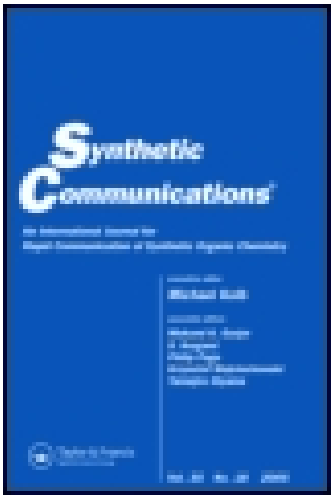

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# Suzuki-Miyaura Cross-Coupling of Unprotected Halopurine Nucleosides in Water—Influence of Catalyst and Cosolvent

Alice Collier [a] & Gerd K. Wagner [a]
[a] Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia , Norwich, UK
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# Suzuki–Miyaura Cross-Coupling of Unprotected Halopurine Nucleosides in Water—Influence of Catalyst and Cosolvent

**Alice Collier and Gerd K. Wagner**
Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich, UK

**Abstract:** Reaction conditions for the Suzuki–Miyaura cross-coupling of unprotected halopurine nucleosides with arylboronic acids in aqueous media were investigated. A series of arylated purine nucleosides was prepared in water without an organic cosolvent, using either $Pd(PPh_3)_4$ or $Pd(OAc)_2$/TPPTS as the catalyst.

**Keywords:** Catalysis, nucleosides, Suzuki–Miyaura reaction, water

Structural analogues of the naturally occurring purine nucleosides adenosine and guanosine (Scheme 1) are of considerable interest as drug candidates,[1] pharmacological and biological tools,[2] and synthetic building blocks.[3] However, the preparation of such analogues in the laboratory is frequently complicated by their physicochemical and structural properties e.g., the generally poor solubility of nucleosides in organic solvents, the presence of multiple functional groups, and the potential sensitivity of the glycosidic bond to hydrolytic cleavage.[4] Although the use of protecting groups is a valid strategy to circumnavigate some of these problems, the direct structural modification of unprotected nucleosides represents a much more elegant and efficient approach.

For an ongoing research program on carbohydrate-modifying enzymes, we require purine nucleosides bearing additional hydrophobic substituents

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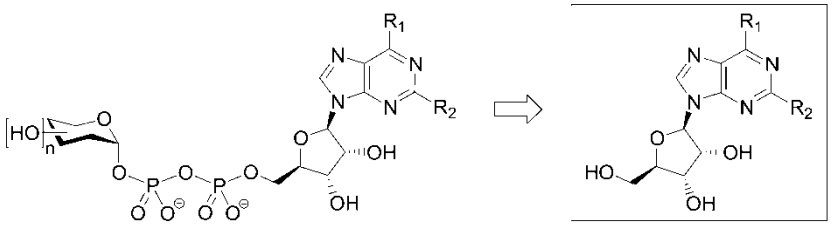
Address correspondence to Gerd K. Wagner, Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK. E-mail: g.wagner@uea.ac.uk




***Scheme 1.*** Analogues of the naturally occurring purine nucleosides adenosine and guanosine as building blocks for the construction of nucleoside diphosphate (NDP) sugars.

