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Tetrahedron Letters 44 (2003) 3359–3362

TETRAHEDRON LETTERS

Regioselective *N*-9 arylation of purines employing arylboronic acids in the presence of Cu(II)

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Received 16 December 2002; revised 13 February 2003; accepted 28 February 2003

Abstract—9-Arylpurines are efficiently formed with complete regioselectivity when purines are treated with arylboronic acids in the presence of copper(II) acetate. A variety of substituents on both coupling partners are well tolerated.

Several 9-arylpurines are agonists or antagonists for various receptors, such as adenosine receptors,[1] and corticotropin-releasing hormone receptors,[2] and for enzymes like xanthine oxidase,[3] phosphatidylinositol 4-kinase,[4] adenosine deaminase,[5] and guanosine deaminase.[6] Other bioactivities reported include antitumor activity,[7] antimicrobial activity,[8] and plant growth stimulating effects.[9]

We have recently reported profound antimycobacterial activity for 6-aryl-9-benzylpurines as in compound **1** (Fig. 1),[10] whereas the 9-phenylethylpurine derivative **2** was only moderately active. In order to gain further insight into the structural requirements for active antimycobacterial purines, we needed easy access to 9-arylpurines such as compound **3**.

Whereas 9-alkylpurines are readily available by direct *N*-alkylation of purines in the presence of a base[11] or under Mitsunobu conditions,[12] 9-arylpurines **6** are generally formed by the reaction of arylamine with chloropyrimidines **4** followed by ring closure as depicted in Scheme 1.[13] The required starting chloropyrimidines are not always readily available and this route contains an additional step compared with direct *N*-alkylation of the purine.

An alternative method for the construction of 9-aryl-6-oxopurines **8** where appropriately substituted 1-arylimidazoles **7** are reacted with formamide or ethyl chloroformate in DMF, has also been reported (Scheme 2).[14]

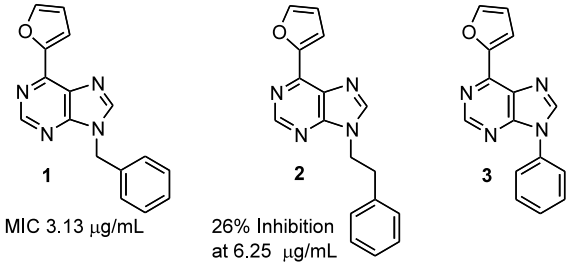
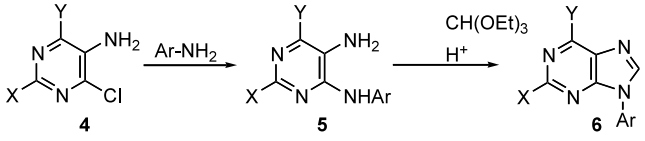
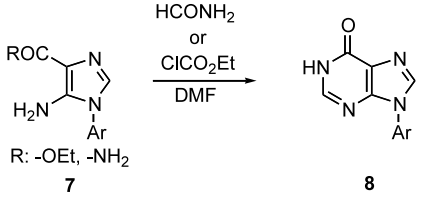


Figure 1. Structure of known and potential antimycobacterial purines **1**–**3** as well as inhibitory activity against *Mycobacterium tuberculosis* found for compounds **1** and **2**.



Scheme 1.



Scheme 2.

Keywords: arylation; boron and compounds; copper and compounds; purines; regiocontrol.

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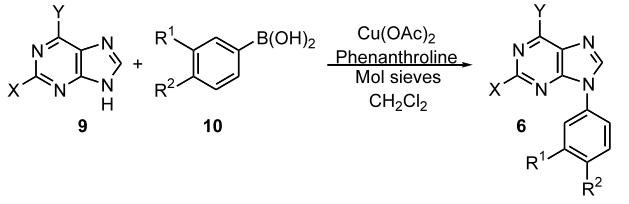
0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00576-8

Recently, efficient procedures for *N*-arylation of amines, amides and heterocyclic NH-functions have been developed. The most commonly used strategy is based on Pd-, Ni- or Cu-catalyzed *N*-arylation with aryl halides or arylsulfonates.[15] In addition, a Cu-mediated *N*-arylation under very mild conditions employing arylboronic acids has been developed[16] and used for *N*-arylation of pyrroles,[17] diazoles[18] and pyridones.[19] *N*-Arylation of exocyclic NH-functions in purines employing the Hartwig–Buchwald strategy has been reported,[20] but except for a single example of *N*-arylation of 2,6-dichloropurine,[21] no one has, to the best of our knowledge, studied direct *N*-arylation of the purine ring nitrogen. We herein report that purines with a variety of substituents, can be efficiently arylated at *N*-9 with complete regioselectivity and in most cases high chemoselectivity, when treated with arylboronic acids in the presence of copper(II) acetate.

