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# Copper-Catalyzed Cross-Coupling Reactions of Nucleobases with Arylboronic Acids: An Efficient Access to *N*-Arylnucleobases

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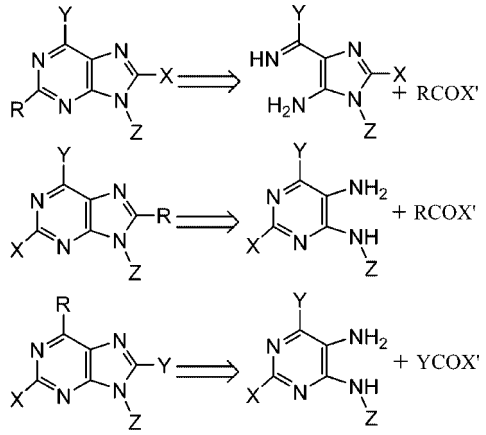
**Keywords:** *N*-arylation / Cytosine / Adenine / Boronic acid / Copper / Cross-coupling

An efficient avenue for the direct *N*-arylation of nucleobases with arylboronic acids that is catalyzed by simple copper salts was discovered. The *N*-arylnucleobases were obtained in excellent yields at room temperature within 45 min when methanol and water were used as a mixed solvent. Under these conditions, the coupling reaction tolerates both electron-donating and electron-withdrawing substituents at the *o*-, *m*-, or *p*-positions of phenylboronic acid and gives the corresponding coupling products in moderate to excellent yields. Experimental results show that this route is the most efficient, facile, and mild method for the synthesis of *N*-arylnucleobases.


*N*-Arylnucleobases are very important compounds because of their significant pharmaceutical, biological, and chemical activities. Several arylnucleobases are agonists or antagonists for various receptors[1] and enzymes.[2] Other bioactivities reported include those against the rubella virus,[3] and inhibition of rabbit skeletal muscle phosphorylase *b*.[4]

The arylation of purine had been reported. To date, there are two ways for the synthesis of arylpurine. One classical method for the preparation of 9-arylpurines is based on heterocyclization[5] (Scheme 1). However, it was not an efficient access because of the many tedious steps involved.




Scheme 1. R = C-substituent; X, Y, Z = other substituents.

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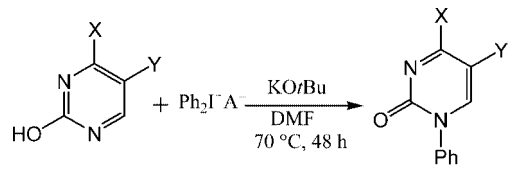
The second method is the direct *N*-arylation of purine with arylboronic acids through a copper-catalyzed reaction.[6] Up to now, only a few examples of the direct *N*-arylation of N9 of purine were reported. Schultz and coworkers reported the reaction of 2,6-dichloropurine with arylboronic acids in the presence of cupric acetate and triethylamine, and the desired N9-aryl product was obtained in moderate yields.[6a] Recently, an efficient procedure for the regioselective arylation of N9 of purines was reported by Bakkestuen and Gundersen,[6b] and these authors found that purines with a variety of substituents can be efficiently arylated at the N9 position with complete regioselectivity and in most cases high chemoselectivity when treated with arylboronic acids in the presence of copper(II) acetate, molecular sieves, and a base. Unfortunately, *N*-arylation of adenine was not successful under these anhydrous reaction conditions.

In addition, there are a few cases for the arylation of cytosine. Tore reported a case (Scheme 2) for the preparation of 1-phenylcytosine **2** in which the appropriately substituted pyrimidinone **1** was reacted with diphenyliodonium salts in DMF.[7] However, low yields of *N*-arylpyrimidinones were obtained.




**1** **2**

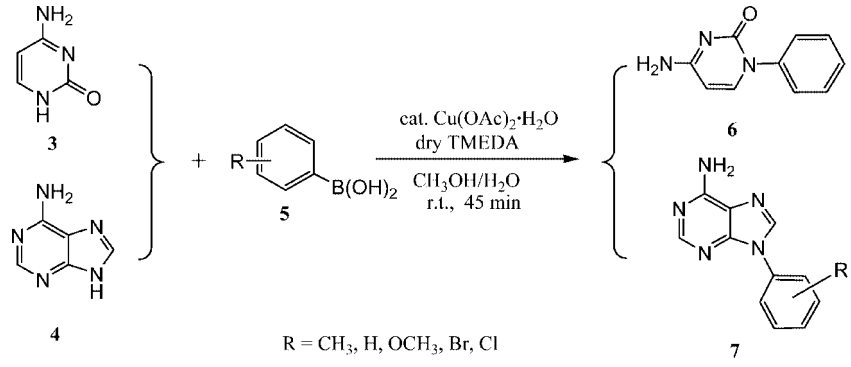
$A^- = Cl^-, BF_4^-, OTf^-$
X = H, OH, OMe, $OCH_2CH_2TMS$, $NH_2$, $NMe_2$
Y = H, F, Cl, Br, Me, OMe

Scheme 2.