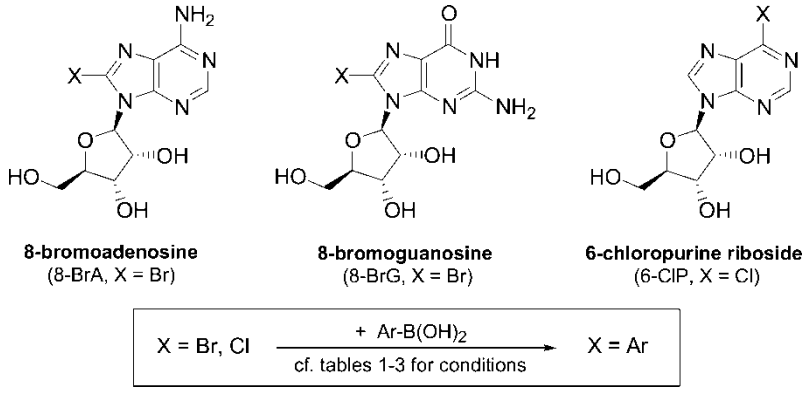


at the nucleobase as synthetic intermediates en route to the corresponding nucleoside diphosphate (NDP) sugars (Scheme 1). The desired substituents can be installed using palladium-catalyzed cross-coupling chemistry such as the Suzuki–Miyaura reaction.[5] The Suzuki–Miyaura cross-coupling of arylboronic acids with fully protected halopurine nucleosides and 2′-deoxynucleosides in organic solvents[6] and, more recently, with unprotected halopurine nucleosides in aqueous media[7–9] using various cosolvents (e.g., MeCN[8] or dimethoxyethane (DME)[9]) has been reported.

The scope of the Suzuki–Miyaura cross-coupling of unprotected halopurine nucleosides in neat water has not previously been explored on a synthetic scale. We were interested in testing the feasibility of such an approach for two reasons: first, to generate the nucleoside building blocks required for our general synthesis in an efficient manner without the use of protecting groups, and second, to assess the potential of such a strategy for the direct structural modification of charged, water-soluble species such as nucleotides and NDP sugars. Western and coworkers have studied the cross-coupling of 8-bromo-2′-deoxyadenosine with phenylboronic acid in different aqueous media but reported only conversion rates based on high performance liquid chromatography (HPLC) data for those experiments carried out in water.[8]

Therefore, we have investigated the adaptability of two standard palladium catalysts for the Suzuki–Miyaura cross-coupling of different halopurine nucleosides (Scheme 2) in water on a preparative scale. Herein, we report the first results from this study.

Our initial experiments were carried out with the traditional Suzuki–Miyaura catalyst $Pd(PPh_3)_4$ (Table 1).[5a] In aqueous media, the use of a palladium catalyst based on a *hydrophobic* triphenylphosphine ligand offers the advantage that the catalyst can be removed from the reaction by simple filtration. The cross-coupling of 8-bromoadenosine (8-BrA)[9] with phenylboronic acid in three different aqueous solvent systems ($DME/H_2O$, $MeCN/H_2O$, and water) was used as a model reaction to assess the influence of the organic cosolvent on cross-coupling efficiency under these




***Scheme 2.*** Suzuki–Miyaura cross-coupling of unprotected halopurine nucleosides with arylboronic acids.

conditions (Scheme 2). At 80°C, this influence was negligible, and 8-phenyladenosine was isolated in moderate to good yield from all three reactions (Table 1, entries 1a–c).

Likewise, the cross-coupling of phenylboronic acid with 6-chloropurine riboside (6-ClP)[10] in water gave 6-phenylpurine riboside, albeit in very low yield (entry 2). However, with 8-bromoguanosine (8-BrG)[11] no reaction was observed by thin-layer chromatography (TLC) under these

***Table 1.*** Suzuki–Miyaura cross-coupling of halopurine nucleosides with phenylboronic acid (Ar = phenyl) in aqueous media using $Pd(PPh_3)_4$[a]

| Entry | Substrate | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1a | 8-BrA | $H_2O$ | 75 |
| 1b | 8-BrA | $MeCN/H_2O$[c] | 90[d] |
| 1c | 8-BrA | $DME/H_2O$[e] | 60 |
| 2 | 6-ClP | $H_2O$ | 15[f] |
| 3 | 8-BrG | $DME/H_2O$, $MeCN/H_2O$, or $H_2O$ | 0[g] |

[a]Reagents and conditions: 10 mol % $Pd(PPh_3)_4$, $K_2CO_3$ (6 eq.), phenylboronic acid (1.5 eq.), 80°C, 24 h.

[b]Isolated yields. Not optimized.

