Palladium-Catalysed Intramolecular C–N versus C–C Coupling: The Effect of 1,8-\textit{peri}\-Interaction in the Naphthalene System

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Abstract Palladium-catalysed competitive intramolecular C–N and C–C coupling of 2-amino-2′-bromodiarylsulfones has been carried out based on 1,8-\textit{peri}\-interactions for the synthesis of phenothiazinedioxide and benzonaphthathiophenedioxide derivatives. A DFT study has been performed that provides support for the influence of the 1,8-\textit{peri}\-interaction.

Key words naphthalene, 1,8-\textit{peri}\-interaction, cyclization, fused-ring, heterocycles

Due to the rigidity of the naphthalene skeleton, the substituents on 1- and 8-positions are forced to be relatively close, at 2.5 Å, which is within the van der Waals radius for many atoms. In contrast, ortho-substituents on a benzene ring are separated by 3.3 Å.\textsuperscript{1} This 1,8-interaction of naphthalenes, also known as a \textit{peri}\-interaction, results in some unique reactivity compared with substituted benzene derivatives.

During our continuing studies on developing novel synthetic routes to heterocycles,\textsuperscript{2} we have prepared phenothiazine dioxides and benzothiophene dioxides are important classes of heterocycles because of their applications in medicinal and materials chemistry (Figure 1).\textsuperscript{3} Moreover thiazine and thiophene cores are also found in various biologically active natural products and synthetic drugs.\textsuperscript{4}

We began this work with 2-amino-2′-bromodiarylsulfones 7, which were prepared from the corresponding 2-bromo-N-alkyl-N-arylenzenesulfonamide derivatives 6 according to our reported procedure (Scheme 1).\textsuperscript{5}
2-Amino-2′-bromodiaryl sulphone 7a was treated with Pd(OAc)_2 catalyst in DMF using Cs_2CO_3 as base at 100 °C for 1 h to effect intramolecular C–N coupling, leading to phenothiazine dioxide 8a in 78% yield. We then optimised the reaction conditions by varying the Pd catalyst, base, solvent, additive, temperature and time. The summarised results are presented in Table 1. Among the three Pd catalysts examined, Pd(OAc)_2 provided the best result. Changing base from Cs_2CO_3 to K_2CO_3 led to a notable decrease in yield; whereas KOAc proved more effective. Among different solvents, DMF showed the best results compared with toluene and DMA. The addition of TBAB did not show any improvement in yield. Increasing time or temperature led to little a slight lowering of reaction yields. At low temperatures (50–70 °C), the reaction did not proceed even with extended reaction periods (entries 15 and 16). Increasing the temperature to 85 °C led to a 30% yield of product. The effect of catalyst loading was also studied and we observed the best result using 5 mol% Pd(OAc)_2 as catalyst, 2.5 equivalents KOAc as base, DMF as solvent at 100 °C for 1 h, obtaining phenothiazine dioxide in 96% yield (entry 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. System (mol%)</th>
<th>Baseb</th>
<th>Solvent</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)_2 (10)</td>
<td>Cs_2CO_3</td>
<td>DMF</td>
<td>–</td>
<td>1</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>Pd(P(Ph)_3)Cl_2 (10)</td>
<td>Cs_2CO_3</td>
<td>DMF</td>
<td>–</td>
<td>1</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)_3 (10)</td>
<td>Cs_2CO_3</td>
<td>DMF</td>
<td>TBAB</td>
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<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)_2 (10)</td>
<td>Cs_2CO_3</td>
<td>DMF</td>
<td>–</td>
<td>1</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)_2 (10)</td>
<td>Cs_2CO_3</td>
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<tr>
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<td>Cs_2CO_3</td>
<td>DMF</td>
<td>TBAB</td>
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<td>100</td>
<td>55</td>
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<tr>
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<td>K_2CO_3</td>
<td>DMF</td>
<td>–</td>
<td>1</td>
<td>100</td>
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<td>KOAc</td>
<td>DMF</td>
<td>–</td>
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<td>9</td>
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<td>DMF</td>
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<td>TBAB</td>
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<td>DMA</td>
<td>–</td>
<td>2</td>
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<td>78</td>
</tr>
<tr>
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<td>DMF</td>
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<td>DMF</td>
<td>–</td>
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<td>100</td>
<td>70</td>
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<td>Pd(OAc)_2 (5)</td>
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<td>DMA</td>
<td>–</td>
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<td>50</td>
<td>np</td>
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<td>Pd(OAc)_2 (5)</td>
<td>KOAc</td>
<td>DMA</td>
<td>–</td>
<td>4</td>
<td>70</td>
<td>np</td>
</tr>
<tr>
<td>17</td>
<td>Pd(OAc)_2 (5)</td>
<td>KOAc</td>
<td>DMA</td>
<td>–</td>
<td>4</td>
<td>85</td>
<td>30</td>
</tr>
</tbody>
</table>

a All reactions were carried out in a sealed tube under nitrogen. 
b In every case 2.5 equivalents of base were used. 
c np = no product

