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RESEARCH ARTICLE

Use of Angular Azachlorophenothiazine as Organic Halide of Choice in Suzuki Coupling

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Abstract: 6-Chloro-10-methyl-1,11-diazaphenothiazin-5-one was synthesized and used in cross-coupling of arylboronic acids using Suzuki protocol under nickel complex catalysis to furnish intense coloured heterocycles. Structures assigned to the synthesized were supported by spectra and analytical data obtained.

Keywords: Phenothiazinone, Suzuki reaction, Cross-coupling, Nickel catalysis

Introduction

The transition metal-catalyzed cross-coupling of organoboron compounds with organic halides or pseudohalides in the presence of a base is known as Suzuki coupling or Suzuki-Miyaura reaction. It is a powerful method for the formation of both aryl and alkyl carbon-carbon bond[1]. Although there are several other cross-coupling reactions such as Stille, Sonogashira, Kumada, Negishi, Heck *etc*., available for the purpose, the Suzuki Miyuara reaction has proven to be more popular as a result of its many advantages which include; mild reaction condition, tolerance of wide range of functional group on the coupling partners and the environmental friendliness of boronic acid and their by- products[2]. Suzuki coupling has been used in the syntheses of many useful compounds[3]. Diverse bases such as K_2CO_3, Cs_2CO_3, TiOH, AcONa, $Ba(OH)_2$, *etc.* and solvents like DMA, DME/H_2O, EtOH, MeOH, H_2O *etc.,* have employed in this reaction[4,5]. There are diverse numbers of organic halides available as coupling partners of which only a few have been utilized. Aza halophenothiazines used in this work have not received much attention as organic halide of choice in Suzuki coupling. The phenothiazine moieties are of great importance in medicine[6] and industry[7] hence the syntheses of new derivatives has remained an area of intense interest for organic chemists.

Experimental

Melting points of the synthesized compounds were determined by the use of Fischer Johns electro-thermal melting point apparatus in open capillaries and are 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 spectrophotometer in NARICT, Zaria, Nigeria, using KBr discs and the absorption values were given in per centimeter (cm^{-1}). Nuclear magnetic resonance was determined with Varian NMR-Mercury Spectrometer in Central Science Laboratory Obafemi Awolowo University, Ile -Ife Nigeria and 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 Analyzer at the Central Science Laboratory University of 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)

*Dichloro-5, 8-quinolinequinone **(2)***

5-Amino-8-hydroxyquinoline **1** (8.0 g, 0.05 mol) was dissolved in 50 cm^3 of concentrated HCl with vigorous stirring at room temperature. An aqueous solution of potassium chlorate (7.5 g, 0.06 mol) in 50 cm^3 of water was gradually added to it. It was stirred at 50 ^oC for 2 h and then at room temperature for 3 h. Cold water was added and the precipitate was filtered out. This crude product was re-crystallized from ethanol to obtain a bright yellow powder (6.8 g, 60%) which melted at 217-219 ^oC (Lit 220-222^oC)[8]. UV λ_{max} 344.8, IR(KBr) ν_{max}; 1640 cm^{-1}, 1579 cm^{-1}, 1505 cm^{-1}, 1458 cm^{-1} and 793 cm^{-1}.

*2-Amino-6-methylpyridine-3-thiol **(4)***

2-Amino-6-methyl-3-thiocyanatopyridine (3.3 g, 0.02 mol) in a 250 cm^3 round bottle flask was added sodium sulphite (2.0 g, 0.01 mol) and potassium hydroxide solution (30 cm^3, 20%) and refluxed for 8 h. The dark brown solution was treated with activated charcoal and heated and filtered. The filtrate was cooled, neutralized with cold acetic acid and chilled overnight. The crude product was re-crystallized from methanol-acetone mixture to obtain a light yellow solid (2.1 g 75%) which melted at 244 ^oC (Lit 245)[9]. IR(KBr)ν_{max} (cm^{-1}), 3255, 3078 and 1431 cm^{-1}.