Purines **9** were reacted with an excess of aryl boronic acid **10** in the presence of copper(II) acetate, molecular sieves and a base (Scheme 3, Table 1).[22,23] Initial screening of bases and/or Cu-ligands revealed that phenanthroline gave somewhat better yields than triethylamine, pyridine, 2,2′-bipyridine, TMEDA and *N*,*N*′-diarylethanediimines. Both electron-donating and electron-withdrawing substituents on the aryl boronic acids **10** were tolerated. For some reactions the isolated yields were somewhat reduced due to tedious separation of the product from the arylboronic acid anhydrides formed.

Even though 6-chloropurines react with aryl boronic acids to give 6-arylpurines under Suzuki coupling conditions,[24] only *N*-arylation took place when 6-chloropurines were reacted with boronic acids in the presence of copper (entries 1–8). In contrast to *N*-alkylation of purines, Cu mediated *N*-arylation of benzodiazoles,[18a,18b] and the recently reported *N*-arylation of 2,6-dichloropurine,[21] the reactions were completely regioselective, resulting only in arylation at *N*-9. The primary amino group in 6-chloroguanine (entry 8) was unaffected. *N*-Arylation of adenine was, however, not successful (entry 9), most probably due to solubility problems. Thiols are easily arylated by boronic acids/Cu[25] or aryl halides/Pd[26] and 6-mercaptopurine reacted with excess phenylboronic acid to give the *N*,*S*-diarylated product in high yield (entry 11).

The melting points found for the known *N*-arylpurines **6a**–**6f** and **6i**, were in good agreement with those reported when the 9-arylpurines were formed by ring closure reactions (see Table 1). The structural assignments were also based on HMBC NMR spectroscopy where a long range correlation between C-1 in the aryl substituent and H-8 in the purine indicate that the aryl group was located on the nitrogen in the imidazole part of the purine. ^{13}C NMR spectroscopy can be used to distinguish between *N*-7 and *N*-9 substitution in purines,[27] and the ^{13}C NMR spectra of compounds **6** were in good agreement with those previously reported for *N*-9 substituted purines. Furthermore, NOESY spectroscopy of the compounds displayed correlations between the *N*-aryl protons and H-8 (Fig. 2), but not between the aryl protons and H-2 or protons in the 6-substituent.



Scheme 3.

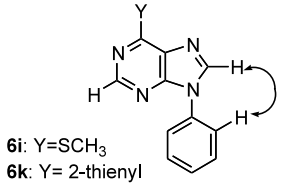


Figure 2. NOESY correlations between the *N*-aryl group and H-8 in selected purines **6**.

Table 1. Cu-mediated reaction between purines **9** and arylboronic acids **10**

Entry	X	Y	R^1	R^2	Yield (%) **6**[a]	Mp/°C (mp Lit.)
1	H	Cl	H	H	71, **6a**	195–197 (202–203)[13]
2	H	Cl	H	CH_3	68, **6b**	179–181 (170–172)[14]
3	H	Cl	H	OCH_3	52, **6c**	202–204 (201–203)[3a]
4	H	Cl	H	Cl	41, **6d**	221–223 (220–222)[13]
5	H	Cl	Cl	H	73, **6e**	199–201 (208–210)[14]
6	Cl	Cl	H	H	52, **6f**	239–241 (244–246)[7a]
7	Cl	Cl	H	CH_3	48, **6g**	202–204
8	NH_2	Cl	H	H	42, **6h**	251–252
9	H	NH_2	H	H	n.r.[b]	–
10	H	SCH_3	H	H	76, **6i**	146–148 (148–149)[13]
11	H	SH/SPh[c]	H	H	81, **6j**	168–171
12	H	2-Thienyl	H	H	68, **6k**	189–191

[a] Yield of isolated product.
[b] No reaction, probably due to poor solubility of the starting material.
[c] 6-Mercaptopurine was converted to 9-phenyl-6-phenylthiopurine.