After optimising the reaction conditions, 2-amino-2′-bromodiaryl sulphone derivatives 7b–g were used for the preparation of the corresponding phenothiazine dioxide derivatives 8b–g. For compounds 7b–e the corresponding phenothiazine dioxides 8b–e were formed in excellent yields under the optimised reaction conditions (Scheme 2); however, for substrates 7f and 7g a different reaction course took place. The 1H NMR spectra of the products obtained from precursors 7f and 7g showed the N-H proton to be present and one aromatic proton was absent; whilst the 13C NMR spectra revealed the presence of two additional fully substituted aromatic carbon atoms. These data indicate that, for precursors 7f and 7g, intramolecular C–C coupling had occurred instead of intramolecular C–N cou-
During cyclisation of compounds 7a–f, two different modes of cyclisation, C–N and C–C, are possible. However, between these two possibilities, C–N coupling is preferred for compounds 7a–e. A plausible mechanism for the formation of compounds 8a–e is shown in Scheme 3. Initially, Pd(OAc)$_2$ is reduced to give the active Pd(0) species, which complexes with 7a–e via coordination with nitrogen to form aryl palladium intermediates 9a–e. The intermediate then leads to the phenothiazine dioxide derivatives 8a–e via oxidative addition followed by reductive elimination.

When compounds 7f and 7g were treated under the same reaction conditions, C–C coupling was observed instead of C–N coupling, leading to benzonaphthathiophene dioxide derivatives 8f and 8g (Scheme 4). A plausible mechanism for the formation of 8f and 8g is shown in Scheme 5. Here N-Pd complex 11 is not formed, which may be due to the peri-interaction between H-8 and the 1-alkyl-NPd group. Instead, Pd(0) first undergoes oxidative addition to form intermediates 12f and 12g, which then lead to the benzonaphthathiophene dioxide derivatives 8f and 8g via carbopalladation followed by elimination of PdBr.

We performed DFT calculations to investigate the 1,8 peri-interaction in naphthalene systems and the results support the mechanism depicted in Scheme 5 for C–C coupling. All calculations were performed with the Gaussian09 program package using hybrid density functional (B3LYP) theory and the 6-31G(d) basis set. For Pd, the LanL2DZ basis set was used with LanL2 effective core potential. This DFT study shows that the formation energy of complex 11 from the anion of 7f is ~420.48 kcal mol$^{-1}$; whereas the formation energy of intermediate 12 is ~490.33 kcal mol$^{-1}$. This indicates that the formation of intermediate 12 is more energetically favourable than that of complex 11 by 69.85 kcal mol$^{-1}$. This could explain why the reaction passes through the successive oxidative addition of Pd(0) to the C-Br bond,
carbopalladation and elimination of PdBr to give the corresponding benzonaphthathiophene dioxides $8f$ and $8g$ instead of phenothiazine dioxides $8f'$ and $8g'$.

In conclusion we have synthesised phenothiazine dioxides $8a$–$e$ and benzonaphthathiophene dioxides $8f$ and $8g$ by Pd-catalysed intramolecular C–N and C–C coupling reactions, respectively. The effect of the 1,8-peri-interaction in the naphthalene system was investigated by DFT calculations and the results support the observed outcomes.

**Synthesis of 7e**

Compound 7e was prepared according to the previously reported procedure.5

IR (KBr): 2934, 1578, 1478, 1269, 1145, 832, 752, 568 cm$^{-1}$.

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{15}$H$_{17}$BrNO$_2$S$: 290.0845; found: 290.0744.

**10-Ethyl-3-methyl-10H-phenothiazine 5,5-dioxide (8b)**

Yield: 92%; white solid; mp 136–138 °C.

**3-Methoxy-10-methyl-10H-phenothiazine 5,5-dioxide (8c)**

Yield: 95%; white solid; mp 168–170 °C.

**10-Ethyl-3-methoxy-10H-phenothiazine 5,5-dioxide (8a)**

A solution of 7a (200 mg, 0.59 mmol) in anhydrous DMF (2 mL) and KOAc (115 mg, 1.17 mmol) was purged with nitrogen for 10 min. Pd(OAc)$_2$ (7 mg, 5 mol%) was then added and the mixture was heated to 100 °C for 1 h in a sealed tube. The reaction mixture was cooled, H$_2$O (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were washed with H$_2$O (10 mL) brine (10 mL), and dried (Na$_2$SO$_4$). The solvent was distilled off to furnish a viscous residue that was purified by column chromatography (EtOAc/petroleum ether, 1:4) on silica gel to yield compound 8a (146 mg, 96%) as a white solid; mp 149–151 °C.

IR (KBr): 2975, 1597, 1477, 1273, 1154, 748, 577 cm$^{-1}$.

HRMS (ESI): $m/z$ [M + H]$^+$ calcd for C$_{14}$H$_{14}$NO$_3$S$: 260.0740; found: 260.0743.

**260.0743.**
IR (KBr): 3404, 2967, 1554, 1280, 1135, 758, 542 cm⁻¹.

Yield: 82%; white solid; mp 183–185 °C.

**N-Methylbenzo[d]naphtho[2,3-b]thiophen-6-amine-5,5-dioxide (8f)**

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611667.

References


(6) The CCDC reference number for the CIF file of compound 8a is CCDC 1481104. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(7) The CCDC reference number for the CIF file of compound 8f is CCDC 1481105. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
