The Suzuki-Miyaura Cross-Coupling Reactions of 6-Halopurines with Boronic Acids Leading to 6-Aryl- and 6-Alkenylpurines

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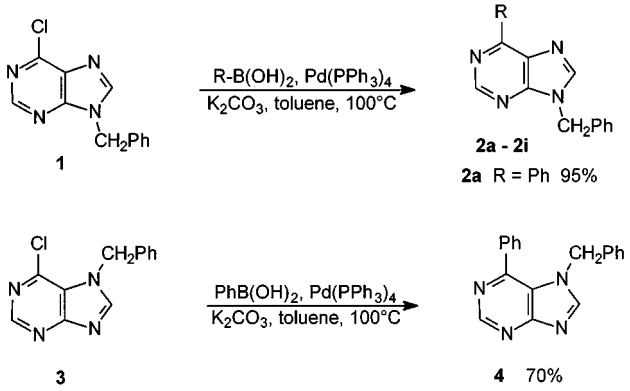
Abstract: The Suzuki-Myiaura cross-coupling reactions of 9-benzyl-6-chloropurine with boronic acids gave 6-alkylated purines in moderate to excellent yields. The best results with electron rich arylboronic acids were obtained in toluene in the presence of anhydrous K_2CO_3 as a base, while electron poor boronic acids and alkenyl boronic acids gave better results using aqueous K_2CO_3 in DME. The reaction was successfully applied for the synthesis of 6-phenylpurine bases and nucleosides.

Key words: purines, nucleosides, cross-couplings, boronic acids

Purine bases modified in the 6-position and their nucleoside and nucleotide derivatives and analogues possess a broad spectrum of biological activity. The cytotoxicity of 6-methylpurine and its nucleosides is well known,[1] while a promising cytostatic activity of 6-(aminoalkyl)purine derivatives (as cytokinines analogues) has been recently discovered.[2] Many 6-alkylaminopurine nucleosides are important adenosine receptors antagonists[3] and acyclic nucleotide analogues derived from 6-(di)alkylaminopurines are strong antivirals, antineoplastic agents and immunomodulators.[4] Recently, several 6-(arylalkynyl)-, 6-(arylalkenyl)- and 6-(arylalkyl)purines were reported[5] to exhibit cytokinine activity.

In the last decade, with the development of the cross-coupling methodology, many 6-C-substituted purines have been prepared.[6] Thus 6-halopurine derivatives react with alkyl(aryl)zinc or tin reagents,[6a-e] trialkylaluminum[6f] or alkylcuprates[6g-i] to give the 6-alkylpurine derivatives. Also another approach based on the reaction of purine-6-zinc iodide with aryl or vinyl halides has recently been described.[7] For the synthesis of 6-arylpurines, an alternative based on radical photochemical reactions of adenine derivatives with aromatic compounds was used,[8] but this method is very unselective and for substituted benzenes, mixtures of all *ortho*-, *meta*- and *para*-substituted derivatives were obtained. To the best of our knowledge, no successful Suzuki-Myiaura type of cross-coupling[9] of 6-halopurines with alkyl- or arylboronic acid has been described. The advantage of this reaction compared to the above mentioned methods would be the high stability of boronic acids, the low toxicity of boron compounds, easy work-up and isolation of the product along with availability of starting boronic acids (a number of boronic acids, especially the aromatic ones, is commercially available). In this communication we wish to report our results in this field.

To test the Suzuki-Myiaura coupling reaction of purine derivatives we chose 6-halo-9-benzylpurines as model compounds. Thus $Pd(PPh_3)_4$ catalysed reaction of 9-benzyl-6-chloropurine (**1**) with phenylboronic acid in the presence of K_2CO_3 in toluene at 100 °C afforded after 24 h 9-benzyl-6-phenylpurine (**2a**) in excellent yield (95%) (Scheme 1).



Scheme 1

9-Benzyl-6-iodopurine reacted faster giving similarly high yield (92%) of **2a**, however, the reaction mixture was not as clean as in the case of **1**. Also 9-benzyl-7-chloropurine (**3**) reacted smoothly with phenylboronic acid giving 70% isolated yield of 7-benzyl-6-phenylpurine (**4**) in 7.5 h under the above mentioned conditions showing the higher reactivity of **3** compared to **1**. Interestingly, bases other than potassium carbonate - Na_2CO_3, Cs_2CO_3, ethyldiisopropylamine and sodium methoxide did not give detectable amounts of **2a**. When xylene was used instead of toluene at 130 °C under otherwise identical conditions, the reaction was completed in nearly quantitative yield in 9 h, but the product was contaminated with small amount of by-products which were difficult to separate. Reaction in the presence of aqueous K_2CO_3 in DME was very fast affording 95% yield in 6 h. In contrary the reaction in DMF at 100 °C was very slow giving **2a** in 35% after 24 h and 68% after 45 h, probably as a result of catalyst decomposition.

