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]phenothiazin-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-dichloronaphthoquinone, 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 biological activities [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 catalysts to 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-aryl substituted 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-methylpyridine (3.8 g, 0.03 mol) was placed in a 500 cm³ two – necked flask containing 50% of methanol (50 cm³). Sodium hydrogen carbonate (8.4 g, 0.1 mol) was added and bromine (5 cm³) was added from a dropping funnel for 40 min while stirring. An additional NaHCO₃ (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 cm³ of hot water stirred until it dissolved, potassium thiocyanate (6.0 g, 0.06 mol) in 30 cm³ of water was added and refluxed for 3 h. The reaction mixture was cooled, filtered and the residue was 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°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 cm³ reaction flask equipped with a reflux condenser. Sodium hydroxide solution (20%, 50 cm³) 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 desiccator to obtain 2-amino-4-methylpyridine-3-thiol (2.9 g, 70%); mp 207°C (IR (KBr) νmax 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-methylpyridine-3-thiol3 (0.7 g, 5.0 mmol), anhydrous potassium carbonate (1.4 g, 10 mmol), 40 cm³ of benzene and 4 cm³ of DMF were added into a two necked flask and stirred with heating for 45 mins. 2, 3-dichloro-1, 4-naphthoquinone4 (1.2 g, 5.0 mmol) was added to the reaction mixture. The mixture was refluxed at 75°C – 80°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 1.48% (88%)  M p = 278°C. UV (EtOH) λ max 269, and 449 nm, IR (KBr) νmax (cm⁻1) 1636, 1547, 1486 and 1430. 1H-NMR (d DMSO) (δ, ppm) 3.8, 7.5. 13C-NMR (d DMSO) (δ, ppm) 175, 40. MS (m/z, % int) 389 (M⁺), 391(M⁺2,50),354(CI,20), 278-(Ph,30). Anal calculated for C₃H₉N₄O₅S, 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 Synthesis of 6-aryl-8-methyl-11-azabenzo[a]phenothiazin-5-one (5 a-d)

NiCl₃(PPh₃)₂ (0.03 g, 0.09 mmol) was added to PPh₃ (0.06 g, 0.18 mmol) and flushed with nitrogen gas. Then 10 cm³ of DMA was added and flushed again with nitrogen gas. DMA (10 cm³) was added and flushed again with nitrogen gas while stirring and heating for 20 min. Arylboronic acids (3.9 mmole), K₂PO₄.2H₂O (0.64 g, 3.0 mmol) and 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.0 mmol) were added and refluxed at 80°C for 5 h. The product was extracted with ether, washed with 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), NiCl₃(PPh₃)₂ (0.03 g, 0.09 mmol), PPh₃ (0.06 g, 0.18 mmol) and K₂PO₄.2H₂O (0.64 g, 3.0 mmol) was refluxed in DMA for 5 hours at 80°C. An intense red powder (0.80 g, 75%) which melted with decomposition at 119-120°C was obtained. UV – visible (EtOH) λ max (nm) (ε) 268 (1547), 449 (562), IR (KBr) νmax (cm⁻1) 3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=C, N), 1HNMR (δ, ppm) 7.7(2H),7.6(10H), 2.5(3,H). MS (m/z, % int) 354(M⁺), 100,277(Ph,75), 262-(Me,35). Analy calculated for C₂₂H₂₉N₄OS, 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 6-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), NiCl₃(PPh₃)₂ (0.03 g, 0.09 mmol), PPh₃ (0.06 g, 0.18 mmol) and K₂PO₄.2H₂O was refluxed in 20 cm³ of DMA at 80°C for 5 hours. The crude product was extracted with ether, washed with water and dried over MgSO₄. It was concentrated to a small bulk and allowed to evaporate leaving a dark-red powder (0.93 g, 80%), mp 130 – 132°C. UV – visible (EtOH) λ max (nm) (ε) 268 (1541), 449 (562), IR (KBr) νmax (cm⁻1) 1633 (C=O), 1542, 1431 (C=C, C=N), 1130 (C-N). 1HNMR (δ, ppm) 8.6(m,2H), 8.1(d,1H), 8.0(d,3H), 7.5(m,4H), 2.5(s,3H). 13CNMR (δ,ppm) 175(C=O), 163(C=N), 130(C=C). MS (m/z, % int) 389 (M⁺), 391(M⁺2,50),354(CI,20), 278-(Ph,30). Anal calculated for C₃H₉N₄O₅S, 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), NiCl₃(PPh₃)₂ (0.03 g, 0.09 mmol), PPh₃ (0.06 g, 0.18 mmol) and K₂PO₄.2H₂O (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) νmax (cm⁻1) 3002 (C-H, aromatic), 1671 (C=O), 1585, 1532, 1467 (C=C, C=N), 721 (C-Br). 1HNMR (δ, ppm) 9.9(d,2H),7.4(d,2H), 7.2(d,1H), 7.1(d,4H), 8.0(d,1H),2.6(3,H). 13CNMR 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). Analy calculated for C₂₂H₁₈N₄O₂Br. C, 63.11; H, 2.74; 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-nitrophenoxy)-11-azabenzo[a]phenothiazin-5-one (5d)