The 9-aryl-6-chloropurines described herein, have been converted to 9-aryl-6-(2-furyl)purines and these compounds are currently being examined as antimycobacterials.

Acknowledgements

The Norwegian Research Council is greatly acknowledged for partial financing of the Bruker Avance DRX 500 instrument used in this study.

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22. *General procedure for N-arylation of purines*: A mixture of purine **9** (0.33 mmol), arylboronic acid **10** (1.0 mmol), phenanthroline (0.66 mmol), anhydrous copper(II) acetate (0.33 mmol) and dried 4 Å molecular sieves (250 mg) in dry CH_2Cl_2 (5 mL) in a 50 mL round bottom flask connected to a reflux condenser open to air was stirred at ambient temperature for 4 days. Methanol (50 mL) was added and the resulting mixture was filtered through celite, evaporated and purified by flash chromatography on silica gel.
23. *Data for novel compounds*. **6g**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (s, 3H, CH_3), 7.37 (d, J 8.3 Hz, 2H, Ph), 7.50 (d, J 8.3 Hz, 2H, Ph), 8.32 (s, 1H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 123.5, 130.7, 130.8, 131.1, 139.6, 144.9, 152.3, 152.6, 153.6; MS EI m/z (rel.%): 282/280/278 (M^+, 10/65/100), 281 (10), 279 (23), 277 (15), 243 (4), 207 (4), 91 (24), 90 (3). HRMS: Found 278.0117; calcd for $C_{12}H_8N_4Cl_2$ 278.0126; **6h**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (br s, 2H, NH_2), 7.45 (m, 1H, Ph), 7.57 (m, 2H, Ph), 7.81 (d, J 7.8 Hz, 2H, Ph), 8.51 (s, 1H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$): δ 123.5, 123.7, 127.8, 129.5, 134.6, 141.9, 149.9, 153.7, 160.2; MS EI m/z (rel.%): 247/245(M^+, 28/100), 211 (3), 210 (55), 209 (4), 129 (3), 104 (6), 77 (18), 50 (5); HRMS: Found 245.0463, calcd for $C_{11}H_8N_5Cl$ 245.0468. Anal.: Found: C, 53.55; H, 3.27; N, 28.03. $C_{11}H_8ClN_5$ requires C, 53.78; H, 3.28;

N, 28.51%; **6j**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (m, 4H, Ph), 7.55 (m, 2H, Ph), 7.67 (m, 4H, Ph), 8.27 (s, 1H, H-8), 8.66 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 123.5, 126.9, 128.5, 129.3, 129.6, 129.9, 131.1, 134.2, 135.6, 142.0, 148.6, 152.9, 161.4; MS EI m/z (rel.%): 304 (M^+, 51), 303 (100), 276 (2), 173 (1), 141 (2), 109 (1), 77 (11); HRMS: Found 304.0774, calcd for $C_{17}H_{12}N_4S$ 304.0783; Anal.: Found: C, 66.77; H, 4.38. $C_{17}H_{12}N_4S$ requires C, 67.08; H, 3.97%; **6k**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (m, 1H, thienyl), 7.47 (m, 1H, Ph), 7.58 (m, 2H, Ph), 7.62 (br d, J 4.6 Hz, 1H, thienyl), 7.71 (d, J 7.6 Hz, 2H, Ph), 8.34 (s, 1H, H-8), 8.70 (br d, J 3.6 Hz, 1H, thienyl), 8.93 (s, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 123.6, 128.5, 128.8, 129.3, 129.9, 131.0, 132.9, 134.3, 139.8, 143.2, 150.6, 151.7, 153.1; MS EI m/z (rel.%): 278 (M^+, 100), 277 (36), 250 (3), 139 (3), 112 (2), 104 (1), 77 (11); HRMS: Found 278.0619, calcd for $C_{15}H_{10}N_4S$ 278.0626; Anal.: Found: C, 64.78; H, 3.70; N, 20.00. $C_{15}H_{10}N_4S$ requires C, 64.73; H, 3.62; N, 20.13%.

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