[c]$MeCN/H_2O$ (1 : 2).

[d]This reaction was complete after 17 h.

[e]$DME/H_2O$ (2 : 1).

[f]This reaction was complete after 7 h.

[g]Reactions were carried out with 6–20 eq. of $K_2CO_3$ or NaOH as the base.

conditions (entry 3). Neither changes in the amount or strength of base nor addition of an organic cosolvent altered this result. Taken together with the successful cross-coupling of phenylboronic acid with 8-BrA, the unsuccessful reaction with 8-BrG in various aqueous media suggests that addition of an organic cosolvent has neither a prohibitive nor a beneficial effect on cross-coupling efficiency.

We next turned our attention to a catalytic system composed of $Pd(OAc)_2$ as the palladium source and the *water-soluble* phosphine ligand TPPTS (triphenylphosphine trisulfonic acid).[8] The reduced reactivity of guanosine analogues in metal-catalyzed reactions has been attributed to the coordination of the catalytic metal by the nucleobase.[8] Western and coworkers have successfully overcome this difficulty by employing the $Pd(OAc)_2$/TPPTS system for the arylation of 8-bromo-2′-deoxyguanosine and 8-BrG in $MeCN/H_2O$.[8] To test the practicability of this catalytic system in water, we set out to obtain isolated yields for the cross-coupling of 8-BrA, 8-BrG, and 6-ClP with a range of phenylboronic acids (Table 2).

Use of the $Pd(OAc)_2$/TPPTS system allowed the clean cross-coupling of 8-BrA with phenylboronic acid in water, $MeCN/H_2O$, and $DME/H_2O$ (Table 2, entries 4a–c). Similar to the results obtained with $Pd(PPh_3)_4$, and in contrast to Western's observations for the $Pd(OAc)_2$/TPPTS system based on HPLC data,[8] we found that the use of a cosolvent did not have a discernible

***Table 2.*** Suzuki–Miyaura cross-coupling of halopurine nucleosides with various phenylboronic acids in aqueous media using $Pd(OAc)_2$/TPPTS[a]

| Entry | Substrate | Aryl (Ar) | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 4a | 8-BrA | Phenyl | $H_2O$ | 75 |
| 4b | 8-BrA | Phenyl | $MeCN/H_2O$[c] | 94 |
| 4c | 8-BrA | Phenyl | $DME/H_2O$[d] | 69 |
| 5 | 6-ClP | Phenyl | $H_2O$ | 70 |
| 6a | 8-BrG | Phenyl | $H_2O$ | 61 |
| 6b | 8-BrG | Phenyl | $MeCN/H_2O$ | 75 |
| 6c | 8-BrG | Phenyl | $DME/H_2O$ | 0[e] |
| 7 | 8-BrA | 4-tolyl | $H_2O$ | 70 |
| 8 | 8-BrA | 4-methoxyphenyl | $H_2O$ | 79 |
| 9 | 8-BrA | 4-Cl-phenyl | $H_2O$ | 96 |
| 10 | 8-BrG | 4-tolyl | $H_2O$ | 83 |
| 11 | 8-BrG | 4-methoxyphenyl | $H_2O$ | 87 |
| 12 | 8-BrG | 4-Cl-phenyl | $H_2O$ | 84 |

[a]Reagents and conditions: 2.5 mol % $Pd(OAc)_2$/TPPTS (Pd : L 1 : 2.5), $K_2CO_3$ (2 eq.), $ArB(OH)_2$ (1.5 eq.), 80°C, 1–4 h.

[b]Isolated yields. Not optimized.

[c]$MeCN/H_2O$ (1 : 2).

[d]$DME/H_2O$ (2 : 1).

