ORGANIC LETTERS

2005
Vol. 7, No. 6
1149−1151

Fluoro, Alkylsulfanyl, and Alkylsulfonyl Leaving Groups in Suzuki Cross-Coupling Reactions of Purine 2′-Deoxynucleosides and Nucleosides†

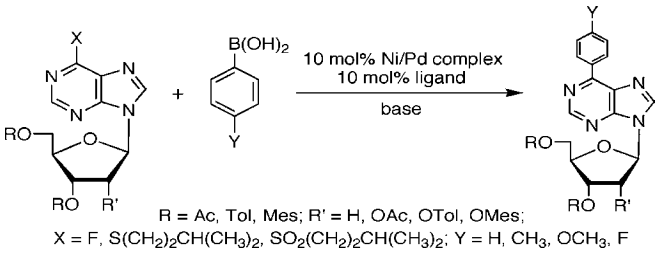
Jiangqiong Liu and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602-5700

morris_robins@byu.edu

Received January 12, 2005

ABSTRACT



Protected 2′-deoxynucleoside and nucleoside derivatives of 6-fluoropurine, 6-(3-methylbutyl)sulfanylpurine, and 6-(3-methylbutyl)ylsulfonylpurine undergo nickel- or palladium-mediated C–C cross-coupling with arylboronic acids to give good yields of 6-arylpurine products.

Modified purines and purine nucleoside derivatives play a major role in biochemistry and biology and as pharmaceutical agents.[1] Recently, 6-arylpurine ribonucleosides have been shown to exhibit cytostatic activity.[2] Classical methods for synthesis of nucleoside biaryls via Suzuki−Miyaura procedures have employed Pd- or Ni-mediated cross-couplings of aryl halides or sulfonates with arylboronic acids.[3] We recently reported a heteroaromatic Finkelstein process for conversion of 6-chloropurine 2′-deoxynucleoside and nucleoside derivatives into the corresponding 6-iodopurine analogues and noted the markedly increased reactivity of the iodo compounds in certain classical organometallic cross-coupling reactions.[4] Aryl fluorides have rarely been used in such processes because of their diminished reactivity.

In 1981, we reported efficient methodology for the synthesis of 2-fluoropurine nucleosides by nonaqueous diazotization fluoro-dediazoniation of the 2-amino group of protected purine nucleosides.[5] Secrist et al. have also applied this protocol for the conversion of 6-amino- to 6-fluoropurine nucleoside derivatives.[6] We now report that this diazotative fluoro-deamination of protected adenosine and 2′-deoxyadenosine analogues gives the 6-fluoropurine compounds in good yields. We then began an investigation of the utility of 6-fluoropurine nucleoside derivatives as cross-coupling

† Nucleic Acid Related Compounds. 125. Paper 124 is ref 9.

(1) (a) Brathe, A.; Gunderesen, L.-L.; Rise, F.; Eriksen A. B.; Vollsnes, A. V.; Wang, L. *Tetrahedron* **1999**, *55*, 211−228. (b) Perez, O. D.; Chang Y.-T.; Rosania, G.; Sutherlin, D.; Schultz, P. G. *Chem. Biol*. **2002**, *9*, 475−483.

(2) (a) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *J. Med. Chem.* **2000**, *43*, 1817−1825. (b) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1683−1697. (c) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *Collect. Czech. Chem. Commun.* **2001**, *66*, 483−499.

(3) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479−1482.

(4) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917−2919.

(5) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2608−2611.

(6) Secrist, J. A.; Bennett, L. L.; Allan, P. W.; Rose, L. M.; Chang, C. H.; Montgomery, J. A. *J. Med. Chem.* **1986**, *29*, 2069−2074.

10.1021/ol050063s CCC: $30.25
Published on Web 02/17/2005

partners with arylboronic acids. We report that this opens an effective new avenue for modifications at C6 of purine nucleosides.

