol) in 30 cm^3 of water was add and refluxed for 3 h. The reaction mixture was cooled, filtered and the crude product re-crystallized from acetone after treatment with activated charcoal. 2-Amino-4-methyl-3-thiocyanatopyridine (2.7 g, 55%) was obtained as white crystals which melted at 178^oC.

Synthesis of 2-Amino-4-methylpyridine-3-thiol 4

2-Amino-4-methyl-3-thiocyanatopyridine (5.0 g, 0.03 mmol) was placed in a 250 cm^3 reaction flask equipped with a reflux condenser. Sodium hydroxide solution (20%, 50 cm^3) was added and refluxed for 3 h. The reaction mixture was then filtered hot and the filtrate was cooled, neutralized with cold acetic acid. The crude product was re-crystallized from acetone and dried in a desiccator to obtain 2-amino-4-methylpyridine-3-thiol (2.9 g, 70%); M.p. 207^oC (IR (KBr) ν_{max} 3304, 3139, 2921, 2611, 1643, 1561, 1451, and 1173 cm^{-1}.

Synthesis of 6, 7-Dibromo-5, 8-quinolinequinole 8

5-Amino-8-hydroxyquinoline sulphate (12.0 g, 0.05 mol) was dissolved in 40 cm^3 of concentrated hydrobromic acid in a 250 cm^3 round bottom flask and stirred with a magnetic stirring bar while aqueous solution of sodium bromate (9.0 g, 0.06 mol) in 50 cm^3 of water was added in portions. It was heated at 50^oC for 2 h and stirred at room temperature for another 3 h. The reaction mixture was diluted with cold water and the precipitate filtered out. The crude product was washed with cold water and recrystallized from ethanol to obtain a dark yellow compound which melted at 245^oC (Lit 248^oC) [11]. UV λ_{max} 300 nm, IR (KBr) ν_{max} (cm^{-1}) 1580 cm^{-1}, 1505 cm^{-1}, 1458 cm^{-1}, and 826 cm^{-1}.

Synthesis of 6-Bromo-8-methyl-1,-11-diazabenzol[a]phenothiazin-5-one 9

2-Amino-4-methylpyridine-3-thiol (0.7 g, 5.0 mmol) and anhydrous sodium carbonate (1.1 g, 10.0 mmol) were placed in a 250 cm^3 two necked flask containing a magnetic stirring bar and 45 cm^3 of chloroform mixed with 3 cm^3 of DMF. The mixture was stirred and refluxed for 1 h before the addition of 6, 7-dibromo-5.8-quinolinequinone (1.6 g, 5.0 mmol). The resulting mixture was refluxed for 6 h with vigorous stirring after which the reaction mixture was filtered hot and the filtrate was allowed to evaporate leaving a dark red solid product which was subjected to column chromatography using benzene-methanol in the ratio of 2: 1 as eluent. The first reddish fraction obtained was identified as 6-brono-8-methyl-1, 11-diazabenzo[a]phenothiazine-5-one (0.9 g, 52.5%), M.p.=289^oC; UV-visible (EtOH) λ_{max}; 299 nm, 444 nm; IR (KBr) ν_{max} (cm^{-1}) 3059, 2965, 167; ^{1}H-NMR (DMSO) δ (ppm)=9.2, 8.9, 8.4, 7.7 and 2.5 ppm; ^{13}C-NMR (DMSO) δ (ppm)=179, C=O, 154, C=N, 148, 138, 128, C=C, MS: (m/z, % intensity); 357 (M^+, 30%), 359 (M^++2, 25%), 278(-Br, 20%), 250(-CO. 50%). Calculated: C, 50.42; H, 2.24; N, 11.76; S0z, 8.9; Br, 22.12. Found: C, 50.30; H, 2.19; N, 11.69; S, 9.00; Br, 22.40.

