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6-Chloropurines and Organostannanes in Palladium Catalyzed Cross Coupling Reactions

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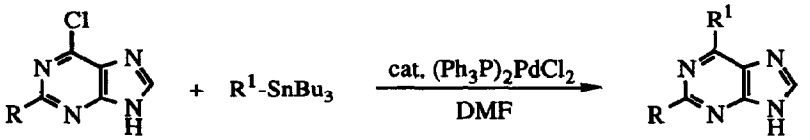
Abstract: Carbon-carbon bond formation in the purine 6-position can easily be accomplished by palladium catalyzed cross coupling between 6-chloropurines and organostannanes without protection of the purine ring *NH* function. This technique provides a convenient route to potent cytokinines.

Kinetin (6-furfurylaminopurine) and related 6-substituted purines, called cytokinines, are known to stimulate cell growth and cell division in plants.[1] Several purines with potent cytokinin activity contain a 6-alkenyl or 6-alkyl substituent.[2] An efficient route to these compounds would be transition metal catalyzed cross coupling of organometallic reagents with readily available 6-halopurines. For instance, 6-chloropurine **1a** (Scheme 1) is commercially available and the substance can also easily be prepared on a large scale.[3] Because of the acidity of the purine ring *NH* function (pKa of 6-chloropurine: 7.88),[4] organometallic reagents with low basisity are desired. Examples of transition metal mediated couplings of purines with a free *NH* function are restricted to palladium catalyzed Heck coupling of terminal alkynes with halopurines,[5] and nickel catalyzed coupling of methylthiopurine with Grignard reagents in which case 2.5 equivalents of the basic Grignard reagents were required.[6] Palladium catalyzed cross coupling between heteroaryl halides and organotin derivatives is an established method for carbon-carbon bond formation in heterocycles,[7] but the scope of this method is rarely investigated in the purine ring system.[8] Only coupling reactions employing *N*-9 alkylated iodopurines are reported. In fact, very recently the first two examples of coupling in the purine 6-position appeared.[8e]

Palladium catalyzed cross coupling of organostannanes **2a - e** with 6-chloropurines **1a - b** has been studied (Scheme 1, Table 1).



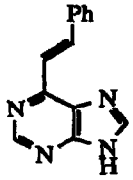
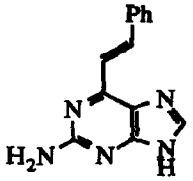
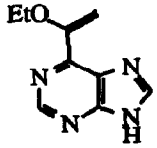
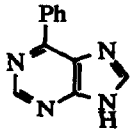
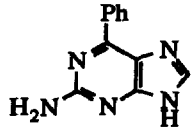
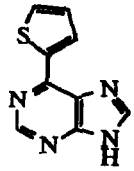
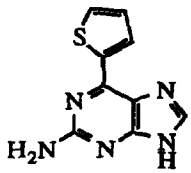
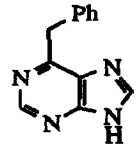
1a: R = H
1b: R = NH_2

2a - e

3a - h

Scheme 1

Table 1. Pd-Catalyzed Coupling between Organostannanes and Chloropurines.

Purine 1	Organostannane 2	React. time (h)	Temp. (°C)	Product 3	Yield (%)
1a	$PhCH{=}CHSnBu_3$ **2a**[11]	20	80	 **3a**[14]	84
1b	**2a**	45	80	 **3b**	75
1a	$CH_2{=}C(OEt)SnBu_3$ **2b**	20	80	 **3c**	58
1a	$PhSnBu_3$ **2c**	20	100	 **3d**[6]	81
1b	**2c**	45	100	 **3e**	73
1a	(2-thienyl)$SnBu_3$ **2d**[12]	20	90	 **3f**	81
1b	**2d**	45	90	 **3g**	76
1a	$PhCH_2SnBu_3$ **2e**[13]	20	130	 **3h**[14b]	36

Organostannanes are known to tolerate a wide variety of functional groups on the coupling partners,[9] and the stannanes **2a** - **e** coupled with the relatively acidic purines **1a** and **1b**. Bis(triphenylphosphine)palladium(II) dichloride was found to be a suitable catalyst.[10]

This methodology makes purines with alkenyl-, aryl-, and heteroaryl substituents in the 6-position easily accessible, and the potent cytokinine 6-*trans*-styrylpurine **3a**, was prepared in a one-step procedure superior to the methods reported earlier.[14] Even the much less reactive benzyl(tributyl)stannane **2e** participated in the coupling to give the 6-benzylpurine **3h** in a moderate yield.

