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Copper-mediated coupling of aminopurines and aminopyrimidines with arylboronic acids

Ramesh A. Joshi,* Pratap S. Patil, M. Muthukrishnan, C. V. Ramana and Mukund K. Gurjar*

Division of Organic Chemistry Technology, National Chemical Laboratory, Dr. Homibhabha Road, Pune 411 008, India

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Dedicated to Professor Goverdhan Mehta on the occasion of his 60th birthday

Abstract—Selective *N*-arylation of aminopurines and aminopyrimidines **1**–**3** with arylboronic acids **4**–**6** was explored using copper(II) acetate and the corresponding *N*-arylated purine and pyrimidine derivatives **7**–**15** were obtained in moderate to good yields.

The purine/pyrimidine substructure and their amino substituted congeners are frequently occurring motifs in commercially available drugs. For example, aryl 2-aminopyrimidines have been reported for the treatment of diseases modulated by the adenosine receptor.[1] The anti-HIV/HBV drugs *abacavir penciclovir* and the anti-atherosclerotic *aronixil*, are some of the aminopurine and aminopyrimidine drugs available presently in the market (Fig. 1).[2] Conventionally, nucleophilic aromatic substitution of electron deficient halogenated purines/pyrimidines with suitable amines is used as a general method for the synthesis of amino substituted purines/pyrimidines.[3] However, the substitution reactions are sluggish in the case of electron rich or even with neutral halogenated purines/pyrimidines.

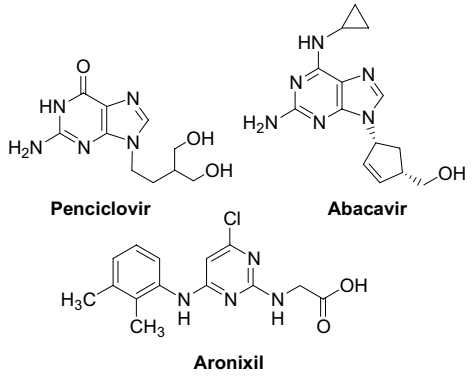

Figure 1. Aminopurine and aminopyrimidine drugs.

Recently, in a drug discovery led structure modification programme, we encountered a need for an efficient methodology for the synthesis of *N*-arylamino purine/pyrimidines. With regard to practicality, we chose to explore Chan–Evans–Lam's[4] copper mediated *O*/*N*-arylations using arylboronic acids. The present communication describes the amenability of this methodology to the successful *N*-arylation of aminopurines as well as of aminopyrimidines for the first time.

Easily available purine **1**,[5] pyrimidines **2**[6] and **3**,[7] and arylboronic acids **4**–**6** (Fig. 2) were chosen as model substrates in this regard. Initial explorations started with

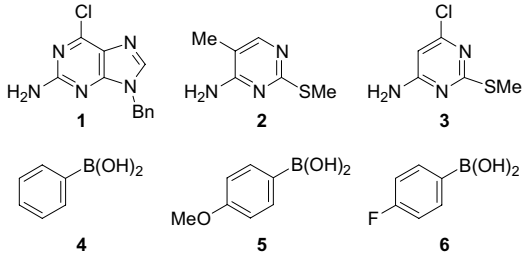

Figure 2. Selected purines/pyrimidines and arylboronic acids.

Keywords: *N*-arylation; arylboronic acid; aminopurine; aminopyrimidine; copper(II) acetate.

* Corresponding authors. Tel.: +91-20-5893614; fax: +91-20-5882456; e-mail: rajoshi@dalton.ncl.res.in; gurjar@dalton.ncl.res.in

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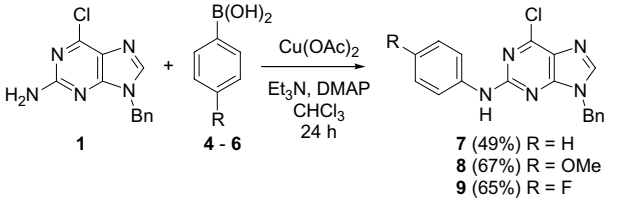
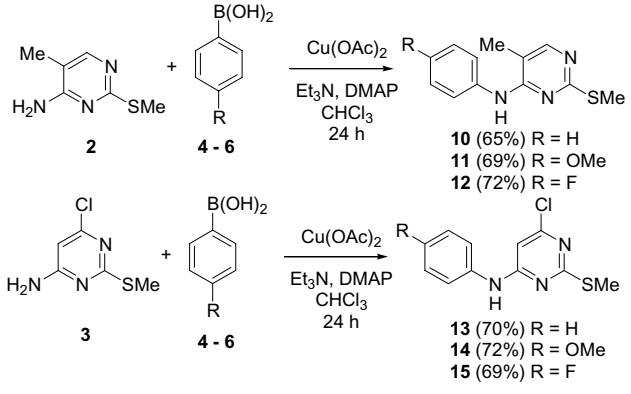
the arylation of the chloro-guanine derivative **1** with phenylboronic acid **4**. After a careful evaluation of a set of parallel experiments we arrived at conditions involving the use of 2 equiv of $Cu(OAc)_2$, DMAP in catalytic amounts and 3 equiv of boronic acid, added in three portions to the reaction mixture at room temperature. The arylated guanine derivative **7** was obtained in 49% yield. Similarly, coupling of guanine **1** with boronic acids **5** and **6** gave the corresponding *N*-aryl guanines **8**[8] and **9** in 67% and 65% yields, respectively. As anticipated, no cross-coupling of the chloro substituent with phenylboronic acid was observed.[9] In general, coupling of halo-purines/pyrimidines with phenylboronic acid is carried out with palladium catalysts (Scheme 1).[9]

