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A Concise and Convenient Synthesis of 6-Aryl Angular Phenothiazinones

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Abstract: ***The synthesis of 6-aryl derivatives of 8-methyl-11-azabenzo[a]phenothiazn-5-one is reported. This was achieved by reacting 2-amino-4-methylpyridine-3-thiol with 2,3-dichloro-1-4-naphthoquinone under anhydrous basic condition to furnish the parent compound while 6-aryl derivatives were prepared by cross-coupling with arylboronic acids under nickel complex catalysis. The structures assigned to the synthesized compound were supported by spectroscopic and analytical data obtained.***

Keywords: Synthesis, 2-amino-4-methylpyridine-3-thiol, 2,3-dichloronapthoquinone, 8-methyl-11-azabenzo[a]phenothiazine-5-one.

1. Introduction

Phenothiazines are important group of compounds which have been used extensively as drugs[1], [4], organic polymeric light emitting diodes [5] and as dyes and pigments[6]. Modification of the main phenothiazine structure have led to producing derivatives with increasing chemical and potential biologicalactivities [7], [8]. However, the method of preparations of these derivatives have mainly been based on the classical methods which are tedious with corresponding low yield of products. There is also paucity of works on the synthesis of phenothiazine derivatives in literature. Our method therefore is based on the use of Suzuki-Miyaura to produce the derivatives. Suzuki-Miyaura Coupling is the reaction between an organic halide and arylboronic acid mediated by a base in the presence of either Pd or Ni complex catalyststo form new carbon-carbon bonds [9], [10]. A lot of advantages are inherent in the use of Suzuki-Miyaura Coupling to form new aryl-aryl carbon bond. These includes availability of diverse boronic acid, environmental friendliness of the boronic acids and their by-products, mild reaction conditions required, tolerance of wide range of functional groups in the starting partners [11]-[13]. It is the interest in extending the list of phenothiazine derivatives using Suzuki-Miyaura Coupling protocol that prompted the synthesis of 6-arylsubstituted derivative of the parent phenothiazinone compound.

2. Experimental

2.1 General

Melting points of the synthesized compounds were determined by the use of Fischer John's 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 1cm 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, and IR Perkin Elmer Spectrometer BX in Turkey using KBr discs. Nuclear Magnetic Resonance (NMR) was determined with Varian NMR – Mercury 200BB Spectrometer in Central Science Laboratory Obafemi Awolowo University, Ile-Ife, Nigeria. 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).

2.2 2-Amino-4-methyl-3-thiocyanatopyridine

2-amino-4-methypryidine (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 (5 cm^3) was added from a dropping funnel for 40 min with stirring. An additional $NaHCO_3$ (5.0 g) was added and the reaction mixture stirred for a period of 2 h and left overnight. The crude product was filtered, washed with water. It was placed in another 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 residue 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^{o}C.

2.3 2-Amino-4-methylpyridine-3-thiol

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 until the cessation of evolution of ammonia gas. At the end of refluxing period, a little amount of activated charcoal was added and the mixture boiled for 30 mins and then filtered. The filtrate was cooled, neutralized with cold acetic acid. The precipitate was re-crystallized from acetone and dried in a desiccators to obtain 2-amino-4-methylpyridine-3-thiol (2.9 g, 70%); mp 207^{o}C (IR (KBr) ν_{max} 3304, 3139, 2921, 2611, 1643, 1561, 1451, and 1173 cm^{-1}.

2.4 Synthesis of 6-Chloro-8-methyl-11-azabenzo [a]phenothiazin-5-one (5)

2-amino-4-methylphyridine-3-thiol**3** (0.7 g, 5.0 mmol), anhydrous potassium carbonate (1.4 g, 10mmol), 40 cm^3 of benzene and 4 cm^3 of DMF were added into a two necked flask and stirred with heating for 45mins. 2, 3-dichloro-1, 4-naphthoquinone**4** (1.2 g, 5.0 mmol) was added to the reaction mixture. The mixture was refluxed at 75^o – 80^{o}C for 6 h. The reaction mixture was filtered hot and the filtrate allowed to evaporate leaving an intense red solid which was re-crystallized twice from acetone. The yield was 1.4g (88%) Mp = 278^{o}C. UV (EtOH) λ_{max} 269, and 449 nm, IR (KBr) ν_{max} (cm^{-1}) 1636, 1547, 1486 and1430. ^{1}H-NMR ($_d$DMSO) (δ, ppm) 3.8, 7.5. ^{13}C-NMR ($_d$DMSO) (δ, ppm) 175, 40. MS :m/z(rel.int.%), 312 (M^+, 35%), 314 (M+2, 10%),287(-Cl,70%) Calculated for $C_{16}H_9N_2OSCl$, C, 61.44; H, 2.87; N, 8.96; O, 5.12; S, 10.24; Cl, 11.36, Found C = 61.60; H = 2.84; N = 8.93; S = 10.40; Cl = 11.42.

