An efficient approach for Ni-Catalyzed cross coupling of 6-chloro-8-azabenzo[a]phenoxazin-5-one and aryl boronic Acids

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Abstract: The synthesis of a new angular monoazabenzo[a]phenoxazine and its substituted aryl derivatives via nickel catalyzed system is reported. This was achieved by the condensation of 3-amino-2-pyridine and 2, 3-dichloro-1,4-napthaquinone in anhydrous basic medium to produce a new heterocycle, 6-chloro-8-azabenzo[a]phenoxazin-5-one as an intense brown product in 64.77% yield. Upon applying, Suzuki - Miyaura cross coupling reaction it resulted to the synthesis of some new aryl derivatives which were obtained in good yields.

Keywords: Angular benzo[a]phenoxazine, nickel, arylation, condensation, Suzuki-Miyaura reaction, synthesis, aryl derivatives

I. Introduction

The use of angular phenoxazine compounds as natural antibiotics [1,2], dyes and pigments [6, 9, 10]; photo-sensitizers [3, 11], chemotherapeutics [5], imaging agents [16] has been recognized. Okafor C. O and co-workers have published numerous spectroscopic and synthetic studies relating to various members of this class, culminating into absolute stereochemical assignments. Although much is known about the isomeric forms of benzo[a]phenoxazine, very little is known about the synthesis of its aza-analogues which are key structures in numerous synthetic compounds having therapeutic importance. In the present study, we have synthesized some series of azabenzo[a]phenoxazines derivatives (7a to 7e) using 6-chloro-8-azabenzo[a]phenoxazin-5-one (3) substituted with aryl boronic acids via nickel-based catalyst system.

II. Materials and Methods

1.1 Material: All the bromo, nitro, chloro and phenylboronic acids, hydrated tribasic potassium phosphate, triphenylphosphine (ligand) were purchased from Sigma-Zayo Chemical Company in sure-seal bottles and were used as received. Compound 3 and compounds 7a to 7e used in this work were synthesized in our laboratory.

1.2 Synthesis of Compound 3: 3-Amino-2-pyridine (2.8g, 0.025 mol), benzene (20mL), DMF (5mL) and sodium acetate (1.0g) were placed in a 250mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser. The mixture was stirred while heating on a water bath at 70 - 75°C for 45 minutes. After which, the flask was charged with 2,3-dichloro-1,4-napthaquinone (7.5g, 0.033 mol) and the resulting mixture was stirred with heating at 70 - 75°C for 6 hours. At the end of 6 hours, the solvent was allowed to evaporate and the residue taken up in water, and worked up to leave an intense brownish crystalline powder which was collected and re-crystallized from methanol to give the desired product (3) as a dark brown solid (1.26g, 64.77%). m.p, 278 - 279°C; IR (KBr): 3358.18, 1530.57, 1265.35, 1129.36, 793.73, 709.83; 1H NMR [DMSO-d6, 200 MHz] δ: 8.20 (d, C 8, 4 protons); 7.90 (d, C-3 and C-4 protons); 7.90 (d, C-3 and C-6 protons), 2.5 (s, DMSO); 13C NMR [DMSO-d6, 50 MHz] δ: 173.71 (>C=O), 140.12 (>C=C< and >C=N), 123.87-122.40 (C of aromatic ring); HRMS [ESI] calculated for C21H12ClN2O2 [M+H+]: 282.6813; Found: 282.6593.