The influence of the catalytic system on the course of the reaction was examined in the reaction of 7-benzyl-6-chloropurine (**3**) and 9-benzyl-6-chloropurine (**1**) with phenylboronic acid in toluene at 100 °C (Table 1). As expected, a lower phosphine to Pd ratio and using $AsPh_3$ instead of PPh_3 resulted in acceleration of the reaction (Table 1). However the reaction was not as clean as the reaction in the presence of $Pd(PPh_3)_4$.

Table 1. Influence of the catalytic system on the yield of the coupling of 7-benzyl-6-chloropurine (**3**) and 9-benzyl-6-chloropurine (**1**) respectively with phenylboronic acid (2.5 mol % Pd, K_2CO_3, toluene, 100°C).

Catalyst	Reaction time[a] (h)	Product (Yield)[b]
$Pd(PPh_3)_4$	24	**2a** (95%)
$Pd(PPh_3)_4$	7.5	**4** (73%)
$Pd(dba)_2/P(o\text{-}tol)_3$ 1:2	7.5	**2a** (70%)
$Pd(dba)_2/P(o\text{-}tol)_3$ 1:2	3	**4** (44%)
$Pd(dba)_2/AsPh_3$ 1:2	3	**4** (70%)
$PdCl_2(PPh_3)_2$	6	**4** (56%)

[a] Time in which all starting compounds were consumed;
[b] Isolated yield.

Table 2. Reaction of 9-benzyl-6-chloropurine (**1**) with boronic acids $RB(OH)_2$ (1.2 eq.)

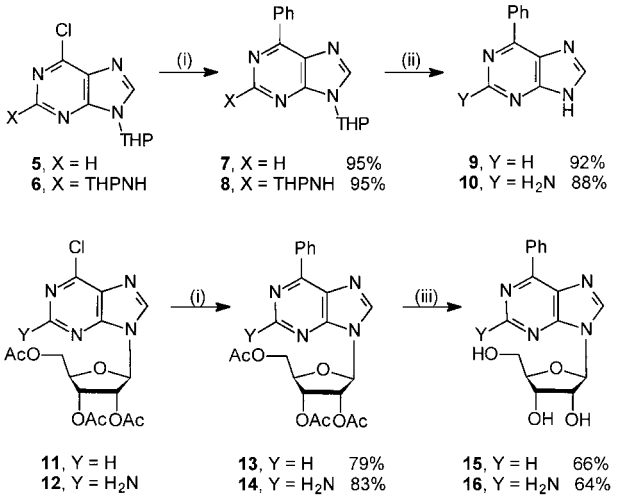
entry	R	Reaction time (h)	Method[a]	Product	Yield (%)
1	C_6H_5	24	A	**2a**	95
2		7	B	**2a**	95
3	3-MeO-C_6H_4	4	A	**2b**	62
4	3-NO_2-C_6H_4	48[b]	A	**2c**	19
5		7	B	**2c**	66
6	2-Me-C_6H_4	24	A	**2d**	86
7	4-F-C_6H_4	24	A	**2e**	89
8	2-thienyl	24[b]	A	**2f**	39
9		7[b]	B	**2f**	82
10	(*E*)-C_6H_5-CH=CH-	24[b]	A	(*E*)-**2g**	14
11		7.5	B	(*E*)-**2g**	76
12	(*E*)-C_5H_{11}CH=CH-	24[b]	A	(*E*)-**2h**	18
13		8	B	(*E*)-**2h**	98
14	C_4H_9	24[b]	A	**2i**	18
15		24	B	**2i**	0
16	C_6F_5	24	A	**2j**	0
17		24	B	**2j**	0

[a] Method A: 2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene, 100°C; Method B: 2.5 mol% $Pd(PPh_3)_4$, 2M aq. K_2CO_3, DME, 85°C.
[b] Unreacted **1** remains in the reaction mixture.

The optimum conditions for the reaction of **1** with phenylboronic acid (2.5 mol% $Pd(PPh_3)_4$, K_2CO_3, toluene, 100 °C) were used for the reaction of **1** with other boronic acids[10] (Table 2). The reaction gives good to excellent results with aromatic boronic acids bearing electron donor, neutral or weak acceptor substituents at the aromatic ring (entries 1,3,6,7) including 4-fluorophenyl derivative and sterically hindered 2-methylphenyl derivative. Introduction of stronger electron acceptors on the aromatic ring resulted in dramatic lowering of the reaction rate. Thus 3-nitrophenylboronic acid gave only 19% yield after 48 h (Table 2, entry 4) and an extreme case of pentafluorophenylboronic acid (entry 16) did not react at all. While 2-thienyl boronic acid gave fair yield of the corresponding coupled product **2f**, somewhat surprisingly alkenylboronic acids (entries 10,12) gave only low yields of the coupled products **2g** and **2h** under the above conditions. Similar low yields were obtained also with butylboronic acid (entry 14). Better results of the coupling of alkenyl as well as 2-thienyl and 3-nitrophenyl boronic acids were obtained in DME in the presence of aqueous K_2CO_3 (entries 5, 9, 11, 13). The *(E)*-geometry on the double bond of the alkenyl boronic acids used, remained unchanged under the both reaction conditions and any isomerised product was observed. None coupled product was obtained using aqueous K_2CO_3 in the case of butylboronic and perfluorophenylboronic acids.