*6-Chloro-10-methyl-1,11-diazabenzo[a]phenothiazin-5-one **(5)***

2-Amino-6-methylpyridine-3-thiol (0.7 g, 5.0 mmol) was suspended in 40 cm^3 benzene and 5 cm^3 of DMF in a 250 cm^3 two-necked flask equipped with a reflux condenser, thermometer and magnetic stirring bar. Sodium acetate (0.7 g, 10 mmol) was added and refluxed for 45 min. 6, 7-Dichloro-5, 8-quinolinequinone (1.5, 5.0 mmol) was added, refluxed for 6 h and filtered hot. This crude product was subjected to column chromatography using benzene-methanol as eluent. The first yellowish fraction was discarded. The next fraction of intense reddish compound of 6-chloro-10-methyl-1,11-diazabenzo[a]phenthiazin-5-one **9** (0.9 g, 56.3%) decomposes at 298 ^oC, UV (EtOH) λ_{max} 291 and 498 nm, IR (KBr) ν_{max} 3078, 1671, 1614, 1543, 1384 and 638 cm^{-1}. MS, *m/z*(rel.int.%); 313(M^+, 20%),278(-Cl, 40%), 263(-Me,10%). ^1H NMR (DMSO)δ; 7.9(d,2H,arom), 7.8(m,1H,arom), 7.7(m,1H,arom), 7.5(m,1H,arom) and 2.6 (s,3H,methyl)ppm. ^{13}C NMR (DMSO)δ 185, 135.0, 131.0, 125.0, 40.0, ppm. Calculated for $C_{15}H_8N_3OSCl$; C, 57.42; H, 2.55; N, 13.40; O, 5.10; S, 10.21; Cl, 11.32. Found C, 57.50; H, 2.63; N, 13.60; S, 10.19; Cl, 11.16.

*6-Chloro-10-methyl-4,11-diazabenzo[a]phenothiazin-5-one **(6)***

The last fraction eluted was reddish brown compound of 6-chloro-10-methyl-4,11-diazabenzo[a]phenothiazin-5-one **10** (0.35 g, 21%) mp: > 300 ^{o}C. UV (EtOH) λ_{max} 291, 446 nm and 497 nm. IR (KBr) ν_{max} 2965, 1672, 1548 and 1384 cm$^{-1,}$ MS: *m/z*(rel.int.%), 313(M^+, 50%), 315 (M+ 2, 15%), 278(-Cl,100%), 263(-Me.30%). ^{1}H NMR ($_d$DMSO)δ; 8(d,1H),7.6(d,2H),7.5(d,1H),7.1(d,1H). ^{13}C NMR (DMSO) δ; 183, C=O,155, C=N, 135, 125, C=C, 41, C-C(methyl).

*General method for the synthesis of 6-aryl-10-methyl-1,11-diazabenzo[a] phenothiazin-5-one (**5a-d**)*

The method reported by Inada *et al.,*[10] was adopted. In a 100 cm^3 two necked flask containing a magnetic stirring bar was added $NiCl_2(PPh_3)_2$ (0.04 g, 0.09 mmol), PPh_3(0.05 g, 0.18 mmol), arylboronic acid (3.9 mmol), K_3PO_4. $2H_2O$ (1.9 g, 7.8 mmol) and then flushed with nitrogen gas. Toluene 15 cm^3 and 6-chloro-10-methyl-1, 11-diazabenzo[a]phenothiazin-5-one (0.92 g, 3.0 mmol) were added and flushed again with nitrogen gas. The reaction mixture was stirred and refluxed at 80 ^{o}C for 4 h. The crude products was extracted with toluene, washed with water and brine, concentrated to small bulk and finally recrystallized from ethanol to obtain high yield of the cross-coupled products.

