PALLADIUM CATALYSED CROSS COUPLING OF
PHENYLSULPHONYLGLUCALS WITH ARYL HALIDES

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Abstract - The lithiation of a number of 2-phenylsulphonylglucals and the resulting 2-arylglucals formed by subsequent Negishi cross coupling with simple aryl halides and desulphonation is described.

Many natural products that show antibiotic or antitumour activity can, at least in a formal sense, be classified as C-arylglycosides or 2-deoxy-C-arylglycosides, or compounds derived from the former by functional group transformation of the carbohydrate moiety. Furthermore, most of these compounds are C-pyranosides rather than C-furanosides. Examples of these natural products include lasalocid A, nogalamycin and chaetiacandin. Numerous synthetic methods, some involving the construction of the aryl-coupled carbohydrate moiety by indirect methods such as [2+4] cycloaddition reactions, have been developed to construct anomeric aryl C-C bonds. The most widely used direct methods involve the reaction of an electrophilic sugar with an electron rich aromatic compound. Among the numerous palladium-mediated reactions developed to assemble C-arylglycosides, a method which appears to have particular potential for wide application involves the cross coupling reaction between C-metallated glycals with aryl halides. The most popular method proceeds via lithiated glycals. However, numerous problems
with this lithiation reaction have been reported. The lithiation requires the use of a large excess of tert-butyllithium and furthermore only a limited amount of O-protecting groups are tolerant to this procedure.\textsuperscript{8,9} After transmetallation the lithiated glycals were subjected to Negishi\textsuperscript{10} or Stille cross couplings\textsuperscript{11} with moderate success.

We now report the preliminary results of an investigation based on the use of directing mettallation groups (DMG's),\textsuperscript{12} aimed at solving some of these problems. Firstly, attention was given to the lithiation of substrates of type (1).\textsuperscript{13}

\begin{align*}
1a & R_1 = R_2 = R_3 = H \\
1b & R_1 = CH_2OMe, R_2 = R_3 = OMe \\
1c & R_1 = CH_2OBn, R_2 = R_3 = OBn
\end{align*}

\[\text{DMG} = \text{OMe, OMOM, OCONe}_2, \text{SPh, SOPh, SO}_{2}\text{Ph,} \]

Compounds in which the DMG is OMe, OMOM and OCONe\textsubscript{2} could not be deprotonated without concomitant decomposition. In the cases where the DMG was SPh or SOPh, lithiation was accomplished with sec-butyllithium/TMEDA and LDA,\textsuperscript{14} respectively. In all other cases (DMG is ArSO\textsubscript{2}) complete lithiation was achieved with treatment with \(n\)-butyllithium (1.2 mol equiv) at -78 C in THF as evidenced by the near quantitative yields of products obtained by quenching with iodine, acetaldehyde or benzaldehyde.

The lithiated derivatives were transmetallated (ZnBr\textsubscript{2}) and subjected to Negishi cross coupling with aryl halides. The best results were obtained with \(SO_2\text{Ph}\) as DMG.

Phenylsulphonylation of dihydropyran, tri-O-methyl-d-glucal and tri-O-benzyl-d-glucal was accomplished by reaction with (i) acyloxsulphonium salt and treatment with triethylamine\textsuperscript{15} or (ii) addition of PhSCI and treatment with DBU (elimination of HCl)\textsuperscript{14} followed by oxidation with oxone and wet alumina\textsuperscript{16} to furnish compounds (2, 3, and 4), respectively, in yields exceeding 75%.
Compound (2) was treated with \( n \)-butyllithium (1.2 mol equiv) in THF at -78 °C, transmetallated with ZnBr\(_2\) (1.2 mol equiv) and subjected to cross coupling with 2-bromopyridine. A variety of palladium catalysts (5 mol %) (PdL\(_n\); L= phosphites, monodentate and bidentate phophines) and different solvents (THF, DME and ether) were explored (Scheme 1). The best results\(^{17}\) were obtained with Pd(PPh\(_3\))\(_2\)Cl\(_2\) in refluxing THF (6-12 h). The results of cross coupling of 2 with various aryl halides (1.5 mol equiv) are summarised in Table 1. The only other products were unchanged starting material and products (6) (<8%) resulting from cross coupling with the phenyl ring of 2.\(^{18}\) The yields of the desired products were generally satisfactory but Entry 3 suggests that steric hindrance results, as expected, in a significant drop in yields.\(^{19}\)

![Scheme 1](image)