1.3 Synthesis of Compound 7a: This compound was prepared from 3 (2.5g, 0.0088 mol), 3-nitrophenvloboronic acid (0.261g, 0.0013 mol) and hydrated tribasic potassium phosphate (0.598g, 0.0026 mol) placed in a Nere flask containing nickel (0) complex treated with zinc dust (0.26g). The flask was thoroughly flushed with nitrogen gas and charged with toluene (2 mL). The resulting mixture was stirred at 80°C for 2 hours under nitrogen atmosphere. The product obtained was collected by filtration, recrystallized with methanol and dried in a dessicator to give the desired product 7a as a dark brown solid (1.25g, 66.30%). m.p. 237- 239°C; IR(KBr): 3339, 1595, 1454, 1326, 1054, 705, 626, 529, 397; 1H NMR [DMSO-d6, 200 MHz] δ: 8.40 (d, s, C-2 and C-4 protons); 7.80 (s, b, C-3 and C-9 protons); 3.50 (s, b, 1H, >NH) and 2.50 (s, DMSO); and 13C NMR
1.4 Synthesis of Compound 7b: This compound was prepared from 3 (2.5g, 0.0088 mol), 3-chlorophenylboronic acid (0.261g, 0.0013 mol) and hydrated tribasic potassium phosphate (0.598g, 0.0026mol) placed in a Nefsk flask containing nickel (0) complex as described for compound 7a. It was obtained as a light brown crystalline powder (1.26g, 66.31%), m.p. 238 - 240 °C; IR[KBr]: 3476, 3058, 235, 1918, 1609, 1449, 1326, 1178, 1039, 717, 619, 525; ¹H NMR [DMSO – d₆, 200 MHz] δ: 8.80 (d, C-2 and C-4 protons), 7.90 (d, C-3 and C-9 protons), 7.60 (m, 4H, Ar-H), 3.50 (s, b, 1H, >NH) and 2.50 (s, DMSO); ¹³C NMR [DMSO-d₆, 50 MHz] δ: 142 (>C=C< and >C=N) and 130 - 126 (C of aromatic ring); HRMS [ESI] calculated for C₂₁H₁₇N₃O₂ [M+H⁺]: 369.3320; Found: 369.333.

1.5 Synthesis of Compound 7c: This compound was prepared from 3 (2.5g, 0.0088 mol), 3-bromophenylboronic acid (0.261g, 0.0013 mol) and hydrated tribasic potassium phosphate (0.598g, 0.0026 mol) placed in a Nefsk flask containing nickel (0) complex as described for compound 7a. It was obtained as a dark brown crystalline powder (1.25g, 67.34%), m.p. 288 - 290 °C; IR [KBr]: 3856, 2362, 1659, 486: ¹H NMR [DMSO-d₆, 200 MHz] δ: 8.20 (d, C-2 and C-4 protons), 7.90 (d, C-3 and C-6 protons), 3.40 (s, b, 1H, >NH) and 2.50 (s, DMSO); ¹³C NMR [DMSO-d₆, 50 MHz] δ: 176.38 (>C=O), 142.87 (>C=C< and >C=N) and 131.39 - 127.54 (C of aromatic ring); HRMS [ESI] calculated for C₂₁H₁₉BrN₂O₂ [M+H⁺]: 358.7772; Found: 358.7778.

1.6 Synthesis of Compound 7d: This compound was prepared from 3 (2.5g, 0.0088 mol), 4-bromophenylboronic acid (0.261g, 0.0013 mol) and hydrated tribasic potassium phosphate (0.598g, 0.0026 mol) placed in a Nefsk flask containing nickel (0) complex as described for compound 7a. It was obtained as brown crystalline powder (1.28g, 66.64%), m.p. 225 - 228 °C; IR [KBr]: 4564, 4403, 4065, 3053, 1591, 1440, 1085, 866, 728, 529 cm⁻¹; ¹H NMR [DMSO-d₆, 200 MHz] δ: 8.25 (d, C-2 and C-4 protons), 8.10 (d, C-3 and C-4 protons), 3.40 (s, b, 1H, >NH) and 2.50 (s, DMSO); ¹³C NMR [DMSO-d₆, 50 MHz] δ: 176.38 (>C=O), 143.88 (>C=C< and >C=N) and 134.38-129.54 (C of aromatic ring); HRMS [ESI] calculated for C₂₁H₁₉BrN₂O₂ [M+H⁺]: 403.2282; Found: 403.2293.

