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Regioselective Pd-Mediated Coupling between 2,6-Dichloropurines and Organometallic Reagents

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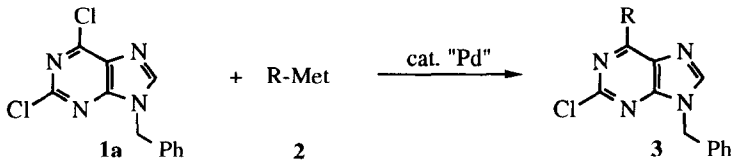
Abstract: Selective coupling in the purine 6-position has been achieved, by reacting *N*-benzylated 2,6-dichloropurines with organotin and organozinc reagents. The positional identity of the products were established from long range HETCOR or nOe NMR experiments.

Halogen atoms in purines can be replaced by nitrogen and oxygen nucleophiles, the ease of replacement in *N*-9 or *N*-7 alkylated halopurines generally being 8 ≈ 6 > 2.[1] Calculations also indicate that the purine 6-position is more reactive towards nucleophiles than the 2-position.[2,3] Selectivity in carbon - carbon bond formation reactions on di- and trihalopurines has received little attention, but sodium diethylmalonate is reported to react in the 6-position with 2,6-dichloro-9-methylpurine.[4] To our knowledge, the regiochemistry of transition metal catalyzed substitution reactions on di- or trihalopurines has not previously been investigated.

Palladium or nickel catalyzed cross coupling reactions between monohalopurines and organometallic compounds, like organotin-,[5,6] organozinc-,[6] organoaluminium-[7] or Grignard reagents,[8] are emerging as favourable methods for carbon - carbon bond formation in the purine 2-, 6- and 8-position. We have recently shown that Pd-catalyzed coupling of 6-chloropurines with organotin derivatives allows smooth introduction of alkenyl- and aryl substituents,[5i,6] and that 6-alkylpurines can be prepared in high yields employing organozinc reagents.[6] As an extension of this work, we are now studying the regiochemistry in transition metal mediated reactions of di- and trihalopurines with organometallic reagents. In this communication, we wish to report our results from couplings between *N*-benzylated 2,6-dichloropurines **1** and organotin- and organozinc derivatives .

9-Benzyl-2,6-dichloropurine **1a**[9] was isolated in 72 % yield, together with 11 % of the *N*-7 benzylated isomer **1b**,[9] by alkylation of 2,6-dichloropurine[10] with benzyl chloride in DMF employing potassium carbonate as base. Regioselective coupling in the 6-position was achieved when 9-benzyl-2,6-dichloropurine **1a** was treated with alkenyl- and aryl(tributyl)tin **2a-c** in the presence of 5 % bis(triphenylphosphine)palladium(II) chloride (Scheme 1, Table 1).[11,12]



1a **2** **3**

Scheme 1

Table 1. Pd-Catalyzed Coupling between 9-Benzyl-2,6-dichloropurine **1a** and Organometallic Reagents **2**.

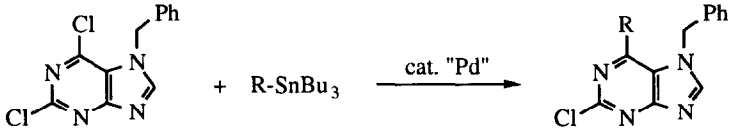
R-Met	2	Catalyst	Solvent	Temp (°C)	Yield (%)[a]; 3
trans PhCH=CHSnBu$_3$	**2a**	$(Ph_3P)_2PdCl_2$	DMF	80	56, **3a**
CH_2=C(OEt)SnBu$_3$	**2b**	"	"	70	70, **3b**
2-thienylSnBu$_3$	**2c**	"	"	70	59, **3c**
PhSnBu$_3$	**2d**	"	"	75	-,[b] **3d**
PhZnBr	**2e**	$(Ph_3P)_4Pd$	THF	50	50, **3d**
$PhCH_2ZnBr$	**2f**	"	"	"	75,[c] **3e**
MeZnBr	**2g**	"	"	"	69, **3f**
n-BuZnBr	**2h**	"	"	"	63, **3g**

a) Yield of isolated products. b) A ca. 2 : 3 mixture of **3d** and 9-benzyl-2,6-diphenylpurine was formed.
c) Contamitated with a small amount of **1a**.