6-bromo-8-methyl-4,11-diazabenzo[a]phenothiazin-5-one 9e

The last fraction eluted which was reddish brown is 6-bromo-8-methyl-4, 11-diazabenzo[a]phenothiazin-5-one (0.32 g, 18%) M.p. 292^oC, UV (EtOH) λ_{max} (nm); 269, 291, and 496, IR (KBr) ν_{max} (cm^{-1}); 3082, 2930, 1635, 1528, 1456, and 1387; ^{1}H-NMR (DMSO) δ (ppm)=9.2, 8.9, 8.4, 7.7 and 2.5 ppm; ^{13}C-NMR (DMSO) δ (ppm)=185(C=O), 164(C=N), 142, 135.125(C=C). MS: (m/z, % intensity) 357 (M^+, 70%), 359(M^++2, 60%), 342(-Me, 20%), 263(-Br, 50%).

General procedure for the synthesis of 6-aryl-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one 9 a-d

In a two-necked round bottom flask was placed 15 cm^3 of methanol and a magnetic stirring bar, 1,4-bis(2-hydroxy-3,5-di-tert-butybenzyl) piperazine (0.02 g, 4 mol%), $PdCl_2$ (0.007 g, 4 mol%) were added and stirred with heating for 30 min. Na_2CO_3 (1.1 g, 11 mmol), arylboronic acid (7.5 mmol) and 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one (1.8 g, 5 mmol) were added and refluxed for 3 h and filtered hot. The filtrate was allowed to evaporate leaving gumming solid which was re-crystallized twice from acetone.

8-Methyl-6-phenyl-1, 11-diazabenzo[a]phenothiazin-5-one 9a

Following the general procedure, a mixture of the piperazine ligand, $PdCl_2$, Na_2CO_3, phenylboronic acid (0.92 g, 7.5 mmol) and 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one (1.8 g, 5 mmol) was refluxed in methanol for 3 h, the crude product was purified by recrystallization from acetone to provide the titled compound as intense red powder (1.42 g, 80% yield) M.p. 120^oC-121^oC UV (EtOH) λ_{max} (nm); 260, 329, 456; IR (KBr) ν_{max} (cm^{-1}); 2924 (C-H, methyl), 1676 (C=O), 1575, 1489, 1399 (C=C, C=N; ^{1}H-NMR δ (ppm)=7.9 (d, 2H), 7.8 (m, 1H), 7.7 (d, 1H), 7.6 (d, 1H), 7.5 (S, 5H), 2.5 (S, 3H); ^{13}C-NMR (DMSO) δ (ppm)=188(C=O), 167(C=N), 135, 125(C=C). MS: m/z 355 (M^+), 320(-Cl). Anal calculated for $C_{21}H_{13}N_3OS$; C, 70.9; H, 3.66; N, 11.83; 0, 4.51; S, 9.01. Found; C, 70.94; H, 3.49; N, 11.75; O, 4.53; S, 9.71.

8-Methyl-6-(3-chlorophenyl)-1,11-diaabenzo[a]phenothiazin-5-one 9b

A mixture of 3-chlorophenylboronic acid (1.2 g, 75 mmol) and 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one (1.8 g, 5 mmol) refluxed in methanol for 3 h gave dark reddish powder (1, 38 g, 71% yield), M.p.130^oC-132^oC. UV (EtOH) λ_{max} (nm); 269, 292, 496; IR KBr ν_{max} (cm^{-1}); 3063 (C-H, aromatic), 2957 (C-H, methyl), 1637 (C=O), 1563, 1439 (C=C, C=N); ^{1}H-NMR δ (ppm)=7.51 (2H, aromatic), 7.63 (2H, aromatic), 7.80 (2H, aromatic) 7.70 (1H, aromatic), 7.75 (2H aromatic), 4.0 (3H, methyl). MS (m/z, % int) (M^+), 389 (M^+, 25), 391 (M^++2, 10), 354 (-Cl, 20). Calculated for $C_{22}H_{12}N_3OSCl$. C, 64.70; H, 3.08; N, 10.78. Found; C, 64.75; H, 3.10; N, 10.75; S, 8.31; Cl, 9.15.