[e]Reaction time was 24 h.

effect on the formation of side products. The yields for the product 8-phenyladenosine were good to excellent for all three reactions, and no side products were isolated. In addition, reaction times were generally much shorter under these conditions than with the $Pd(PPh_3)_4$ system. The $Pd(OAc)_2$/TPPTS catalyst also successfully catalyzed the cross-coupling of phenylboronic acid with 6-ClP in water (entry 5) and, different from the $Pd(PPh_3)_4$ system, with 8-BrG in water and MeCN/$H_2O$ (entries 6a,b). Representative procedure: a flask containing 8-BrG (99.9 mg, 0.276 mmol), potassium carbonate (80.7 mg, 0.584 mmol), phenylboronic acid (50.4 mg, 0.413 mmol), palladium acetate (2.1 mg, 0.009 mmol), and TPPTS (13.6 mg, 0.024 mmol) was purged with nitrogen. Water (distilled, 6 ml) was added through a septum, and the reaction was stirred under nitrogen at 80°C until TLC ($CHCl_3$/MeOH 16 : 5) showed completion (3 h). The reaction was cooled to room temperature and diluted with water (20 ml). Upon neutralization of the aqueous solution with hydrochloric acid (10%), a precipitate formed. The precipitate was dissolved by heating, and the clear solution was kept at 0°C for several hours. The precipitate was collected by filtration and dried in vacuo to give 8-phenylguanosine as a white powder (60.1 mg, 61%). $^1$H NMR (DMSO-$d_6$, 400 MHz, assignments based on COSY) $\delta$ 10.75 (s, 1H, exchangeable, NH), 7.65–7.62 (m, 2H, ph), 7.51–7.49 (m, 3H, ph), 6.38 (bs, 2H, exchangeable, $NH_2$), 5.61 (d, 6.4 Hz, 1H, H-1′), 5.37 (d, 6.4 Hz, 1H, OH-2′), 5.05–4.97 (m, 3H, partly exchangeable, H-2′, OH-3′, OH-5′), 4.07–4.03 (m, 1H, H-3′), 3.82–3.79 (m, 1H, H-4′), 3.68–3.62 (m, 1H, $H_a$-5′), 3.55–3.49 (m, 1H, $H_b$-5′); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 157.3, 153.8, 152.7, 148.2, 130.7, 130.1, 129.9, 129.3, 117.8, 89.6, 86.5, 71.3, 70.9, 62.8; HRMS (ES) m/z 360.1301, calcd. for $C_{16}H_{18}N_5O_5$ $[M + H]^+$: 360.1302.

However, in DME/$H_2O$, only very slow formation of 8-phenylguanosine was observed by TLC, and decomposition became predominant during the course of the reaction (entry 6c).

Next, we explored the scope of the $Pd(OAc)_2$/TPPTS protocol in water with regard to the cross-coupling of 8-BrA and 8-BrG with several substituted phenylboronic acids (Table 2, entries 7–12). Under these conditions, the cross-coupling of 4-tolylboronic acid, 4-methoxyphenylboronic acid, and 4-chlorophenylboronic acid with both 8-BrA (entries 7–9) and 8-BrG (entries 10–12) went to completion in 1–4 h. The 8-arylated nucleosides were purified by column chromatography (adenosine analogues) or through precipitation from aqueous solution (guanosine analogues) and were isolated in generally good to excellent yields. To assess the potential effect of an organic cosolvent, we also carried out all of these reactions in MeCN/$H_2O$ under otherwise identical conditions. In agreement with the findings for the cross-coupling of 8-BrA and 8-BrG with the parent phenylboronic acid (entries 4a,b and 6a,b), the organic cosolvent did not affect reaction times or yields for the reactions with substituted phenylboronic acids. For comparison, the isolated yields for the cross-coupling of 8-BrA (8-BrG) in MeCN/$H_2O$ with substituted phenylboronic acids using the

$Pd(OAc)_2$/TPPTS system were as follows: 4-tolylboronic acid 83% (89%); 4-methoxyphenylboronic acid 66% (87%); 4-chlorophenylboronic acid 84% (78%).

