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Copper catalyzed arylation with boronic acids for the synthesis of N^1-aryl purine nucleosides

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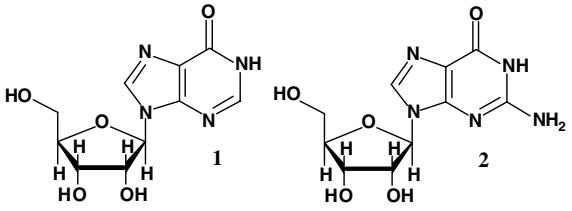
Abstract—The synthesis of a series of N^1-aryl inosine and guanosine derivatives is described. The procedure for chemoselective N^1-arylation involves the mild oxidative copper(II) mediated coupling with boronic acids. This approach provides access to substituted N^1-aryl purines with interesting structural characteristics and novel scaffolds for drug discovery.

Modified nucleosides exhibit biomedical significance due to their antiviral and anticancer chemotherapeutic properties, and are also of interest for applications as probes for investigating biological processes.[1] Derivatization of the purine heterocyclic bases of inosine **1** and guanosine **2** with sterically hindered or polar functional groups affects hydrogen bonding, π-stacking, and other interactions associated with base-pairing and protein receptor binding.



Nucleophilic aromatic substitution reactions (S_NAr) have been widely used for the syntheses of aryl-purine derivatives, particularly at the C-6 and C-2 position.[2] The application of palladium catalyzed C–C and C–N coupling procedures have extended the synthetic versatility and efficiency to a broad range of aryl-purine derivatives.[3] Complementary chemoselectivity has been observed with palladium and copper(I) catalyzed C–N couplings using aryl halides, with preferential arylation of amines or amides, using Pd or Cu(I) catalysts, respectively.[4] The methodology for copper(II) mediated N/O-arylation with aryl-boronic acids developed by Chan–Evans–Lam accommodates a broad range of substrates.[5] Copper catalyzed coupling procedures with boronic acids have been used for N-arylation at the N-9 position of purines, and the C-2 amine of aminopurines.[6]

Our interest was drawn to N^1-aryl purines as a novel structural class and potential scaffold for drug discovery. Few examples of N^1-aryl purines have been described. The S_NAr reaction of highly electron deficient aryl-halides was used to synthesize N^1-nitrophenyl inosine derivatives.[7] N^1-phenylinosine was prepared by arylation of tetrahydropyran-2-yl-protected inosine with iodobenzene and cuprous oxide under forcing conditions at high temperature (190 °C) with low yield.[8] Considering the successful C–N arylation of 2-pyridinones with Cu(II)/aryl-boronic acids, we were encouraged to investigate the possible N^1-arylation of purines.[9] Herein, we report a general procedure for N^1-arylation of inosine and guanosine that employs copper catalyzed coupling with boronic acids. This approach provides efficient access to N^1-aryl derivatives and accommodates diverse functionality in the aryl substrate.

The β-D-ribose groups of inosine **1** and guanosine **2** were tri-protected as *tert*-butyldimethylsilyl (TBS) ethers

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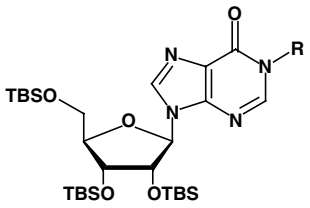
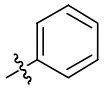
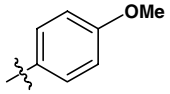
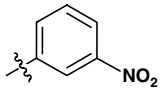
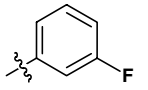
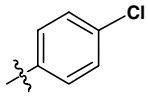
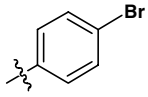
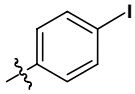
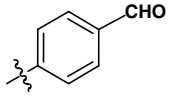
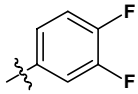
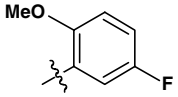
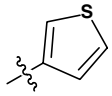
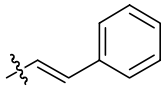
under standard conditions. In route to the optimized conditions, various modifications were explored, based on the results from Lam et. al.[9a] With these substrates, conditions without co-oxidant or added oxygen were low yielding and required longer reaction times. Using triethylamine base also resulted in reduced yields. Optimal catalytic reaction conditions for N^1-arylation of inosine with phenylboronic acid to produce **3** (Table 1, entry 1) were achieved using pyridine as base and pyridine N-oxide co-oxidant in dichloromethane at ambient temperature under an atmosphere of oxygen.[10]