2.5 Synthesis of 6-aryl-8-methyl-11-azabenzo[a]phenothiazin-5-one (5 a- d)

$NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol) was added to PPh_3 (0.06 g, 0.18 mmol) and flushed with nitrogen gas. Then 10 cm^3 of DMA was added and flushed again with nitrogen gas.DMA (10 cm^3) was added and flushed again with nitrogen gas while stirring and heating for 20 min. Arylboronic acids (3.9 mmole), $K_3PO_4.2H_2O$ (0.64 g, 3 mmol) and 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.0 mmol) were added and refluxed at 80^{o}C for 5 h. The product was extracted with ether, washed water and allowed to evaporate to obtain various products depending on the particular arylboronic acid used.

2.5.1 Synthesis of 8-methyl-6-phenyl-11-azabenzo[a]phenothiazin-5-one (5a)

Following the general procedure above, a mixture of 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.9 mmol), $NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol), PPh_3 (0.06 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (0.64 g, 3.0 mmol) was refluxed in DMA for 5 hours at 80^{0}C . An intense red powder (0.80 g, 75%) which melted with decomposition at 119-120^{0}C was obtained. UV – visible (EtOH) λ_{max} (nm) (ε) 268 (1547), 449 (562), IR (KBr) ν_{max} (cm^{-1}) 3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=N), ^{1}HNMR (δ, ppm) 7.7(2H),7.6(s,10H), 2.5(s,3H). MS (m/z, % int) 354(M^+, 100),277(-Ph,75), 262(-Me,35). Anal calculated for $C_{22}H_{14}N_2OS$, C, 74.58; H, 3.95; N, 7.61; S, 9.04. Found: C, 74.61; H, 4.00; N, 7.85; S, 9.15.

2.5.2 Synthesis of 8-methyl-6-(3-chlorophenyl)-11-azabenzo[a]phenothiazin-5-one (5b)

A mixture of 3-chlorophenylboronic acid (0.61 g, 3.9 mmol), 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.0 mmol), $NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol), PPh_3 (0.06 g, 0.18 mmol) and $K_3PO_2.2H_2O$ was refluxed in 20 cm^3 of DMA at 80^{0}C for 5 hours. The crude product was extracted with ether, washed with water and dried over $MgSO_4$. It was concentrated to a small bulk and allowed to evaporate leaving a dark-red powder (0.93 g, 80%), mp 130 – 132^{o}C. UV – visible (EtOH) λ_{max} (nm) (ε) 268 (1541), 449 (562), IR (KBr) ν_{max} (cm^{-1}) 1633 (C=O), 1542, 1431 (C=C, C=N), 1130 (C-N). ^{1}HNMR (δ, ppm) 8.6(m,2H), 8.1(d,1H), 8.0(d,3H), 7.5(m,4H), 2.5(s,3H).^{13}CNMR (δ,ppm) 175(C=O), 163(C=N), 130(C=C). MS (m/z, % int) 389 (M^+,70), 391(M^+2,50),354(-Cl,20), 278(-Ph,30). Anal calculated for $C_{22}H_{13}N_2OSCl$, C, 67.95; H, 3.35; N, 7.21; S, 8.24; Cl, 9.14. Found: C, 66.79; H, 3.60; N,7.49; S, 8.52; Cl, 9.48.