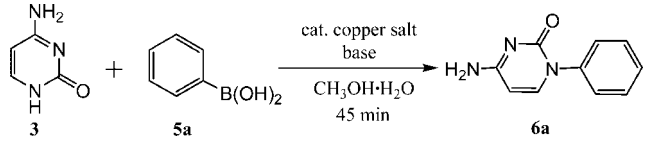
Our experience with the copper-catalyzed *N*-arylation of a number of NH-containing substrates with arylboronic acids[8] inspired us to take a closer look at the *N*-arylation of nucleobases. In this paper, we report a new method for the synthesis of *N*-arylnucleobases. By using this method, nucleobases can be efficiently arylated at the N9 position of adenine (**4**) and the N1 position of cytosine (**3**) with complete regioselectivity when treated with arylboronic acids in the presence of copper(II) acetate as depicted in Scheme 3 To the best of our knowledge, the direct coupling of nucleobases with arylboronic acids performed in protic solvents and with the use of simple copper salts has not been explored previously. Experimental results show that this route is the most efficient, facile, and mild method for the synthesis of *N*-arylnucleobases.

Typically, the coupling reaction of N-heterocycles with arylboronic acids is usually performed under anhydrous conditions.[9] To our surprise, the coupling reaction of cytosine (**3**) with phenylboronic acid (**5a**) that is catalyzed by $Cu(OAc)_2$ only gave trace amounts of the coupling product **6a** with $CH_3OH$ as the reaction solvent and in the presence of 4 Å molecular sieves even after 24 h. On the contrary,




Scheme 3.

Table 1. Optimization of the reaction conditions for the coupling reaction.




| Entry[a] | $PhB(OH)_2$ [mmol] | Copper salt [0.5 mmol] | Base [1 mmol] | $CH_3OH/H_2O$ [v:v] | Reaction temperature [°C] | Yield of **6a** [%][b] |
|---|---|---|---|---|---|---|
| 1 | 1 | $Cu(OAc)_2$ | TMEDA | $CH_3OH$ | r.t. | trace |
| 2 | 1 | $Cu(OAc)_2$ | TMEDA | 8:1 | r.t. | 44 |
| 3 | 1 | $Cu(OAc)_2$ | TMEDA | 5:1 | r.t. | 84 |
| 4 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | r.t. | 90 |
| 5 | 1 | $Cu(OAc)_2$ | TMEDA | 3:1 | r.t. | 86 |
| 6 | 1 | $Cu(OAc)_2$ | TMEDA | 2:1 | r.t. | 69 |
| 7 | 1 | $Cu(OAc)_2$ | TMEDA | 1:1 | r.t. | 22 |
| 8 | 1 | $Cu(OAc)_2$ | TMEDA | $H_2O$ | r.t. | 0 |
| 9 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | r.t. | 90 |
| 10 | 1 | $Cu(OAc)_2$ | Pyridine | 4:1 | r.t. | trace |
| 11 | 1 | $Cu(OAc)_2$ | DMAP | 4:1 | r.t. | trace |
| 12 | 1 | $Cu(OAc)_2$ | 1,10-Phenanthroline | 4:1 | r.t. | trace |
| 13 | 1 | $Cu(OAc)_2$ | TEA | 4:1 | r.t. | trace |
| 14 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | 0 | 58 |
| 15 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | 40 | 40 |
| 16 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | 60 | 16 |
| 17 | 1 | $Cu(OAc)_2$ | TMEDA | 4:1 | 80 | 11 |
| 18 | 1 | $CuSO_4·5H_2O$ | TMEDA | 4:1 | r.t. | 82 |
| 19 | 1 | CuCl | TMEDA | 4:1 | r.t. | 75 |
| 20 | 1 | $CuCl_2$ | TMEDA | 4:1 | r.t. | 54 |
| 21 | 1 | CuBr | TMEDA | 4:1 | r.t. | 88 |
| 22 | 1 | $Cu(OTf)_2$ | TMEDA | 4:1 | r.t. | 86 |
| 23 | 0.5 | $Cu(OAc)_2$ | TMEDA | 4:1 | r.t. | 67 |
| 24 | 1.5 | $Cu(OAc)_2$ | TMEDA | 4:1 | r.t. | 90 |
| 25 | 2 | $Cu(OAc)_2$ | TMEDA | 4:1 | r.t. | 91 |

[a] Conditions: **3** (0.5 mmol), 45 min. [b] Isolated yield.