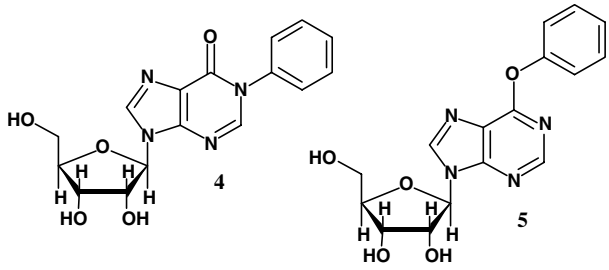
Table 1. Protected[a] N^1-aryl inosine derivatives



Entry	Compd	R	Yield (%)
1	**3**		86
2	**6**		97
3	**7**		89
4	**8**		100
5	**9**		97
6	**10**		78
7	**11**		93
8	**12**		40
9	**13**		95
10	**14**		29
11	**15**		61
12	**16**		99

[a] TBS = *tert*-butyldimethylsilyl.

The chemoselectivity of this reaction for the 2-pyridinone moiety of the purine ring system is of interest, considering the potential for N- versus O-arylation with substrate **1**. The reaction product **3** was deprotected using standard tetrabutylammonium fluoride conditions. The structural assignment was confirmed by comparison of the spectral data for **4** to the known N^1-phenyl derivative.[8] None of the possible *O*-phenyl product **5** was observed under these reaction conditions.



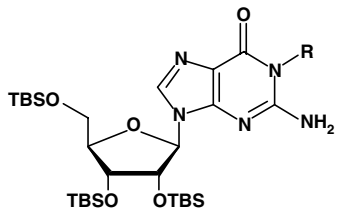
A variety of aryl-boronic acids with diverse functionality were coupled in moderate to excellent yields as shown in Table 1. The reaction was effective with electron donating, withdrawing, and neutral functional groups. Maximum conversion of aryl-boronic acids to products were typically obtained within 24 h for the full range of substituents. The vinylation reaction with *trans*-2-phenylvinylboronic acid was complete within 5 h and provided a quantitative yield (entry 12). Reduced yields were obtained for *ortho*-substituted 5-fluoro-2-methoxyphenylboronic acid, presumably due to the increased steric hindrance of the *ortho* methoxy group. The isolated yield of the 4-formylphenyl product was significantly reduced due to competitive oxidation of the aldehyde group under these conditions (entry 8).

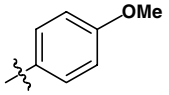
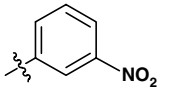
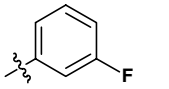
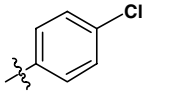
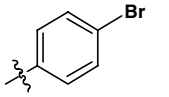
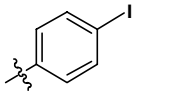
The products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.[11] The exchangeable N^1–H of the protected inosine starting material was not present in the products, and both IR C=O stretches and ^{13}C NMR shifts of the purine ring system were consistent throughout the range of aryl substituents.

Guanosine reacted similarly at the N^1-position, although isolated product yields were generally lower than for the inosine counterparts as shown in Table 2. Improved yields were achieved by increasing the amount of copper from 20% to a stoichiometric ratio (see, entries 1–3).