2.5.3 Synthesis of 8-Methyl-6-(3-bromophenyl)-11-azabenzo[a]phenothiazin-5-one (5c)

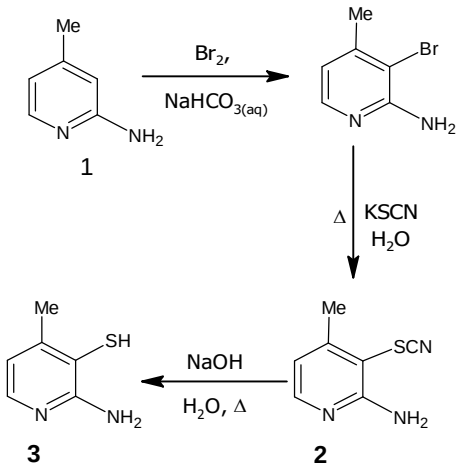
A mixture of 3-bromophenylboronic acid (0.78 g, 3.9 mmol), 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.0 mmol), $NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol), PPh_3 (0.06 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (0.64 g, 3.0 mmol) was obtained the titled compound . Reddish brown powder (1.1g, 83% yield), UV – visible (EtOH) λ_{max} (nm) (ε) 278 (2111), 492 (270) IR (KBr) ν_{max} (cm^{-1}) 3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=N), 721 (C-Br). ^{1}HNMR (δ,ppm) 9.9(d,2H),7.4(d,2H), 7.2(d,1H), 7.1(d,4H), 8.0(d,1H),2.6(s,3H). ^{13}CNMR δ 178(C=O), 165(C=N), 138(C=C), 40(C-C), MS (m/z, % int) 432(M^+,40),434(M^++2,25),357(-Br,30), 281(-Ph,55), 266(-Me,25). Anal calculated for $C_{22}H_{13}N_2OSBr$, C, 61.11; H, 3.01; N, 6.48; S, 7.41; Br = 18.29. Found: C, 70.00; H, 2.98; N, 6.39; S, 7.40, Br, 18.53.

2.5.4 Synthesis of 8-Methyl-6-(3-nitrophenyl)-11-azabenzo[a]phenothiazin-5-one (5d)

A mixture of 3-nitrophenylboronic acid (0.65 g, 3.9 mmol), 6-chloro-8-methyl-11-azabenz0[a]phenothiazin-5-one (0.94 g, 3.0 mmol), $NiCl_2(PPh_3)_2$ (0.03 g, 0.09 mmol), PPh_3 (0.06 g, 0.18 mmol) and $K_3PO_4.2H_2O$ (0.64 g, 3.0 mmol) was refluxed in DMA for 5 hours to obtain the titled compound, a brownish powder which melted with decomposition at 138-139 ^{0}C (1.12 g, 86 % yield) , UV – visible (EtOH) λ_{max} (nm) (ε) 286 (441), 428 (653), 493 (536) IR (KBr) ν_{max} (cm^{-1}) 3062, 2964, 1641, 1569, 1537, 1459, 1214. MS (m/z,% int) 399(M^+,50), 353(-NO_2,30), 338(-Me,60), 262(-Ph,100) Calculated for $C_{22}H_{13}N_3O_3S$, C, 66.17; H, 3.26; N_3, 10.53; O, 12.03; S, 8.02. Found: C, 66.27; H, 3.30; N, 10.60; S, 8.00.

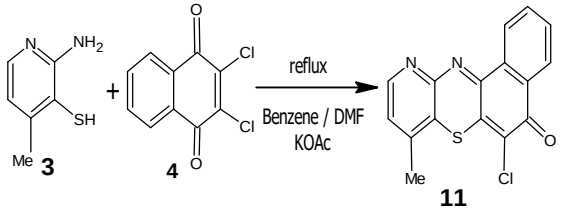
3. Results and Discussion

Thiocyanation of 2-amino-4-methylpyridine **1** was achieved indirectly by first brominating to obtain the 3-bromo derivative as earlier attempt at direct thiocyanation using potassium thiocyanate and bromine in glacial acetic acid at 0^{0}C gave very low yield of the product[14]. The 3-bromoderivative was then refluxed in aqueous potassium thiocyanate to obtain the 3-thiocyanated derivative which was subsequently converted 2-amino-4-methyl-pyridine-3-thiol **3** by base catalyzed hydrolysis and this is represented by scheme 1 below.



Scheme 1: Conversion of 2-amino-4-methylpyridine to give 2-amino-4-methylpyridine-3-thiol

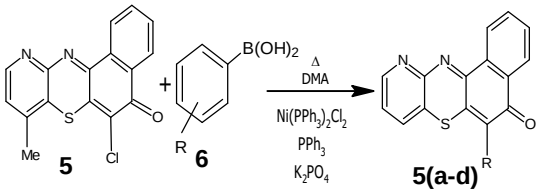
An equimolar mixture of properly dried 2-amino-4-methyl pyridine-3-thiol **3** and 2,3-dichloro-1,4-naphthoquinone **4** in benzene (mixed with little DMF) was treated with anhydrous potassium acetate and