*10-Methyl-6-phenyl-1, 11-diazabanzo[a]phenolhinzin-5-one (**5a**)*

Following the general procedure given above, a mixture of 6-chloro-10-methyl-1,11-diabenzo[a] phenothiazin-5-one (0.92 g, 3.0 mmol), $NiCl_2(PPh_3)_2$ (0.04 g, 0.09 mmol), PPh_3(0.05 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (1.9 g, 7.8 mmol) was refluxed in toluene for 4 hours at 80 ^{o}C gave an intense red powder (0.93g, 85% yield), mp 120-123 ^{o}C. UV-Visible (EtOH) λ_{max} (nm) (ε) 273 (1748) 348 (297), 404 (222). IR (KBr) ν_{max} (cm^{-1}); 3059 (C-H, aromatic), 2928 (C-H, methyl), 1636 (C=O), 1562, 1486, 1430 (C=C, C=N). ^{1}H NMR δ; 7.50 (5H, aromatic), 8.2- 8.3 (3H, aromatic), 8.7 (2H, aromatic), 3.5 (3H, CH_3).^{13}C NMR δ; 182 (C=O), 167 (C=N), 134, 126 (C=C). MS (*m/z*, % int); 355 (M^+,75),340 (-Me,40), 263 (-Ph, 50). Calculated for $C_{21}H_{13}N_3OS$; C, 70.79; H, 3.66; N, 11.83; O, 4.51; S, 9.01. Found: C, 70.94; H, 3.50; N, 11.87; S, 9.20.

*10-Methyl-6-(3-chlorophenyl)-1,11-diazabenzo[a]phenothiazin-5-one (**5b**)*

Following the general procedure reported above, a mixture of 3-chlorophenylboronic acid (0.61 g, 3.9 mmol), 6-chloro-10-methyl-1,11-diazabenzo[a]phenothiazin-5-one (0.92 g, 3.0 mmol), $NiCl_2(PPh_3)_2$ (0.04 g, 0.09 mmol) PPh_3 (0.05 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (1.9 g, 7.8 mmol) was refluxed in toluene at 80 ^{o}C for 4 hours to obtain dark red powder (0.96 g, 80% yie1d) mp 142- 4 3^{o}C. UV-Visible (EtOH) λ_{max} (nm) (ε); 265 (1910), 370 (1040), 466 (905). IR (KBr) ν_{max} (cm^{-1}); 3078 (C-H, aromatic), 1672(C=O), 1543 (C=C, C=N), 683(C-Cl). ^{1}H NMR δ; 7.9 (d,1H),7.8 (d,2H), 7.6 (m,4H), 7.5 (t,2H), 2.5 (s,3H). ^{13}C NMR δ; 172 (C=O), 160 (C=N), 126-136 (C=C). MS (*m/z*, % int); 389 (M^+, 20), 354 (-Cl,10), 339 (-Me,50), Calculated for $C_{21}H_{12}N_3OSCl$; C, 64.70; H, 3.08; N, 10.78; O, 4.11; S, 8.22; Cl = 9.11. Found: C, 64.82; H, 3.10; N, 10.83; S, 8.25; Cl, 9.20.

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

From the reaction between 6-chloro-10-methyl-1,11-benzo[a]phenothiazin-5-one (0.9 g, 3.0 mmol) and 3-nitropheylboronic acid (0.65 g, 3.9 mmol) in presence of $NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol), PPh_3 (0.06 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (0.64, 7.8 mmol) was obtained a reddish brown powder (0.91 g, 70%), mp 150-152 ^{o}C, UV-Visible (EtOH) λ_{max} (nm) (ε);