A certain limitation of the $Pd(OAc)_2$/TPPTS protocol became apparent when this system was applied to the cross-coupling of 8-BrA with 4-hydroxyphenylboronic acid (Table 3). In water and DME/$H_2O$, the cross-coupling reaction did take place but was accompanied by cleavage of the glycosidic bond (Table 3, entries 13a,c). After chromatographic purification, the deribosylated nucleobase 8-(*p*-hydroxyphenyl)adenine was obtained as the only product from both reactions. In MeCN/$H_2O$, no cross-coupled product was detected at all (entry 13b). Phenol was isolated in 15% yield as the only product from this reaction, indicating that under these conditions deboronation occurs as an important side reaction that prevents cross-coupling.

The successful conversion of 8-BrA into 8-(*p*-hydroxyphenyl)adenosine was finally accomplished with $Pd(PPh_3)_4$ as the catalyst. In water, MeCN/$H_2O$, and DME/$H_2O$, this approach cleanly provided the cross-coupled nucleoside (entries 14a–c). The comparatively low yields of 8-(*p*-hydroxyphenyl)-adenosineisolated from all three reactions can be attributed to the loss of the very polar material during chromatography, as TLC indicated complete consumption of starting material and only minor formation of side products.

In summary, we have identified suitable reaction conditions for the cross-coupling of unprotected halopurine nucleosides with phenylboronic acids in

***Table 3.*** Suzuki–Miyaura cross-coupling of 8-bromoadenosine and 4-hydroxyphenylboronic acid (Ar = 4-hydroxyphenyl) in aqueous media

| | | | Yield[a] (%) | |
|---|---|---|---|---|
| Entry | Conditions | Solvent | Product[b] | Side product |
| 13a | A[c] | $H_2O$ | 0 | 55[d] |
| 13b | A | MeCN/$H_2O$[e] | 0 | 15[f] |
| 13c | A | DME/$H_2O$[g] | 0 | 45[d] |
| 14a | B[h] | $H_2O$ | 26 | 0 |
| 14b | B | MeCN/$H_2O$ | 35 | 0 |
| 14c | B | DME/$H_2O$ | 25 | 0 |

[a]Isolated yields. Not optimized.

[b]8-(*p*-Hydroxyphenyl)adenosine.

[c]System A: 2.5 mol % Pd acetate/TPPTS (2.5 : 1 L : Pd), $K_2CO_3$ (2 eq.), 4-hydroxyphenylboronic acid (1.5 eq.), 80°C, 24 h.

[d]8-(*p*-Hydroxyphenyl)adenine.

[e]MeCN/$H_2O$ (1 : 2).

[f]Phenol.

[g]DME/$H_2O$ (2 : 1).

[h]System B: 10 mol % $Pd(PPh_3)_4$, $K_2CO_3$ (6 eq.), 4-hydroxyphenylboronic acid (1.5 eq.), 80°C, 24 h.

water. $Pd(PPh_3)_4$ is a useful catalyst for the cross-coupling of a range of phenylboronic acids including 4-hydroxyphenylboronic acid with 8-BrA and, to a lesser extent, with 6-ClP, but fails with the less reactive 8-BrG. The $Pd(OAc)_2$/TPPTS system allows the cross-coupling of all three halopurine nucleosides with the same family of phenylboronic acids, apart from 4-hydroxyphenylboronic acid. Interestingly, with neither Pd(PPh3)4 nor Pd(OAc)2/TPPTS does the presence of an organic cosolvent have a pronounced effect on cross-coupling efficiency, and the target arylnucleosides were generally isolated from reactions in water in good to excellent yields.

We are currently applying the cross-coupling protocols described herein to the direct structural modification of the corresponding nucleotides and NDP sugars under similar conditions, and results from these studies will be reported in due course.