**Scheme 1**

**Table 1. Negishi Cross Coupling of 2 with Aryl Halides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArX</th>
<th>Ar</th>
<th>Products (Yield, %)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>4-IC(_6)H(_4)Me</td>
<td>4-C(_6)H(_4)Me</td>
<td>5a (75) 6a (7)</td>
</tr>
<tr>
<td>2</td>
<td>4-IC(_6)H(_4)(CO(_2)Me)</td>
<td>4-C(_6)H(_4)(CO(_2)Me)</td>
<td>5b (70) 6b (5)</td>
</tr>
<tr>
<td>3</td>
<td>2-IC(_6)H(_4)(CO(_2)Me)</td>
<td>2-C(_6)H(_4)(CO(_2)Me)</td>
<td>5c (25) 6c (4)</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC(_6)H(_4)CN</td>
<td>4-C(_6)H(_4)CN</td>
<td>5d (81) 6d (5)</td>
</tr>
<tr>
<td>5</td>
<td>2-BrPy</td>
<td>2-Py</td>
<td>5e (73) 6e (7)</td>
</tr>
</tbody>
</table>
Comparable results were obtained by converting the lithiated 2 into the corresponding boronic acid, followed by Suzuki cross coupling\textsuperscript{20} under the specific conditions.\textsuperscript{21} It is of interest to note that the simple boronic acids (without a DMG) did not undergo cross coupling, but only dehydroboronation\textsuperscript{22} under these conditions. The 2-iodo compound obtained by the treatment of lithiated 2 with I\textsubscript{2} gave poor yields of coupled products using both Negishi and Suzuki methods.

The sulfonated glycals (3) and (4) were subjected to the above Negishi cross coupling conditions with three different aryl halides to give compounds (7) and (8), respectively, in yields in excess of 70% (Table 2).

![Chemical structures](image)

**Table 2. Negishi Cross Coupling of 3 and 4 with Aryl Halides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Product (Yield, %)</th>
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</thead>
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<tr>
<td>1</td>
<td>3</td>
<td>7a (72)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>7b (74)</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>7c (85)</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>8a (73)</td>
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<tr>
<td>5</td>
<td>4</td>
<td>8b (70)</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>8c (80)</td>
</tr>
</tbody>
</table>
The corresponding Suzuki cross coupling resulted in significantly lower yields of compounds (7) and (8). Both 7 and 8 could be desulphonated by reaction of an excess of SmI₂. However, a large excess of the reagent was required. Quantitative desulphonation was readily achieved with Mg turnings in the presence of a catalytic amount of HgCl₂ in MeOH at 50 °C to furnish compounds (9) and (10) in yields in excess of 95%. These compounds can be converted into 2-deoxy-C-arylglycosides or C-arylglycosides by hydrogenation or hydroboration/oxidation reactions, respectively.

The method described here therefore represents an alternative approach to an important class of natural products.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES


17. The use of more than 1 mol equiv of n-butyllithium resulted in some lithiation of the phenyl ring. Formation of the isomeric cross coupling products could be eliminated by reducing the n-butyllithium to 1 mol equiv. This resulted in an improved conversion into the desired products but not in overall yields.

18. BuLi (570 µL, 0.910 mmol) was added dropwise to a stirred solution of 2 (170 mg, 0.758 mmol) in dry THF (2 mL) at -78 °C. After 15 min at -78 °C a solution of anhydrous ZnBr₂ (256 mg, 1.140 mmol) in THF (2 mL) was added dropwise to the yellow reaction mixture. The mixture was stirred at -78 °C for 30 min and allowed to warm to rt. A solution of 2-bromopyridine (191 mg, 1.140 mmol) and Pd(PPh₃)₂Cl₂ (8 mg, 114 µmol) in THF (3 mL) was added and then the reaction mixture was heated under reflux for 12 h. The mixture was allowed to cool to rt, diluted with CHCl₃ (20 mL) and washed with 2M NH₄Cl (2 x 10 mL). The organic phase was dried (Na₂SO₄) and the solvent evaporated *in vacuo*. The residue (233 mg) was chromatographed over silica gel (hexane-EtOAc,
3:1) to furnish 5e (166 mg, 73%) and 6e (16 mg, 7%) as colourless oils. This method has also been applied for the synthesis of 5a to 5d.


24. A solution of 8b (100 mg, 0.155 mmol) in MeOH (3 ml) was treated with Mg turnings (37 mg, 1.550 mmol) and HgCl₂ (4 mg, 0.020 mmol) for 12 h at 50 °C. The reaction mixture was filtered, diluted with water (10 ml) and extracted with CHCl₃ (2 x 10 ml). The organic phase was dried (Na₂SO₄) and evaporated to dryness. The residue (88 mg) was chromatographed over silica (hexane-EtOAc, 3:1) to furnish 10b (76 mg, 97%) as a colourless oil. This method has also been applied for the synthesis of 10a and 10c.

25. All products provided satisfactory analytical data. For example, for product (10b); [α]D<sup>21</sup> +43.17° (c 1.13, CHCl₃); NMR (200 MHz, in CDCl₃): ¹H NMR δ 2.33 (3H, s), 3.45 (1H, m), 3.88 (2H, m), 4.36 (1H, dd, J = 6.1 and J = 3.1 Hz), 4.60 (2H, s), 4.61 (1H, d, J = 11.8 Hz), 4.62 (1H, d, J = 11.8 Hz), 4.69 (1H, d, J = 11.8 Hz), 4.83 (1H, d, J = 11.8 Hz), 5.36 (1H, d, J = 3.1 Hz), 7.32 - 7.51 (19H, m); ¹³C NMR δ 21.24, 68.69, 70.41, 73.47, 73.49, 74.49, 76.72, 77.32, 95.22, 127.49, 127.52, 127.58, 127.65, 127.71, 127.72, 127.93, 128.33, 128.39, 128.41, 128.81, 131.77, 132.20, 138.33, 138.58, 152.86; MS: m/z (FAB): 507 (M+1).

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