1.7 Synthesis of Compound 7e: This compound was prepared from 3 (2.5g, 0.0088 mol), phenylboronic acid (0.261g, 0.0013 mol) and hydrated tribasic potassium phosphate (0.598g, 0.0026 mol) placed in a Nefsk flask containing nickel (0) complex as described for compound 7a. It was obtained as brown crystalline powder (1.28g, 64.34%), m.p. 256 - 258 °C; IR: 344, 1652, 1449, 1040, 712, 609 cm⁻¹; ¹H NMR [DMSO-d₆, 200 MHz] δ: 8.40 (d, C-2 and C-4 protons), 7.90 (2, C-3 and C-9 protons), 8.00 – 7.80 (m, 5H, Ar-H), 3.40 (s, b, 1H, >NH) and 2.50 (s, DMSO); ¹³C NMR [DMSO-d₆, 50 MHz] δ: 173.71 (>C=O), 143.87 (>C=C< and >C=N) and 131.40 - 127.53 (C of aromatic ring); HRMS [ESI] calculated for C₂₁H₁₇N₂O₂ [M+H⁺]: 323.3322; Found:323.3324.

III. Results And Discussion

In furtherance to the studies on angular benzo[a]phenoxazine and its derivatives, it was reasoned that the synthesis from readily available 3-amino-2-pyridone and 2, 3-dichloro-1, 4-naphthaquinone would serve as appropriate precursors. The benzene-DMF induced reaction exclusively furnished the desired intermediate 3 in 64.77% yields via a selective intermolecular condensation and intramolecular cyclization pathway.

[Diagram of Structure of compound 3]

The mechanism of the reaction result from the formation of the oxide ion 4, which mounts a nucleophilic attack on the halogen atom of the napthaquinone to form oxide 5. Cyclization of 5 by the nucleophilic attack of the amino group on the carbon of the carbonyl gave 6. Due to proton migration it results to lose of water molecules leading to the intermediate 3.
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The selective zinc promoted Suzuki-Miyaura reaction of nickel (II) complex which on an in situ arylation with varied aryl boronic acids under nitrogen atmosphere gave the required aryl-aza-benzo[a]phenoxazine derivatives 7a to 7e.

The Suzuki-Miyaura reaction of masked angular benzo[a]phenoxazine 3 results in the overall substitution of the chloride group in 3 by the aryl group. The chemical structures of all new synthesized compounds 3, 7a to 7e were confirmed by FTIR, $^1$H NMR, $^{13}$C NMR, mass spectral and found appreciable yields with satisfactory spectral data in good agreement with the assigned structure. Physical data of all the synthesized aryl compounds have been tabulated in Table 1.
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<table>
<thead>
<tr>
<th>Compd</th>
<th>Substrate</th>
<th>Aryl boronic acids</th>
<th>Mol Formula</th>
<th>Mol Wt</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>6-chloro-8-aza...</td>
<td>3-nitrophenylboronic</td>
<td>C_{21}H_{13}N_{5}O_{4}</td>
<td>369.3320</td>
<td>237–239</td>
<td>66.30</td>
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<tr>
<td>7b</td>
<td>6-chloro-8-aza...</td>
<td>3-chlorophenylboronic</td>
<td>C_{21}H_{13}N_{5}O_{4}</td>
<td>358.7772</td>
<td>238–240</td>
<td>66.31</td>
</tr>
<tr>
<td>7c</td>
<td>6-chloro-8-aza...</td>
<td>3-bromophenylboronic</td>
<td>C_{21}H_{13}BrN_{5}O_{4}</td>
<td>403.2282</td>
<td>288–290</td>
<td>67.34</td>
</tr>
<tr>
<td>7d</td>
<td>6-chloro-8-aza...</td>
<td>4-bromophenylboronic</td>
<td>C_{21}H_{13}BrN_{5}O_{4}</td>
<td>403.2282</td>
<td>225–228</td>
<td>66.64</td>
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<tr>
<td>7e</td>
<td>6-chloro-8-aza...</td>
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<td>C_{21}H_{13}N_{5}O_{4}</td>
<td>324.3322</td>
<td>256–258</td>
<td>64.34</td>
</tr>
</tbody>
</table>

### IV. Conclusion
In summary, one intermediate 3 and five derivatives 7a to 7e were synthesized in good yields using 1 mol percent nickel and with reaction time of 2 hour under nitrogen atmosphere. The approach is general in nature and will be useful to design the focused mini-library of analogues and congeners for SAR studies.

### Acknowledgement
The authors’ wishes to express their gratitude to Professor U. C. Okoro for his advice, encouragement and contribution to this research study.

### References


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