Our first challenge was to identify a catalytic complex that would insert readily into the purine C6−F bond. Several methods involving different transition metal centers have been described for activation of aromatic carbon−fluorine bonds.[7] Cross-couplings of phenylmagnesium halides and fluorobenzenes have been performed at ambient temperature with nitrogen-heterocyclic carbene ligands and nickel catalysts.[8]

We first tried $Ni(COD)_2$ with addition of 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene (IPr) (Figure 1) for

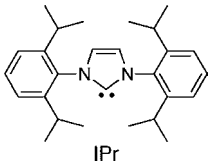
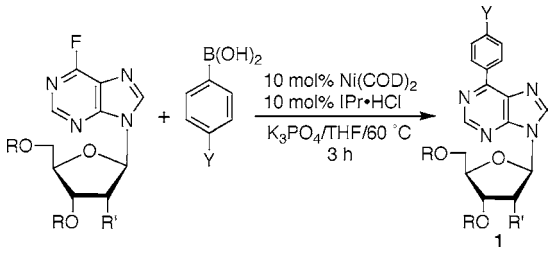


Figure 1. Structure of the imidazolium-carbene ligand IPr.

attempted cross-coupling of 4-methoxyphenylboronic acid and 6-fluoro-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine. At ambient temperature, none of the coupling product was detected. However, we were delighted to find that the desired 6-(4-methoxyphenyl)-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (**1c**) was produced in high yield (84% isolated) in THF at 60 °C (Scheme 1) (Table 1). Different boronic acids were employed

Scheme 1. Couplings with 6-Fluoropurine Nucleosides



to evaluate the scope of this coupling reaction. Both electron-rich and electron-poor arylboronic acids underwent coupling in good yields with 6-fluoropurine nucleoside derivatives. Application of this coupling protocol with a protected 6-fluoropurine 2′-deoxynucleoside also gave 6-arylpurine products in good isolated yields (Table 1).

(7) (a) Braun, T.; Foxon, S. P.; Perutz, R. N.; Walton, P. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3326−3329. (b) Mongin, F.; Mojovic, L.; Guillamet, B.; Trecourt, F.; Queguiner, G. *J. Org. Chem.* **2002**, *67*, 8991−8994. (c) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696−1697. (d) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578−579.

(8) Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387−3389.

Table 1. Yields of Coupling Products from Fluoropurines

entry	R	R′	Y	product (% yield)
1	Mes	OMes	H	**1a** (84)
2	Mes	OMes	CH_3	**1b** (82)
3	Mes	OMes	OCH_3	**1c** (84)
4	Mes	OMes	F	**1d** (73)
5	Tol	H	CH_3	**1e** (60)
6	Tol	H	F	**1f** (67)

It is noteworthy that poor results were obtained upon replacement of $Ni(COD)_2$ by $Pd(PPh_3)_4$ as the catalyst. With $Pd(PPh_3)_4$, major formation of an oxygen-insertion[9] compound **2** (Figure 2) was observed.

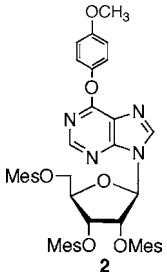
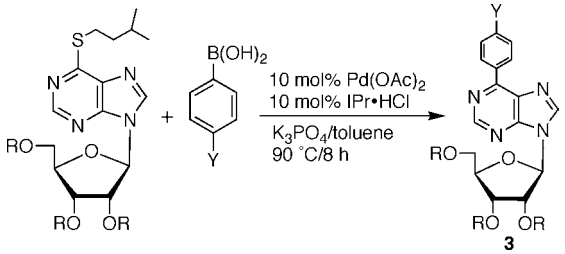


Figure 2. Structure of the oxygen-insertion compound **2**.