The 6-styryl purines **3a** - **b** were prepared from a 1 : 9 mixture of *cis* and *trans* styryltin reagent **2a** (1.3 equiv.), but only the *trans* products were formed as judged by ^{1}H NMR of the crude products, indicating a slightly higher reactivity of the *trans* organotin reagent. Isomerization of the alkenes in the reaction can not be excluded, but retention of the alkenylstannane double bond geometry is generally observed in palladium catalyzed cross couplings.[9]

The order of reactivity of aryl halides in palladium mediated cross coupling reactions is found to be Ar-I > Ar-Br >> Ar-Cl.[9] Only aryl chlorides with an electron deficient *ipso* carbon will participate in the reaction. For instance, 2- and 4-chloropyrimidines are shown to be sufficiently activated for the coupling to occur.[7] In earlier reports, iodopurines have been employed in couplings with organostannanes,[8] and even though the yields in Heck couplings of 6-chloropurines are rather moderate compared to the corresponding iodopurines,[5,15] the present study shows that the 6-chloropurines **1a** and **1b** are reactive enough to give high yields of the coupling products in palladium catalyzed reactions with alkenyl- and aryltin derivatives. This is a great advantage since iodopurines are less available. In fact, iodopurines are often prepared from the corresponding chloropurines.[15,16]

The lower reaction rate observed in the couplings of 2-amino-6-chloropurine **1b** compared to 6-chloropurine **1a** might be attributed to higher electron density in the former ring, making the compound less activated for nucleophilic attack from Pd(0).[9] Initially, the coupling reactions with the 2-amino compound **1b** were carried out in a much less concentrated solution due to poor solubility, but reactions of the purine **1a** seem not to be significantly affected by concentration.

In summary, carbon-carbon bond formation in the purine 6-position can easily be accomplished by palladium catalyzed cross coupling of readily available 6-chloropurines with organostannanes without protection of the purine ring *NH* function. This technique provides an efficient route to potent cytokinines.

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10. The organostannane **2** (1.3 mmol) was added to a mixture of bis(triphenylphosphine)palladium(II) dichloride (39 mg, 0.03 mmol) and 6-chloropurine **1a** (1.0 mmol) in dry DMF (6 ml) or 2-amino-6-chloropurine **1b** (1.0 mmol) in DMF (15 ml) and the mixture was stirred under N_2 at the temperature indicated in Table 1, before the reaction mixture was filtered and evaporated, and the residue was washed with ether. The crude product was purified by flash chromatography or recrystallization. **3b**: ^{1}H NMR (DMSO-d_6) δ 6.32 (s, 2H), 7.4 - 7.5 (m, 4H), 7.7 (m, 2H), 8.10 (s, 1H), 8.25 (d, *J* 16 Hz, 1H), 12.6 (bs, 1H). MS (E.I.): 237 (2, M^+), 207 (100). **3c:** ^{1}H NMR (DMSO-d_6) δ 1.46 (t, *J* 7 Hz, 3H), 4.15 (q, *J* 7 Hz, 2H), 4.77 (d, *J* 2 Hz, 1H), 5.68 (d, *J* 2 Hz, 1H), 8.77 (s, 1H), 8.91 (s, 1H), 13.6 (bs, 1H). MS (E.I.): 190 (100, M^+). **3e:** ^{1}H NMR (DMSO-d_6) δ 6.38 (s, 2H), 7.5 - 7.6 (m, 3H), 8.11 (s, 1H), 8.7 - 8.8 (m, 2H), 12.7 (bs, 1H). MS (E.I.): 211 (100, M^+). **3f:** ^{1}H NMR (DMSO-d_6) δ 7.36 (m, 1H), 7.92 (m, 1H), 8,66 (m, 2H), 8.84 (s, 1H), 13.7 (bs, 1H). MS (E.I.): 202 (100, M^+). **3g**: ^{1}H NMR (DMSO-d_6) δ 6.40 (s, 2H), 7.28 (m, 1H), 7.80 (m, 1H), 8.12 (s, 1H), 8.57 (m, 1H), 12.7 (bs, 1H). MS (E.I.): 217 (100, M^+).
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