After initial success in the arylation of guanine derivative **1**, we extended the same protocol to the *N*-arylation of 5-methyl-2-methylthiopyrimidin-4-amine **2**[6] and of 4-chloro-2-methylthiopyrimidin-6-amine **3**[7] with arylboronic acids **4**–**6**. *N*-arylated pyrimidines **10**–**12** and **13**–**15**, respectively, were obtained in moderate to good yields.[8] It has already been reported by Liebeskind and Srogl, that Pd (cat.) in the presence of stoichiometric amounts of Cu(I) salts can be used for thioether cross-coupling with arylboronic acids.[10] However, in our present experiments [using Cu(II) salts] with either **2** or **3**, we have not noticed the presence of any products resulting from the thioether cross-coupling. The stability of both chloro and thiomethyl groups under these conditions provides an opportunity for orthogonal *N*/*C*-arylations using all three substituents of pyrimidine **3** (Scheme 2).



Scheme 1.



Scheme 2.

To conclude, a general methodology for coupling aminopurines and aminopyrimidines with arylboronic acids has been explored using stoichiometric amounts of Cu(II) acetate. Studies on orthogonal *C*- and *N*-arylation of **1**–**3** using arylboronic acids in the presence of copper and/or palladium are in progress.

Acknowledgements

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8. At room temperature, a suspension of purine **1** (260 mg, 1 mmol), *p*-methoxyphenylboronic acid **5** (150 mg, 1 mmol) and cupric acetate (36 mg, 2 mmol) in chloroform (15 mL) was treated with triethylamine (200 mg, 2 mmol) and DMAP (20 mg) and the stirring was continued at room temperature. The reaction mixture was treated with additional **5** (150 mg, 1 mmol) after 6 h and again after 12 h and stirring continued for another 24 h. The reaction mixture was filtered through Celite and the Celite pad was washed with chloroform and the combined filtrates were concentrated and purified over a silica gel column. The *N*-aryl purine **8** (245 mg, 67%) was obtained as a colourless solid. (a) Spectral data of **8**: mp 198 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 3H), 5.16 (br s, 2H), 6.72 (d, 2H, $J = 8.9$ Hz), 7.17–7.23 (m, 5H), 7.45 (d, 2H, $J = 8.9$ Hz), 7.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.1, 55.1, 113.5, 120.4, 127.5, 128.1, 128.6, 132.6, 134.9, 141.7; MS-ESI: 389.05 (85%), 366.05 ([M+1]$^+$, 100%), 296.05 (20%), 279.05 (20%), 252.05 (50%), 250.05 (50%); Anal. Calcd for $C_{19}H_{16}ClN_5O$: C, 62.38; H, 4.41; N, 19.14; Found: C, 62.06; H, 4.69; N, 18.91. (b) Spectral data of **11**: mp: 112 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.48 (s, 3H), 3.82 (s, 3H), 6.36 (br s, 1H), 6.92 (d, 2H, $J = 8.9$ Hz), 7.45 (d, 2H, $J = 8.9$ Hz), 7.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.3, 14.1, 55.5, 108.9,

113.9, 123.4, 131.4, 154.4, 156.4, 158.7, 169.3; MS-ESI: 300.05 ($[M+K]^+$, 5%), 278.05 ($[M+NH_3]^+$, 15%), 264.05 (30%), 262.05 ($[M+1]^+$, 100%); Anal. Calcd for $C_{13}H_{15}N_3OS$: C, 59.74; H, 5.79; N, 16.08; S, 12.27; Found: C, 59.89; H, 6.07; N, 15.76, S, 11.83. (c) Spectral data of **14**: mp: 124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.84 (s, 3H), 6.18 (s, 1H), 6.92 (d, 2H, $J = 8.9$ Hz), 7.20 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 55.5, 97.6, 114.8, 125.9, 129.5, 157.7, 159.9, 162.1, 172.3; MS-ESI: 284.05 (80%), 282.05 ($[M+1]^+$, 100%), 209.05 (45%); Anal. Calcd for $C_{12}H_{12}ClN_3OS$: C, 51.15; H, 4.29; N, 14.91; S, 11.38; Found: C, 50.89; H, 4.51; N, 14.56; S, 10.97.

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