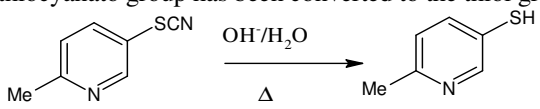
286 (160), 353 (257), 473 (174). IR (KBr) ν_{max} (cm^{-1}); 1684 (C=O), 1576, 1609, 1563 (C=N, C=C). MS (*m/z*, % int); 433($M^{+\cdot}$75), 435(M^{+}+2,70), 418 (-Me,40). ^{1}H NMR δ; 7.5 (2H, aromatic), 7.65 (2H, aromatic), 7.80 (2H, aromatic), 7.85 (2H aromatic), 4.0 (3H, methyl). ^{13}C NMR δ; 181 (C=O), 167 (C=N, aromatic), 113-148 (C=C). Calculated for $C_{21}H_{12}N_3OSBr$; C, 58.20 H, 2.77; N, 9.70; O, 3.70; S , 7.39; Br , 18.24. Found: C, 58.15; H, 2.80; N, 9.65; S, 7.30; Br, 18.50.

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

Following the general procedure reported above, a mixture of 3-nitrophenylboronic acid (0.78 g, 3.9 mmol), 6-chloro-10-methyl-1-14-diazaphenothiazin-5-one (0.92 g, 3.0 mmol) $NiCl_2(PPh_3)_2$ (0.04 g, 0.09 mmol), PPh_3 (0.05 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (1.9 g, 7.8 mmol) refluxed in toluene for 4 hours at 80 ^{o}C gave the titled compound, brown powder (0.93 g, 78% yield), mp 128-130 ^{o}C. UV-Visible (EtOH) λ_{max} (nm) (ε); 291 (660), 498 (166), 658 (37). IR (KBr)ν_{max} (cm^{-1}); 2965 (C-H, methyl), 1675 (C=O), 1548, 1384 (C=C, C=N). MS (*m/z*, % int); 400 ($M^{+\cdot}$30), 354(-NO_2,35),278(-Ph,100). ^{1}H NMR δ; 7.5 (2H, aromatic), 7.6 (2H, aromatic), 7.8 (2H, aromatic), 7.9 (2H aromatic) 3.5 (3H, methyl) 113-135 (C=C). Anal 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, 63.20; H, 2.94; N, 14.09; S, 7.89.

Results and Discussion

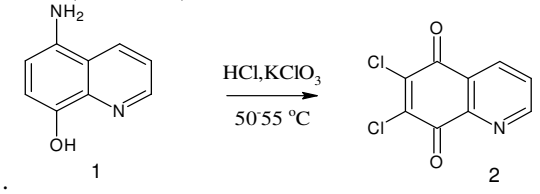
2-Amino-6-methyl-3-thiocyantopyridine **(3)** was converted to 2-amino-6-methyl-pyridine-3-thiol (**4**) by alkaline hydrolysis. The IR spectrum of compound **4** showed band at 2611 cm^{-1} is due to S-H vib stretch. The absence of absorption band in the triple bond region of 2100- 2300 cm^{-1} showed that the thiocyanato group has been converted to the thiol group (Scheme 1).



3 4

Scheme 1

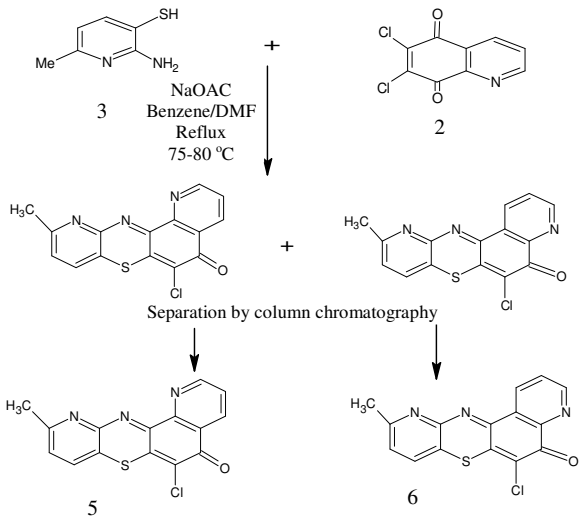
6,7-Dichloroquinolinequinone **2** which is the second key intermediate was obtained by chloroxidation of 5-amino-8-hydroxyquinoline **1** using conc HCl and potassium chlorate while maintaining the temperature at 55-60 ^{o}C. The crude product obtained was recrystallized twice from ethanol to furnish a bright yellow compound. The IR spectrum of the compound showed band at 1639 cm^{-1} which has been attributed to C=O stretching vibration. The absence of absorption band at 3200 cm^{-1} showed that the hydroxyl and amino groups have been oxidized (Scheme 2).