## EXPERIMENTAL

### 8-Phenyladenosine (Entry 1a)

A flask containing 8-BrA (109.7 mg, 0.476 mmol), potassium carbonate (271.6 mg, 1.97 mmol), phenylboronic acid (61.0 mg, 0.500 mmol) and $Pd(PPh_3)_4$ (51.4 mg, 0.044 mmol) was purged with nitrogen. Water (distilled, 6 ml) was added through a septum and the reaction was stirred under nitrogen at 80°C until TLC ($CHCl_3$/MeOH 16 : 5) showed completion (24 h). The reaction was cooled to room temperature and filtered through Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica, $CHCl_3$/MeOH 8 : 1) to give 8-phenyladenosine as a white powder (82.0 mg, 75%). $^1$H NMR (DMSO-$d_6$, 400 MHz, assignments based on COSY) $\delta$ 8.13 (s, 1H, H-2), 7.74–7.72 (m, 2H, ph), 7.57–7.56 (m, 3H, ph), 7.50 (bs, 2H, exchangeable, $NH_2$), 5.81 (dd, 2.8/8.9 Hz, 1H, exchangeable, OH-5′), 5.74 (d, 7.2 Hz, 1H, H-1′), 5.47 (d, 6.4 Hz, 1H, exchangeable, OH-2′), 5.18–5.15 (m, 1H, H-2′), 5.13 (d, 3.9 Hz, 1H, exchangeable, OH-3′), 4.14 (m, 1H, H-3′), 3.92 (m, 1H, H-4′), 3.70–3.66 (m, 1H, $H_a$-5′), 3.56–3.50 (m, 1H, $H_b$-5′); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 156.9, 152.7, 151.6, 150.5, 130.8, 130.3, 130.1, 129.4, 119.8, 89.8, 87.4, 71.9, 71.8, 63.0; HRMS (ES) m/z 344.1356, calcd. for $C_{16}H_{18}N_5O_4$ $[M + H]^+$: 344.1353.

### 8-Phenylguanosine (Entry 6a)

A flask containing 8-BrG (99.9 mg, 0.276 mmol), potassium carbonate (80.7 mg, 0.584 mmol), phenylboronic acid (50.4 mg, 0.413 mmol), palladium acetate (2.1 mg, 0.009 mmol) and TPPTS (13.6 mg, 0.024 mmol) was purged with nitrogen. Water (distilled, 6 ml) was added through a

septum and the reaction was stirred under nitrogen at 80°C until TLC ($CHCl_3$/MeOH 16 : 5) showed completion (3 h). The reaction was cooled to room temperature and diluted with water (20 ml). Upon neutralisation of the aqueous solution with hydrochloric acid (10%) a precipitate formed. The precipitate was dissolved by heating and the clear solution was kept at 0°C for several hours. The precipitate was collected by filtration and dried *in vacuo* to give 8-phenylguanosine as a white powder (60.1 mg, 61%). $^1$H NMR (DMSO-$d_6$, 400 MHz, assignments based on COSY) $\delta$ 10.75 (s, 1H, exchangeable, NH), 7.65–7.62 (m, 2H, ph), 7.51–7.49 (m, 3H, ph), 6.38 (bs, 2H, exchangeable, $NH_2$), 5.61 (d, 6.4 Hz, 1H, H-1′), 5.37 (d, 6.4 Hz, 1H, OH-2′), 5.05–4.97 (m, 3H, partly exchangeable, H-2′, OH-3′, OH-5′), 4.07–4.03 (m, 1H, H-3′), 3.82–3.79 (m, 1H, H-4′), 3.68–3.62 (m, 1H, $H_a$-5′), 3.55–3.49 (m, 1H, $H_b$-5′); $^{13}$C NMR (DMSO-$d_6$, 400 MHz) $\delta$ 157.3, 153.8, 152.7, 148.2, 130.7, 130.1, 129.9, 129.3, 117.8, 89.6, 86.5, 71.3, 70.9, 62.8; HRMS (ES) m/z 360.1301, calcd. for $C_{16}H_{18}N_5O_5$ $[M + H]^+$: 360.1302.

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