Long range HETCOR NMR experiments were performed to establish the positional identity of the products **3** (*vide infra*). The less reactive phenyl(tributyl)tin **2d** gave a ca. 2 : 3 mixture of 9-benzyl-2-chloro-6-phenylpurine **3d** and 9-benzyl-2,6-diphenylpurine as judged by NMR. This result shows that even 2-chloropurines are reactive enough to participate in Pd-catalyzed cross couplings, although less readily than 6-chloropurines. Benzyl(tributyl)tin required much harsher reaction conditions (ca. 150 °C), and a complex mixture of products was formed. We identified not only 2-chloro-6,9-dibenzylpurine **3e** and 2,6,9-tribenzylpurine but also 9-benzyl-6-*n*-butyl-2-chloropurine **3g** and both regioisomers of butyldibenzylpurine. Even though a butyl group is believed to be transferred much less readily from tin than a benzyl group,[13] unexpected transfer order from unsymmetrically organostannanes has previously been noted.[14]

Organozinc reagents are known to transfer aryl and alkyl groups more readily than organostannanes, allowing coupling at milder conditions.[6,15] When the dichloropurine **1a** was reacted with aryl- or alkylzinc reagents **2e-h** in the presence of tetrakis(triphenylphosphine)palladium(0) in THF at 50 °C, coupling took place exclusively in the 6-position (Scheme 1, Table 1).[16]

Also 7-benzyl-2,6-dichloropurine **1b** was subjected to Pd-catalyzed couplings with organotin reagents (Scheme 2, Table 2). In the cases examined, coupling took place exclusively in the 6-position to give the products **4**, even though the 6-position in the purine **1b** is more sterically hindered than in the isomer **1a**.



1b **2** **4**

Scheme 2

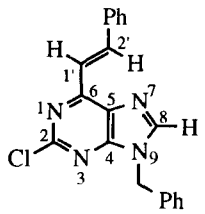
Table 2. Pd-Catalyzed Coupling between 7-Benzyl-2,6-dichloropurine **1b** and Organometallic Reagents **2**.

R-$SnBu_3$	**2**	Catalyst	Solvent	Temp (°C)	Yield (%)[a] **4**
CH_2=C(OEt)$SnBu_3$	**2b**	$(Ph_3P)_2PdCl_2$	DMF	70	74, **4a**
2-thienyl$SnBu_3$	**2c**	"	"	70	57, **4b**
Ph$SnBu_3$	**2d**	"	"	75	68, **4c**

a) Yield of isolated products.

Determination of the site of *N*-alkylation in purines has been achieved by long range HETCOR[17] or long range selective INEPT NMR experiments.[18] We now report that the same techniques are applicable for the verification of carbon substituents in the purine 6-position. Long range HETCOR spectra of the coupling products **3** revealed correlations between protons and carbons up to three bonds away, allowing unequivocal identification of *C*-4, *C*-5 and *C*-8 (Table 3). Furthermore, in the long range HETCOR spectra of the coupling products **3a** and **3e** - **g** correlations between the α-hydrogens in the substituents and *C*-6 and *C*-5 in the purine ring were observed, proving that the substituents were located in the 6-position. The identification of the coupling products **3b** - **d** as 6-substituted 2-chloropurines, is based on analogy. Selected correlations observed in the long range HETCOR spectrum of the styrylpurine **3a** are shown in Table 3. The structures of the compounds **4** were verified by nOe effects between the 6-substituents and the benzylic CH_2-protons or by long range HETCOR as described above.

Table 3. Selected Correlations from the Long Range HETCOR Spectrum of the 6-Styrylpurine **3a**.



3a

	C-4	C-5	C-6	C-8
CH_2	X			X
H-8	X	X		X
H-1'		X	X	
H-2'			X	

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11. A mixture of the 2,6-dichloropurine **1a** or **1b** (1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (0.05 mmol) and organostannane (1.2 mmol) in dry DMF (3 ml) was heated under N_2 at the temperatures given in Table 1 until TLC showed the reaction to be complete, and evaporated. A sat. solution of potassium fluoride in methanol (20 ml) was added to the residue, the resulting mixture stirred at ambient temperature for ca. 4 h and evaporated together with a small amount of silica gel. The residue was added on top of a silica gel column and the product isolated by flash chromatography.
12. All new compounds were fully characterized with ^1H NMR, ^{13}C NMR, MS and elemental analysis or HRMS.
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16. A 1 M solution of anhydrous zinc bromide in dry THF (1.2 mmol) was added dropwise to a stirred solution of the desired Grignard reagent (1.2 mmol) in dry THF (4 ml) under N_2 at -78 °C. After 1 h, the cooling bath was removed and the reaction mixture allowed to reach ambient temperature before tetrakis(triphenylphosphine)palladium(0) (0.05 mmol) and 9-benzyl-2,6-dichloropurine **1a** (1.0 mmol) were added. The resulting mixture was heated at 50 °C until TLC showed the reaction to be complete, and cooled. Sat. aq. ammonium chloride (10 ml) was added and the aq. phase extracted with EtOAc (4 x 25 ml). The combined organic extracts were washed with brine (2 x 20 ml) dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel.
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