1 2

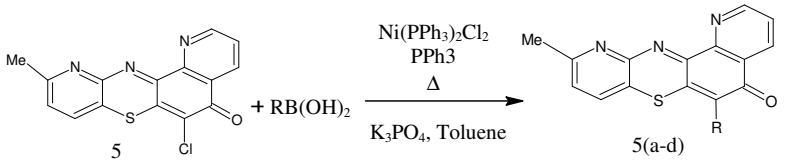
Scheme 2

Equimolar mixture of 2-amino-6-methylpyridine-3-thiol **3** and 6,7-dichloro-5,8-quinolinequinone **4** in benzene mixed with DMF was reacted in the presence of anhydrous sodium acetate to furnish the isomeric mixture which was later separated by column chromatography to obtain the regio isomers. This is represented by Scheme 3 below.



Scheme 3

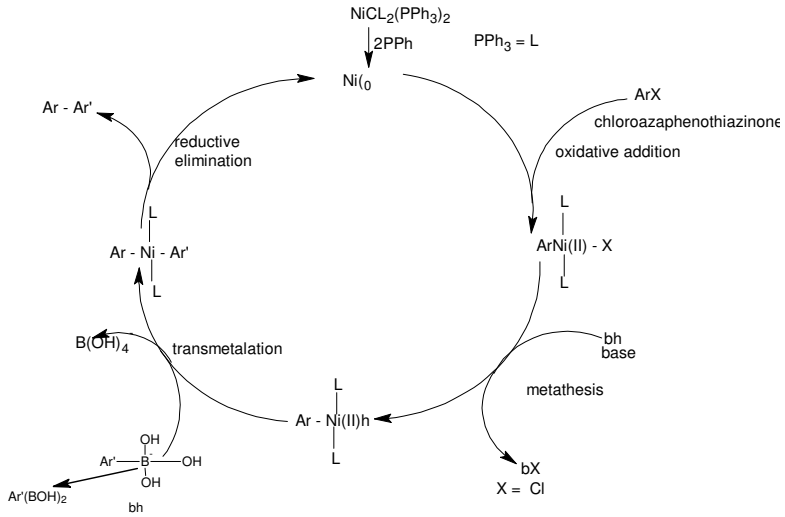
Compound **5** was subjected to Suzuki Miyuara coupling with arylboronic acids to produce its 6-aryl-derivatives under nickel complex catalysis while employing K_3PO_4 as a base (Scheme 4).



a = C_6H_5, b = 3-BrC_6H_4, c = 3-ClC_6H_4,, d = 3-$NO_2C_6H_4$

Scheme 4

The probable mechanism for this nickel-catalyzed cross-coupling is depicted in the scheme 5 below.



Scheme 5

The first step is probably the reduction of Ni(II) to Ni(0) by the excess triphenylphosine introduced.

$$NiCl_2(PPh_3)_2 + 2PPh_3 \longrightarrow Ni(0)(PPh_3)_4$$

This is followed by the oxidative addition of chlorophenothiazine to form the aryl nickel complex Ar-NiL_2-X. The base displaces the chloride ion (metathesis) and also acted on the phenylboronic acid to form the boronate anion which enhances the transmetalliation. Finally through reductive elimination the product is formed and the nickel catalyst regenerated.

Conclusion

6-Chloro-10-methyl-1,11-diazaphenothiazin-5-one was synthesized and cross-coupled with arylboronic acids to furnish 6-substituted azaphenothiazinones with intense colours which can be used as vat dyes in industry.

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