8-Methyl-6-(3-bromophenyl)1,11-diazabenzo[a]phenothiazin-5-one 9c

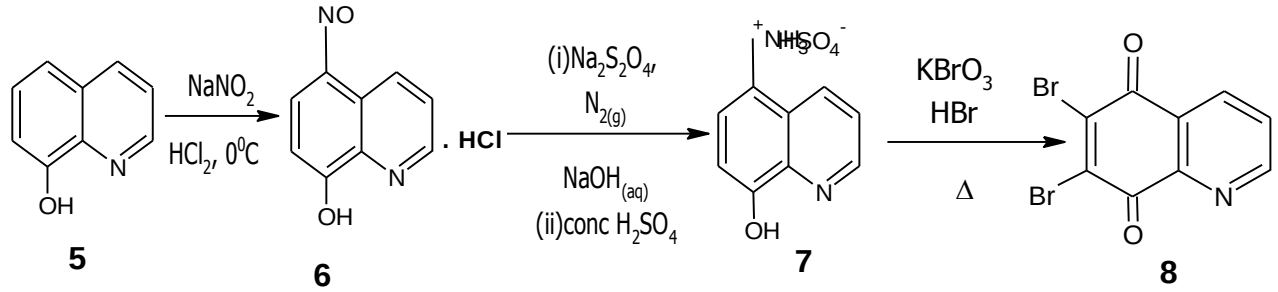
Using the general procedure reported above, from 3-bromophenylboronic acid (1.5 g, 7.5 mmol) and 6-bromo-8-methyl-1-11-diazaphenothiazin-5-one (1.8 g, 5 mmol) was obtained (1.34 g, 62 % yield) of title compound as reddish brown powder upon repeated recrystalization from acetone. UV-visible (EtOH) λ_{max} (nm); 291, 497, 657. IR (KBr) ν_{max} (cm^{-1}); 1639 (C=O). 1559, 1412 (C=C. C=N), 806 (C-Br). MS (m/z, % int), 433 (M^+), ^{1}H-NMR δ (ppm)=7.52 (2H. aromatic), 8.20 (2H, aromatic), 8.3 (2H, aromatic) 8.6 (1H, aromatic), 9.4 (2H, aromatic), 3.5 (3H, methyl); ^{13}C-NMR (DMSO) δ (ppm)=183, C=O, 167, C=N, 148, 135, 112 C=C. Calculated for $C_{21}H_{12}N_3OSBr$: C, 58.20; H, 2.7; N, 9.70; S, 7.39; Br, 18.24. Found: C, 58.09; H, 2.75; N, 9.70; S, 7.40; Br, 18.51.

8-Methyl-6-(3-nitrophenyl)-1,11-diazabenzo[a]phenothiazin-5-one 9d

A mixture of 3-nitrophenylboronic acid (1.3 g, 75 mmol) and 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one (1.8 g, 5 mmol) yielded the title compound, brown powder (1.62 g, 75% yield) M.p. 150^oC-150^oC. UV-visible λ_{max} (nm); 291, 498, 658; IR (KBr)ν_{max} (cm^{-1}); 1614 (C=O), 1563, 1411, 1385 (C=C,C=N); ^{1}H-NMR δ (ppm)=8.9 (m, 2H), 8.7 (d, 2H), 7.7 (m, 2H), 7.3 (m, 1H), 174, C=O, 161, C=N, 135, 125, C=C MS (m/z, % int); 400 (M^+, 70), 354 (-NO_2, 50), 339 (-Me, 30), 263 (-Ph, 100). Calculated for $C_{21}H_{12}N_4O_3S$: C, 63.00; H, 3.00; N, 14.00; O, 12.00; S, 8.00. Found: C, 62.96; H, 3.08; N, 14.12; S, 8.05.

