PALLADIUM CATALYSED CROSS COUPLING OF PHENYLSULPHONYLGLUCALS WITH ARYL HALIDES

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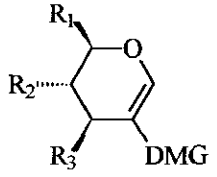
Abstract - The lithiation of a number of 2-phenylsulphonylglucals and the resulting 2-arylglucals formed by subsequent Negishi cross coupling with simple aryl halides and desulphonation is described.

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,[1] nogalamycin[2] and chaetiacandin.[3] 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.[4] The most widely used direct methods involve the reaction of an electrophilic sugar with an electron rich aromatic compound.[5] Among the numerous palladium-mediated reactions developed to assemble *C*-arylglycosides,[6] a method which appears to have particular potential for wide application involves the cross coupling reaction between *C*-metallated glycals with aryl halides.[7] 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.[8,9] After transmetallation the lithiated glycals were subjected to Negishi[10] or Stille cross couplings[11] with moderate success.

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



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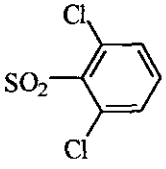
1a $R_1 = R_2 = R_3 = H$
1b $R_1 = CH_2OMe$, $R_2 = R_3 = OMe$
1c $R_1 = CH_2OBn$, $R_2 = R_3 = OBn$

DMG = OMe, OMOM, $OCONEt_2$, SPh, SOPh, SO_2Ph,



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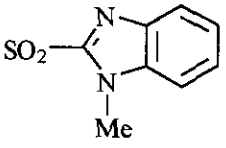
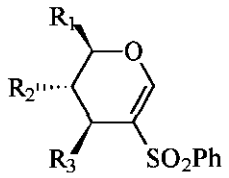


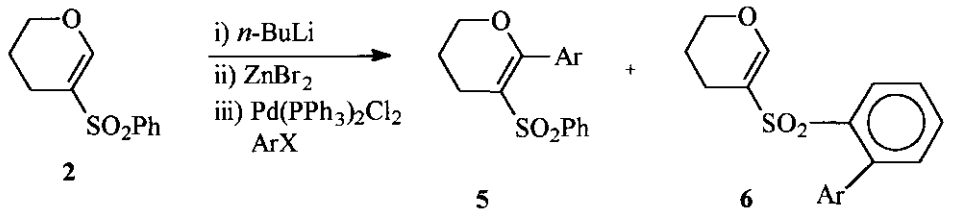
Compounds in which the DMG is OMe, OMOM and $OCONEt_2$ could not be deprotonated without concomitant decomposition. In the cases where the DMG was SPh or SOPh, lithiation was accomplished with *sec*-butyllithium/TMEDA and LDA,[14] respectively. In all other cases (DMG is $ArSO_2$) complete lithiation 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 ($ZnBr_2$) and subjected to Negishi cross coupling with aryl halides. The best results were obtained with SO_2Ph as DMG.

Phenylsulphonylation of dihydropyran, tri-*O*-methyl-D-glucal and tri-*O*-benzyl-D-glucal was accomplished by reaction with (i) acyloxysulfonium salt and treatment with triethylamine[15] or (ii) addition of PhSCl and treatment with DBU (elimination of HCl)[14] followed by oxidation with oxone and wet alumina[16] to furnish compounds (**2**, **3**, and **4**), respectively, in yields exceeding 75%.



2 $R_1 = R_2 = R_3 = H$
3 $R_1 = CH_2OMe$, $R_2 = R_3 = OMe$
4 $R_1 = CH_2OBn$, $R_2 = R_3 = OBn$

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 $Pd(PPh_3)_2Cl_2$ 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]



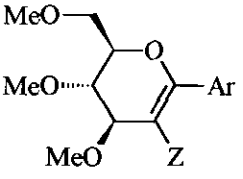
Scheme 1

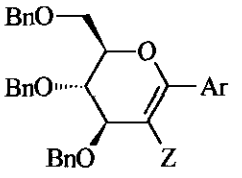
Table 1. Negishi Cross Coupling of 2 with Aryl Halides.

Entry	ArX	Ar	Products (Yield, %)	
1	4-IC_6H_4Me	4-C_6H_4Me	**5a** (75)	**6a** (7)
2	4-$IC_6H_4(CO_2Me)$	4-$C_6H_4(CO_2Me)$	**5b** (70)	**6b** (5)
3	2-$IC_6H_4(CO_2Me)$	2-$C_6H_4(CO_2Me)$	**5c** (25)	**6c** (4)
4	4-BrC_6H_4CN	4-C_6H_4CN	**5d** (81)	**6d** (5)
5	2-BrPy	2-Py	**5e** (73)	**6e** (7)

Comparable results were obtained by converting the lithiated **2** into the corresponding boronic acid, followed by Suzuki cross coupling[20] under the specific conditions.[21] It is of interest to note that the simple boronic acids (without a DMG) did not undergo cross coupling, but only dehydroboronation[22] under these conditions. The 2-iodo compound obtained by the treatment of lithiated **2** with I_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).





7a Z = SO_2Ph, Ar = Py
7b Z = SO_2Ph, Ar = C_6H_4Me
7c Z = SO_2Ph, Ar = C_6H_4CN
9a Z = H, Ar = Py
9b Z = H, Ar = C_6H_4Me
9c Z = H, Ar = C_6H_4CN

8a Z = SO_2Ph, Ar = Py
8b Z = SO_2Ph, Ar = C_6H_4Me
8c Z = SO_2Ph, Ar = C_6H_4CN
10a Z = H, Ar = Py
10b Z = H, Ar = C_6H_4Me
10c Z = H, Ar = C_6H_4CN

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

Entry	Starting material	Product (Yield, %)
1	**3**	**7a** (72)
2	**3**	**7b** (74)
3	**3**	**7c** (85)
4	**4**	**8a** (73)
5	**4**	**8b** (70)
6	**4**	**8c** (80)

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 SmI_2.[23] 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 $HgCl_2$ in MeOH at 50 °C to furnish compounds (**9**) and (**10**) in yields in excess of 95%.[24,25] These compounds can be converted into 2-deoxy-*C*-arylglycosides or *C*-arylglycosides by hydrogenation or hydroboration/oxidation[14] reactions, respectively.

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

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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 $ZnBr_2$ (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 $Pd(PPh_3)_2Cl_2$ (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 $CHCl_3$ (20 mL) and washed with 2M NH_4Cl (2 x 10 mL). The organic phase was dried (Na_2SO_4) 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**.

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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 $HgCl_2$ (4 mg, 0.020 mmol) for 12 h at 50 °C. The reaction mixture was filtered, diluted with water (10 ml) and extracted with $CHCl_3$ (2 x 10 ml). The organic phase was dried (Na_2SO_4) 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**); $[\alpha]_D^{21}$ +43.17° (*c* 1.13, $CHCl_3$); NMR (200 MHz, in $CDCl_3$): ^{1}H 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); ^{13}C 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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