A mixture of 3-nitrophenoxyboronic acid (0.65 g, 3.9 mmol), 6-chloro-8-methyl-11-azabenzo[a]phenothiazin-5-one (0.94 g, 3.0 mmol), NiCl₃(PPh₃)₂ (0.03 g, 0.09 mmol), PPh₃ (0.06 g, 0.18 mmol) and K₂PO₄.2H₂O (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°C (1.12 g, 86% yield), UV – visible (EtOH) λ max (nm) (ε) 286 (441), 428 (653), 493 (536) IR (KBr) νmax (cm⁻1) 3062, 2964, 1614, 1569, 1537, 1459, 1214. MS (m/z, % int) 399(M⁺), 353(NO,30), 338-(Me,60), 262-(Ph,100) Calculated for C₂₃H₂₃NO₂S, C, 66.17; H, 3.26; N, 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°C gave very low yield of the product14. 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.
The aryl derivatives of compound 5 were obtained by cross-coupling compound 5 with arylboronic acids in the presence of K$_3$PO$_4$.H$_2$O 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°C for 4 hours.

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

![Scheme 1](image1)

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

An equimolar mixture of properly dried 2-aminoo-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](image2)

**Scheme 2:** Preparation of 6-chloro-8-methyl-11-anabeno[a]phenothiazine

**Table 1:** Physical and analytical data of compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Melting point (°C)</th>
<th>Colour</th>
<th>Percentage yield (%)</th>
<th>Elemental analysis Calculated: Found:</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>278</td>
<td>Red</td>
<td>88</td>
<td>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.</td>
</tr>
<tr>
<td>5a</td>
<td>119-120</td>
<td>Intense red</td>
<td>75</td>
<td>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.</td>
</tr>
<tr>
<td>5b</td>
<td>130-132</td>
<td>Dark red</td>
<td>80</td>
<td>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.</td>
</tr>
<tr>
<td>5c</td>
<td>138-140</td>
<td>Reddish brown</td>
<td>83</td>
<td>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.</td>
</tr>
<tr>
<td>5d</td>
<td>138-139</td>
<td>brown</td>
<td>86</td>
<td>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.</td>
</tr>
</tbody>
</table>
Table 2: Spectral data of compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>UV-Visible(EtOH) λmax (c)</th>
<th>IR (KBr) νmax (cm⁻¹)</th>
<th>¹HNMR (δDMSO)δ</th>
<th>¹³CNR (δDMSO)δ</th>
<th>Mass spec (m/z, % intensity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>269, and 449 nm</td>
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<td>7.9(m,1H)</td>
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<td>40,C-C</td>
</tr>
<tr>
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<td>268 (1547), 449 (562)</td>
<td>3002 (C=H, aromatic), 1671(C=O), 1585, 1532, 1467(C=C, C=O)</td>
<td>7.7(2H)</td>
<td>163(C=O)</td>
<td>130(C=O)</td>
</tr>
<tr>
<td>5b</td>
<td>268 (1541), 449 (562)</td>
<td>1633 (C=O), 1542, 1431 (C=C, C=O), 1130 (C-N)</td>
<td>8.6(m,2H)</td>
<td>165(C=O)</td>
<td>138(C=O)</td>
</tr>
<tr>
<td>5c</td>
<td>278 (2111), 492 (270)</td>
<td>3002 (C=H, aromatic), 1671(C=O), 1585, 1532, 1467(C=C, C=O)</td>
<td>7.6(4H)</td>
<td>165(C=O)</td>
<td>138(C=O)</td>
</tr>
<tr>
<td>5d</td>
<td>(441), 428 (653), 493 (536)</td>
<td>3062, 2964, 1641(C=O 1569, 1537, 1459, 1214</td>
<td>7.6(4H)</td>
<td>185(C=O)</td>
<td>145(C=O)</td>
</tr>
</tbody>
</table>

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.

References