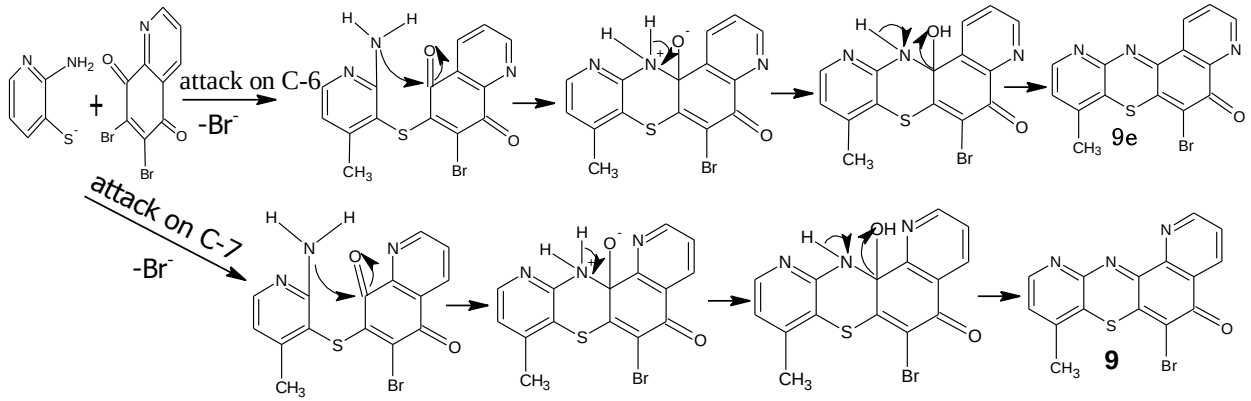
RESULTS AND DISCUSSION

Thiocyanation of 2-amino-4-methylpyridine was achieved indirectly by first brominating to obtain the 3-bromo derivative which was then refluxed in potassium thiocyanate to obtain the 3-thiocyanated derivative and subsequently converted to 2-amino-4-methyl-pyridine-3-thiol by base catalyzed hydrolysis. Higher yield of the product was obtained through this indirect route [12]. The absorption band at 2230 cm^{-1} in the IR spectrum of compound 3 showed that the thiocyanato group has been attached and this disappeared upon hydrolysis. The IR spectrum of compound 4 showed bands at 3304 cm^{-1} and 3139 cm^{-1} which are due to N-H stretching vibration of the amino group of primary amines. The band at 2921 cm^{-1} has been assigned to C-H stretching vibration of the methyl group. The band at 2611 cm^{-1} has been ascribed to S-H vibrational stretching which showed that the thiol group has been attached. The bands at 1561 cm^{-1} and 1458 cm^{-1} are due to C=C and C=N stretching vibration of the aromatics. This key intermediate compound 4 was coupled with 6,7-dibromoquinolinequinone 5, obtained from 8-hydroxyquinoline by stepwise conversion depicted by Scheme 1 below.



Scheme 1: Conversion of 8-hydroxyquinoline to 6,7-dibromoquinolinequinone

A stiochiometric mixture of 2-amino-4-methylpyridine-3-thiol 4 and 6,7-dibromo-5,8-quinolinequinone 8 in chloroform mixed with little quantity of Dimethyl Formamide DMF was refluxed for 6 hours in the presence of Na_2CO_3. The colour of the reaction mixture changed from dark yellow to brown and finally reddish brown at end of the reaction. The isometric mixture of 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one 9 and 6-bromo-8-methyl-4,11-diazabenzoi[a]phenothiazin-5-one 9e was obtained. Separation by column chromatography using benzene- acetone as eluent gave the isomers in the ratio of 3: 1. The structures assigned to these isomers were based on analytical and spectra evidence. The 6-bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one 9 was identified by comparing its UV, IR, NMR and mixed melting point with the authentic sample which was prepared by the condensation of 2-amino-4-methylpyridine-3-thiol with 7-chloro-5,8-squinolinequinone followed bromination in acetic acid. 6-Bromo-8-methyl-1,11-diazabenzo[a]phenothiazin-5-one 9 was obtained in higher yields. The reaction probably proceeded through the mechanistic pathway shown in Scheme 2 below.