Finally, to test the synthetic utility of this method, we have applied the Suzuki reaction of phenylboronic acid with 6-chloropurines for the synthesis of 6-phenylpurine bases and nucleosides. To prevent hydrolysis of acetate protecting groups the non-aqueous conditions were used. Thus the tetrahydropyran-2-yl (THP) protected 6-chloropurine **5** or bis(THP)-protected 2-amino-6-chloropurine **6** reacted under the above mentioned conditions with phenylboronic acid to give the THP-protected 6-phenylpurines **7** and **8** in nearly quantitative yields. They were deprotected by a standard procedure[11] with the use of wet Dowex 50X8 (H^+) in methanol to give the known 6-phenylpurine bases **9** and **10** in high yields. For comparison, unprotected 6-chloropurine and 2-amino-6-chloropurine bases were submitted for direct cross-coupling reactions to phenylboronic acid under the same conditions but the conversions were very low even after prolonged reaction times probably due to both lower reactivity and lower solubility of the free purines. Analogously, the tri-*O*-acetyl protected nucleosides derived from 6-chloropurine and 2-amino-6-chloropurine **11** and **12** reacted with phenylboronic acid to give the corresponding 6-phenylpurine derivatives **13** and **14** in high yields (the conversion was quantitative, the yields were somewhat lowered by partial deacetylation during work-up). Base-catalyzed deacetylation[12] of the protected nucleosides **13** and **14** using sodium methoxide in methanol afforded quantitatively the free nucleosides **15** and **16** that were purified by crystallisation.

In conclusion, the Suzuki-Miyaura cross-coupling reactions of 6-chloropurines with various alkyl-, alkenyl- and arylboronic acids were investigated. Under anhydrous conditions the best results were achieved with the use of electron rich arylboronic acids (Ar = phenyl, electron-donating group substituted phenyl), while electron poor aryl- (nitro-, pentafluorophenyl), alkenyl- and alkylboronic acids gave low or negligible conversions. Reaction in the presence of aqueous K_2CO_3 is faster and can be used to prepare coupling products of alkenyl- and some electron poor arylboronic acids in reasonable yield in cases of substrates stable to aqueous K_2CO_3. The relatively mild con-



(i) $PhB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, toluene; (ii) Dowex 50X8 (H^+), MeOH, H_2O; (iii) NaOMe; THP = tetrahydropyran-2-yl

Scheme 2

ditions used, good yields of cross-coupling reactions, the use of relatively cheap, stable and non-toxic boronic acids and tolerance to various functionalities (including amino groups) makes this methodology a good alternative for the synthesis of 6-arylpurines. An application of this methodology for the synthesis of a series of 6-arylpurine bases and nucleosides of potential biological interest is in progress and will be published in due course.

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(10) **Typical procedure: Coupling of 9-benzyl-6-chloropurine (1) with 3-methoxyphenylboronic acid.** A mixture of 9-benzyl-6-chloropurine (**1**) (0.122 g; 0.5 mmol), 3-methoxyphenylboronic acid (0.114g; 0.75 mmol), anhydrous K_2CO_3 (0.086 g; 0.625 mmol), $Pd(PPh_3)_4$ (0.014 g; 0.012 mmol) and toluene (10 ml) was stirred under argon at 100 °C for 4 h, filtered, evaporated and chromatographed on silicagel (Chromatotron, 2 mm plate, $CHCl_3$: MeOH 98:2) to give 9-benzyl-6-(3-methoxyphenyl)purine (**2b**) (0.097 g; 62%) as a white solid, m.p. 111-114 °C, ref.[8b] 114-116 °C), ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.93 (s, 3H, *CH_3*), 5.49 (s, 2H, *CH_2*), 7.08 (m, 1H, *ArH*), 7.35 (m, 5H, CH_2*Ph*), 7.47 (t, *J* = 8 Hz, *ArH*), 8.09 (s, 1H, *H-8* Pu), 8.36 (m, 1H, *ArH*), 8.45 (m, 1H, *ArH*), 9.06 (s, 1H, *H-2* Pu).
The reaction under aqueous conditions was analogous, except of the higher amount of K_2CO_3 (0.187 g; 1.35 mmol) together with water (0.7 ml) in DME (5ml) was used. The reaction mixture was than stirred under argon at 80 °C for the time reported in Table 2. The following work up was the same as above.
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