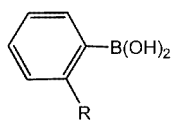
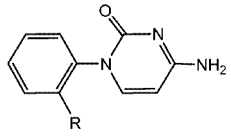
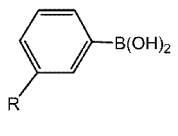
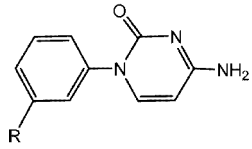
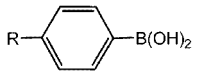
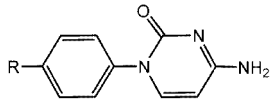
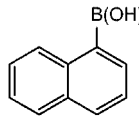
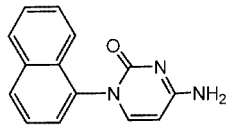
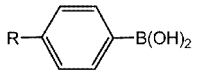
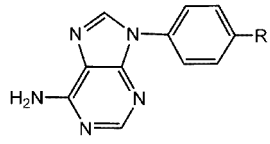
  

when $Cu(OAc)_2$ was replaced by $Cu(OAc)_2 \cdot H_2O$, the yield of the coupling product was increased significantly in the absence of 4 Å molecular sieves. On the basis of this result we tried to study the coupling reaction in a mixed protic solvent and found that when a small quantity of water ($CH_3OH/H_2O$ 8:1) was added, the coupling yield was increased to 44%, and when a 4:1 ratio for $CH_3OH/H_2O$ was used, the coupling yield was 90% (Table 1, entries 2 and 4). However, below a ratio of 3:1, the yield of the coupling product continuously decreased (Table 1, entries 5, 6, 7 and 8). So the mixed solvent with a 4:1 ratio for $CH_3OH/H_2O$ is the optimum solvent for the coupling of cytosine with arylboronic acid, and the results are shown in Table 1. It can therefore be deduced that the solvent effect is one of the most important factors that influence the coupling of nucleobases with arylboronic acids – the mixed solvent is essential to the coupling reaction.

Subsequently, our exploration focused on the cross-coupling of cytosine and phenylboronic acid under different reaction conditions. Detailed results are summarized in Table 1. The effect of various bases and/or Cu ligands on the reaction of cytosine and phenylboronic acid was studied (Table 1, entries 9–13). Only with TMEDA can the coupling product be obtained in good yield (90%, entry 9); however, the cross-coupling reaction is not efficient with TEA, pyridine, DMAP, and 1,10-phenanthroline as base (Table 1, entries 10–13). The effect of reaction temperature on the chemical yield was also examined. The results show that at room temperature, a yield of 90% was obtained (Table 1, entry 9); however, lower yields, 58, 40, 16, and 11%, were obtained when the reaction was carried out at 0, 40, 60 and 80 °C, respectively (Table 1, entries 14–17). Therefore, the optimum temperature is room temperature. In addition, several simple copper salts such as $CuSO_4 \cdot 5H_2O$, CuCl, $CuCl_2$, CuBr, and $Cu(OTf)_2$ were tested as catalysts to promote the coupling reaction. As shown in Table 1, all the copper salts that we used gave the desired products in high yields (Table 1, entries 18, 19, 21 and 22), except for $CuCl_2$, which gave the coupling product in moderate yield (Table 1, entry 20). The ratio of phenylboronic acid to cytosine is also an important factor for this coupling reaction. We found that when the ratio is more than 1:1, $N^1$-phenylcytosine was obtained in over 90% yield (Table 1, entries 9, 24 and 25). Decreasing the ratio to 0.5:1, $N^1$-phenylcytosine was obtained in only 67% yield (Table 1, entry 23). So the effect of the amount of phenylboronic acid on the coupling reaction was slight with an increase in phenylboronic acid loading from 1 equiv. to 2 equiv.