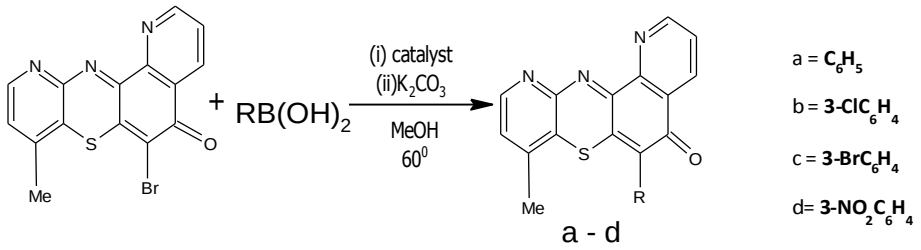


Scheme 2: Reaction Mechanism for the formation of the isomeric products

The first step is the abstraction of a proton from the thiol by the anhydrous sodium carbonate to form the mercaptide. The mercaptide mounts a neuclophilic attack on either of the carbon atom bearing the bromine atom of the quinolinequinone to form two different sulfides. The sulfide cyclizes by nucleophilic attack of the amino group on the carbon atom of the carbonyl group. Proton migration and loss of a molecule of water gave the angular phenothiazine. Separation by column chromatography gave the isomers in yield of 3: 1. For the reason already stated above, the higher yield isomer is 6-bromo-8-methyl-1,11 diazabenzo[a]phenothiazin-5-one 9, while the lower yield isomer is 6-bromo-8-methyl-4, 11-diazabenzo[a]phenothiazin-5-one 9e.

6-Bromo-methyl-1, 11-diazabenzio[a]phenothiazin-5-one 9, an intense red powder melted at 289^oC. In the uv-visible spectrum the absorption band at 299 nm is typical of phenothiazinoid ring system, while the peak at 444 nm agrees with the red colour of the compound. In the IR spectrum the band at 2965 cm^{-1} is due to C-H stretching vibration of the methyl, the band at 1675 cm^{-1} is due to C=O stretching vibration. In the MS spectrum the peak at m/z 357 is due to the molecular ion (M^+). The isotopic peak at m/z 359 is typical of a molecule containing bromine atom. The peak at m/z 278 corresponds to loss of bromide fragment. Result of elemental analysis agrees with the assigned molecular formula of $C_{15}H_8N_3OSBr$. In ^{1}H-NMR spectra, the absorption signals at δ 9.0-7.6 are due to the aromatic protons while the signal δ 2.5 is due to the methyl proton. In the ^{13}C-NMR spectrum, the absorption signal δ 179.0 is due to carbonyl carbon, the absorption signal at 154 is due to C=N while the signals at δ 148.0 - 110 are due to aromatic carbons. The parent compound 6-bromo-8-methyl-1, 11-diazabenzo[a]phenothiazin-5-one 9 was derivatized by coupling it with arylboronic acids in presence of 4 mol% of the catalyst and base using methanol as solvent [13]. Good yield of the coupled products were obtained after 3 hours of refluxing. The catalyst was an equimolar mixture of $PdCl_2$ and 1, 4-*bis* (2-hydroxy-3, 5-di-

tert-butylbenzyl) piperazine. At the end of the refluxing period, the reaction mixture was filtered hot and allowed to evaporate leaving gummy products which were extracted with acetone to obtain products with percentage yields ranging from 60%-65%. The elemental and spectra data obtained were in agreement with the assigned structures. The coupling of the compound 9 with the arylboronic acid is represented by Scheme 3 below.



Scheme 3: Cross coupling of compound 9 with arylboronic acids

The dyeing potentials of these compounds were explored by using them to dye white cotton and silk fabrics. They left colours ranging from red to brown on the dyed materials. Reduction of these compounds to the corresponding azaphenothiazin-5-ols was accomplished by the use of sodium dithionithe under nitrogen atmosphere which reverted back to the original intensely coloured compound under atmospheric condition. Due to this property, these compounds can be applied as vat dyes in textile industries [14].

CONCLUSION

In the present study, novel 1,11-diazabenzo[a]phenothiazin-5-one derivatives were designed and synthesized in good yields. All the synthesized compounds were characterized by using UV, elemental analysis, 1H & 13C NMR and Mass spectral data. In addition, we have also established and reported the reaction mechanism for the formation of the isomeric products of parent compound i.e. 1,11-diazabenzo[a]phenothiazin-5-one (9). Furthermore, 1,11-diazabenzo[a]phenothiazin-5-one derivatives (9a-e) possesses to have an aptitude as vat dyes. From the above results it can be concluded that the synthesized compounds could be a best initiation to find new lead to class of vat dyes in the future.

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