Scheme 2: Preparation of 6-choloro-8-methyl-11-anabenzo[a]phenothiazine

The aryl derivatives of compound **5** were obtained by cross-coupling compound **5** with arylboronic acids in the prescence of $K_3PO_4.2H_2O$ as base under the catalytic influence of bis(triphenylphosphine)nickel(II) chloride and triphenylphosphine mixed in the ratio of 1:2. The solvent employed was DMA while maintaining the refluxing temperature at 80^0C for 4 hours

3.1 Synthesis of 6-aryl derivatives of compound 5a-d



R = (a) C_6H_5
(b) 3-ClC_6H_4
(c) 3-BrC_6H_4
(d) 3-$NO_2C_6H_4$

Scheme 3: Preparation of 6-aryl derivatives of 6-chloro-8-methylazabenzo[a]phenothiazin-5-one **5**(a-d). The structures assigned to the synthesized compounds were supported by the spectral and micro analytical data.

Table 1: Physical and analytical data of compounds

Compound	Melting point (^{0}C)	Colour	Percentage yield (%)	Elemental analysis Calculated: Found:
5	278	Red	88	C = 61.44, H = 2.87, N = 8.96, O = 5.12, S = 10.24 Cl = 11.36, C = 61.60; H = 2.84; N = 8.93; S = 10.40; Cl = 11.42.
5a	119-120	Intense red	75	C = 74.58, H = 3.95 N = 7.61, O = 4.52, S = 9.04. C=74.61; H= 4.00; N= 7.85; S= 9.15.
5b	130-132	Dark red	80	C = 67.95, H = 3.35, N = 7.21, O = 4.12, S = 8.24, Cl = 9.14. C, 66.79; H, 3.60; N,7.49; S, 8.52; Cl, 9.48.
5c	138-140	Reddish brown	83	C = 61.11, H = 3.01, N = 6.48 O = 3.70, S = 7.41 Br = 18.29. C= 70.00; H= 2.98; N=6.39; S=7.40, Br= 18.53.
5d	138-139	brown	86	C = 66.17, H = 3.26, N3 =10.53,O= 2.03, S = 8.02. C, 66.27; H, 3.30; N, 10.60; S, 8.00.

Table 2: Spectral data of compounds

Compound	UV-Visible(EtOH) λmax (ε)	IR (KBr) νmax (cm^{-1})	^{1}HNMR ($_{\delta}$DMSO)δ	^{13}CMR (δDNMSO)δ	Mass spec (m/z, % intensity)
5	269, and 449 nm	1636, 1547, 1486 and 1430.	7.9(m,1H) 7.8(m,1H) 7.5(m,2H) 7.1(m,2H) 2.5(s,3H)	175, C=O 40,C-C	312 (M^{+}, 35%), 314 (M+2, 10%), 287(-Cl,70%)
5a	268 (1547), 449 (562)	3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=N)	7.7(2H) 7.6(s,10H) 2.5(s,3H)		354(M^{+}, 100) 277(-Ph,75) 262(-Me,35)
5b	268 (1541), 449 (562)	1633 (C=O), 1542, 1431 (C=C, C=N), 1130 (C-N)	8.6(m,2H) 8.1(d,1H) 8.0(d,3H) 7.5(m,4H) 2.5(s,3H)	175(C=O) 163(C=N) 130(C=C)	389 (M^{+},70) 391(M^{+} 2,50) 354(-Cl,20) 278(-Ph,30).
5c	278 (2111), 492 (270)	3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=N), 721 (C-Br)	9.9(d,2H) 7.4(d,2H) 7.2(d,1H) 7.1(d,4H) 8.0(d,1H) 2.6(s,3H)	178(C=O) 165(C=N) 138(C=C) 40(C-C)	432(M+,40) 434(M++2,25) 357(-Br,30) 281(-Ph,55) 266(-Me,25)
5d	(441), 428 (653), 493 (536)	3062, 2964, 1641,C=O 1569, 1537, 1459, 1214	7.6(4H) 7.5(3H) 7.4(5H) 2.5(3H)	185(C=O) 145(C=N) 135,111(C=C) 40(C-C)	339(M+,50) 353(-NO2,30) 338(-Me,60) 262(-Ph,100)

4. Future Scope

The intense colour of these compounds suggests that they could be used as dyes. Studies of their dying potential and screening them to determine their antimicrobial activities is ongoing in our laboratory

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