The N^1-aryl guanosine products exhibited C=O IR stretches that were very similar to that of the corresponding inosine analogs, indicating similar electronic environments in both heterocycles.[12] The ^{1}H NMR of the C-2 amine group in the N^1-aryl guanosine derivatives were consistently observed at $\delta \sim 6.5$ with integration values representing two protons.

Table 2. Protected[a] N^1-aryl guanosine derivatives



Entry	Compd	R	Yield (%)
1	**17**		46 (61)[b]
2	**18**		32 (51)[b]
3	**19**		84 (89)[b]
4	**20**		53
5	**21**		56
6	**22**		43

[a] TBS = *tert*-butyldimethylsilyl.
[b] Yield with 1.1 equiv $Cu(OAc)_2$.

In summary, we have described an efficient procedure for synthesizing novel N^1-aryl inosine and guanosine derivatives. We are currently investigating the anti-viral activity, metabolism, and toxicological properties of these compounds.

Acknowledgments

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10. Typical procedure: To an oven dried Schlenk tube were added the protected nucleoside (0.2 mmol), the boronic acid (0.4 mmol), anhydrous copper(II) acetate (0.04 mmol), pyridine-*N*-oxide (0.4 mmol), ground 4 Å molecular sieves (~20 mg), and a stir bar. The tube was sealed with a septum then evacuated and flushed with oxygen. Dry pyridine (0.4 mmol) and dichloromethane (2 mL, dried over molecular sieves) were then added and the solution was stirred vigorously at room temperature for 24 h. The reaction was then quenched with ammonium hydroxide in methanol (~0.05 mL in 1 mL, respectively) followed by dilution with hexanes (to 50 mL) and washed with one 25 mL portion each of water, saturated ammonium chloride, 1 M sodium hydroxide, and saturated sodium chloride. The organics were dried over sodium sulfate and concentrated in vacuo. Compounds were purified by medium pressure flash chromatography (Isco CombiFlash) with methanol/dichloromethane.
11. Selected data for Table 1: Entry **2**, white solid, mp 78 °C (dec), IR (PTFE card, cm^{-1}) 1716; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19, 8.01 (each 1H, s, H-8, H-2), 7.29 (2H, br d, $J = 9.0$ Hz), 7.01 (2H, br d, $J = 9.0$ Hz), 6.00 (1H, d, $J = 4.9$ Hz, H-1′), 4.50 (1H, m, H-2′), 4.30 (1H, m, H-3′), 4.13 (1H, m, H-4′), 3.98 (1H, m, H-5′), 3.85 (3H, s, $-OCH_3$), 3.79 (1H, m, H-5′), 0.95–0.92 (mult. s, 27H), 0.13–0.14 (mult. s, 18H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.9, 156.6, 147.2, 147.1, 138.7, 129.9, 128.3, 124.8, 114.7, 88.1, 85.4, 76.6, 71.7, 62.3, 55.5, TBS signals not listed;

Elem. Anal. Found: C, 58.70; H, 8.71; N, 7.63; Calcd for $C_{35}H_{60}N_4O_6Si_3$: C, 58.62; H, 8.43; N, 7.81.

12. Selected data for Table 2: Entry **6**, white solid, mp 114 °C (dec), IR (PTFE card, cm^{-1}) 1708; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, s, H-8), 7.21 (2H, br d, $J = 9.0$ Hz), 7.05 (2H, br d, $J = 9.0$ Hz), 5.86 (1H, d, $J = 5.0$ Hz, H-1′), 4.54 (2H, br s, $-NH_2$), 4.42 (1H, m, H-2′), 4.28 (1H, m, H-3′), 4.09 (1H, m, H-4′), 3.93 (1H, m, H-5′), 3.85 (3H, s, $-OCH_3$), 3.77 (1H, m, H-5′), 0.94–0.84 (mult. s, 27H), 0.12–0.10 (mult. s, 18H); Elem. Anal. Found: C, 57.18; H, 8.40; N, 9.45; Calcd for $C_{35}H_{61}N_5O_6Si_3$: C, 57.42; H, 8.40; N, 9.57.