We next focused our attention on cross-couplings of 6-alkylsulfanylpurine nucleoside derivatives, which are readily accessible by S_NAr displacements with 6-(imidazol-1-yl)-,[10] 6-(1,2,4-triazol-4-yl)-,[11] and 6-halopurine[12] precursors. They also are easily prepared by alkylation of thioinosine derivatives,[12,13] which can be obtained by deoxygenative thiation of inosine or deaminative sulfhydrolysis of 6-N-substituted adenosine intermediates.[12] Cross-coupling of Grignard reagents and 6-(methylsulfanyl)purine derivatives with a nickel−phosphine complex had been reported.[14]

Our first cross-coupling of 6-[(3-methylbutyl)sulfanyl]-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine and 4-methoxyphenylboronic acid was incomplete after 8 h with $Pd(OAc)_2$/IPr/K_2CO_3/THF at 60 °C. However, when the solvent was changed from THF to toluene and the temperature was

Scheme 2. Couplings with Sulfanylpurine Nucleosides



increased to 90 °C, the coupling reaction was complete in 8 h. Electron-rich and electron-poor arylboronic acids were also well tolerated with the alkylsulfanylpurine substrates (Scheme 2; Table 2).

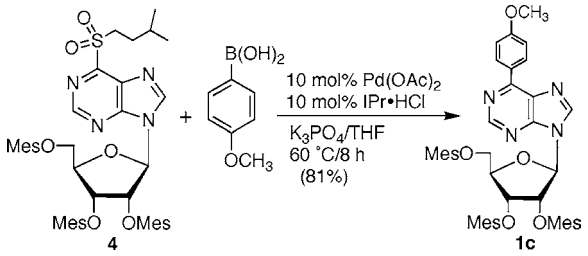
Table 2. Yields of Coupling Products from Sulfanylpurines

entry	R	Y	product (% yield)
1	Tol	CH_3	**3a** (69)
2	Ac	OCH_3	**3b** (78)
3	Tol	F	**3c** (71)

The oxidation state of the sulfur substituent at C6 was then briefly probed. Oxidation of 6-benzylsulfanylpurine nucleoside derivatives with Oxone in buffered brine had given 6-benzylsulfonyl compounds in high yields.[10] Oxidation of a protected 6-(isopentylsulfanyl)purine nucleoside gave 6-[(3-methylbutyl)sulfonyl]-9-[2,3,5-tri-*O*-(2,4,6-trimethylbenzoyl)-β-D-ribofuranosyl]purine (**4**). The sulfone **4** and 4-methoxyphenylboronic acid underwent coupling at 60 °C in 8 h [$Pd(OAc)_2$/IPr/K_3PO_4/THF] to give **1c** (81%, isolated yield) (Scheme 3).

This coupling with the sulfone **4** occurred more readily (60 °C, THF) than with the corresponding thioether (90 °C, toluene). It was known that arylsulfonyl chlorides function as substrates for Suzuki and Stille couplings,[15] but we did not find prior examples of Suzuki couplings with sulfones.

Scheme 3. Coupling with a Sulfonylpurine Nucleoside



In summary, we have developed nickel- and palladium-based systems with imidazolium-carbene ligands that catalyze efficient Suzuki cross-couplings of arylboronic acids and 6-fluoro-, 6-[(3-methylbutyl)sulfanyl]-, and 6-[(3-methylbutyl)sulfonyl]purine nucleoside derivatives to give the corresponding 6-arylpurine products. These reactions enlarge the scope of our complementary Suzuki couplings of arylboronic acids and 6-(azolyl)purine derivatives and expand possibilities for new medicinal applications.

Acknowledgment. We gratefully acknowledge pharmaceutical company gift funds in support of this research (M.J.R.) and the award of a Roland K. Robins Graduate Research Fellowship (J.L.) by Brigham Young University.

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050063S

(9) Liu, J.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421−3423.
(10) Lin, X.; Robins, M. J. *Org. Lett.* **2000**, *2*, 3497−3499.
(11) (a) Samano, V.; Miles, R. W.; Robins, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 9331−9332. (b) Miles, R. W.; Samano, V.; Robins, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 5951−5957.
(12) Srivastava, P. C.; Robins, R. K.; Meyer, R. B., Jr. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum: New York, 1988; Vol. 1, pp 113−281.
(13) (a) Lin, T.-S.; Cheng, J.-C.; Ishiguro, K.; Sartorelli, A. C. *J. Med. Chem.* **1985**, *28*, 1481−1485. (b) Gupte, A.; Buolamwini, J. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2257−2260.
(14) Sugimura, H.; Takei, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 664−666.
(15) (a) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292−15293. (b) Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95−98.