Several substituted arylboronic acids were evaluated under the above-mentioned reaction conditions, and adenine was also used as a coupling substrate. As shown in Table 2, the catalytic system has proven to be highly efficient for the coupling of other arylboronic acids with cytosine or adenine. The results show that when the *o*-, *m*-, and *p*-tolylboronic acids, phenylboronic acids, and naphthylboronic acid were used, the corresponding *N*-arylation products were obtained in over 80% yield (Table 2, entries 1, 2, 6, 7, 9, 11 and 12). Moderate yields were obtained with substituted phenylboronic acids by both electron-donating and electron-withdrawing substituents at the *o*-, *m*-, or *p*-position of the phenyl group (Table 2, entries 3, 4, 5, 8, 10 13 and 14).

Table 2. Coupling reaction of **3** and **4** with various substituted phenylboronic acids.[10]

| Entry[a] | $ArB(OH)_2$ | Product | Yield [%] [b] |
|---|---|---|---|
| |  |  | |
| 1 | **5a**: R = H | **6a** | 90 |
| 2 | **5b**: R = $CH_3$ | **6b** | 83 |
| 3 | **5c**: R = $OCH_3$ | **6c** | 50 |
| |  |  | |
| 4 | **5d**: R = $OCH_3$ | **6d** | 53 |
| 5 | **5e**: R = Br | **6e** | 74 |
| 6 | **5f**: R = $CH_3$ | **6f** | 90 |
| |  |  | |
| 7 | **5g**: R = $CH_3$ | **6g** | 85 |
| 8 | **5h**: R = Br | **6h** | 68 |
| 9 | **5i**: R = $OCH_3$ | **6i** | 82 |
| 10 | **5j**: R = Cl | **6j** | 72 |
| |  |  | |
| 11 | **5k** | **6k** | 83 |
| |  |  | |
| 12 | **5a**: R = H | **7a** | 85 |
| 13 | **5h**: R = Br | **7h** | 60 |
| 14 | **5i**: R = $OCH_3$ | **7i** | 66 |

[a] Conditions: **3** or **4** (0.5 mmol), substituted boronic acid (1 mmol), TMEDA (1 mmol), $Cu(OAc)_2$ (0.5 mmol), methanol (36 mL), water (9 mL), r.t., 45 min. [b] Isolated yield.

In summary, a mild and efficient avenue for the direct *N*-arylation of nucleobases with arylboronic acids that is catalyzed by simple copper salts, which is cost-effective, easy to handle, and does not need an insert atmosphere, was developed for the first time. The *N*-arylnucleobases were obtained in excellent yields at room temperature within 45 min when methanol and water was used as a mixed sol-

vent. Under these conditions, the reaction tolerates both electron-donating and electron-withdrawing substituents at the *o*-, *m*-, or *p*-positions of phenylboronic acid and gives corresponding coupling products in moderate to excellent yields.

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[10] **General Procedure for the Cross-Coupling Reaction:** Compound **3** (0.0556 g, 0.5 mmol), **5** (1 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.099 g, 0.5 mmol), TMEDA (150 μL, 1 mmol), $CH_3OH$ (36 mL), and $H_2O$ (9 mL) were placed in a 100 mL vial. The reaction mixture was vigorously stirred under an atmosphere of air at room temperature for 45 min. The solvents were evaporated, and the product purified by flash column chromatography on silica gel ($CH_2Cl_2/CH_3OH$, 5:1) to give **6**. **Selected Data for *N*$^1$-Phenylcytosine (6a):** White powder solid. M.p. >300 °C. IR (neat): 3334, 3066, 1638, 1486, 1372, 1294, 1174, 1128, 784, 698 $cm^{-1}$. $^1H$ NMR (400 M Hz, [$D_6$]DMSO): $\delta$ = 5.78–5.80 (d, $J$ = 8.0 Hz, 1 H, CH), 7.24 (s, 1 H, NH), 7.32 (s, 1 H, NH), 7.34–7.38 (m, 3 H, Ph-H), 7.45 (t, 2 H, $J$ = 7.6 Hz, Ph-H), 7.62–7.64 (d, $J$ = 8.0 Hz, 1 H, CH) ppm. $^{13}C$ NMR (200 MHz, [$D_6$]-DMSO): $\delta$ = 94.26, 126.75, 127.50, 128.99, 141.46, 146.03, 154.93, 166.21 ppm. MS (ESI): $m/z$ = 188.3 $[M + H]^+$. HRMS (ESI): for $C_{10}H_{10}N_3O$ $[M + H]^+$: calcd. $m/z$ = 188.0818; found $m/z$ = 188.0822.

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