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A New Efficient Route to 5-Substituted β-2′-Deoxyribosylpyrrolo[2,3-*d*]pyrimidines. Palladium-Catalyzed Functionalizations of a C-5 Triflate Intermediate

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Summary: An efficient synthesis of a β-2′-deoxyribosyl-5-[(trifluoromethanesulfonyl)oxy]pyrrolo[2,3-*d*]pyrimidine-2,4-dione **9**, starting from 6-chlorouracil, is presented along with its subsequent functionalization at C-5 using four types of palladium-catalyzed reactions.

Over the past three decades, pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) nucleoside analogues, both of natural[1] and nonnatural[2] origin, have revealed significant biological profiles, including broad spectrum antitumor, antiviral, and antibacterial activities. More recently, 2′,3′-dideoxyribosyl derivatives of pyrrolo[2,3-*d*]pyrimidines have been developed as chain-terminating DNA-sequencing reagents.[3] In this time considerable effort has been directed toward the synthesis of the variously substituted base portions[4] and their nucleoside derivatives.[5] In nearly all cases, the synthetic source of the pyrrolo[2,3-*d*]pyrimidine base portion comes from the early work of Davoll[6a] or Robins and Noell.[6b] In some cases these methods can limit the overall synthetic pathway by requiring lengthy reaction sequences to introduce desired functionality, exhibiting poor regioselectivies and/or low-yielding steps, and revealing undesirable solubility and manipulation properties of key intermediates. Although a few new methods have appeared in recent years,[7] they tend to be applicable to specific ring substitution patterns and lack in generality. We are interested in the development of a new approach for the elaboration of these compounds using a cyclodehydrative pyrrole annulation reaction being developed in our laboratories.[8] This strategy has the advantage of using a common synthetic intermediate which uses a differentially protected pyrimidine-2,4-dione ring portion and a C-5 triflate functional handle for the introduction of a variety of ring substitution patterns and sugar units. In this regard, we report the ready access to a β-2′-deoxyribosyl-5-[(trifluoromethanesulfonyl)oxy]pyrrolo[2,3-*d*]pyrimidine-2,4-dione **9**, which serves as a flexible template for the synthesis of a variety of C-5 substituted derivatives via palladium-catalyzed carbon–carbon bond-forming reactions.[9]

The preparation of the key intermediate **9** is shown in Scheme 1. Starting with 6-chlorouracil, sequential alkylation at *N*-1[10] and then *N*-3 using LiH in DMF with the appropriate alkyl chloride provides the differentially protected uracil derivative **2** in 78% yield. Treatment of **2** with the sodium salt **3**, derived from ethyl *N*-(*p*-nitrophenethyl)glycinate,[11] afforded a substitution adduct which was isolated as its crude acid. Subsequent exposure of this material to acetic anhydride and amine base, with heating, afforded the 5-(acetyloxy)pyrrolo[2,3-*d*]-pyrimidine-2,4-dione **4** in 74% isolated yield for the two steps. It proved advantageous at this stage to remove the *p*-nitrophenethyl blocking group[12] using mild base conditions to afford the free pyrrolo[2,3-*d*]pyrimidine **5**. In this way the sodium salt glycosidation reaction[5c] using 1-chloro-2-deoxy-3,5-ditoluoyl-α-D-*erythro*-pentofuranose (**6**) could be effected with the best preference for the β anomer (α:β, 1:4).[13] Glycosidations at later stages[14] resulted in lower α:β ratios due to the lower reactivity of the pyrrolo[2,3-*d*]pyrimidine anion. The resulting adduct **7** was then treated with mild base to effect hydrolysis of the 5-(acetyloxy) group and provide the pyrrolo[2,3-*d*]-

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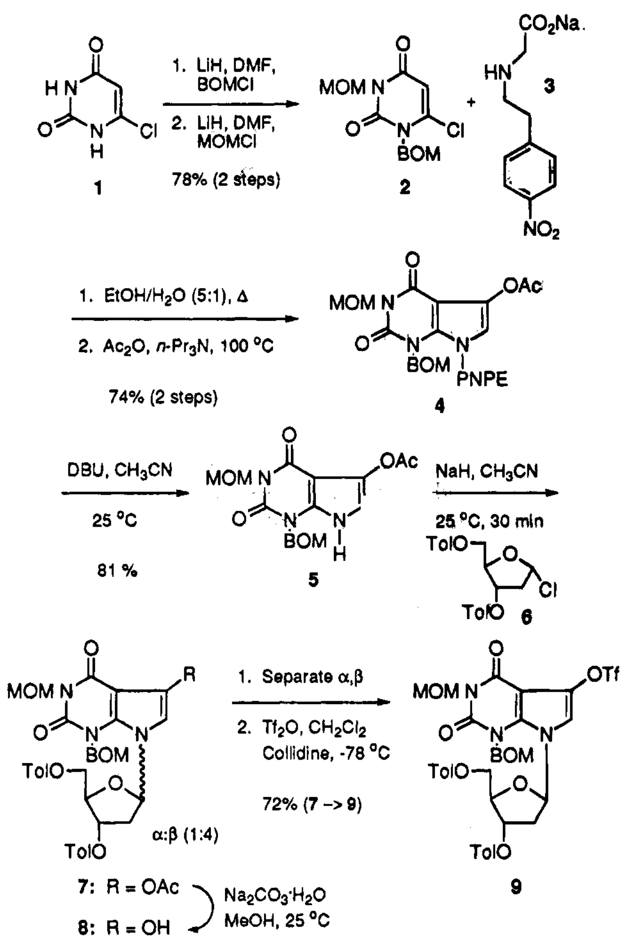
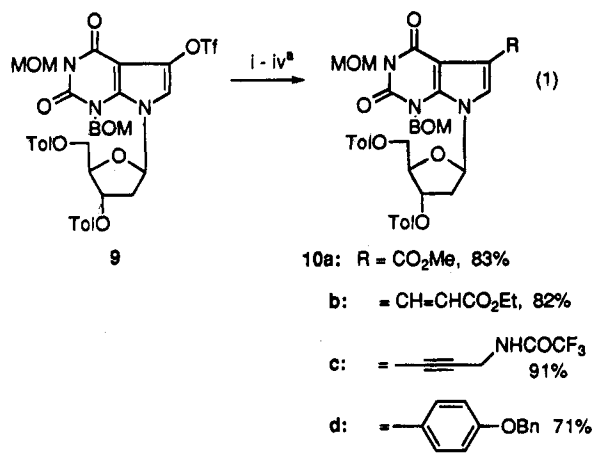
Scheme 1



pyrimidine-2,3,5-trione **8**. This mixture of α and β anomers revealed the unique advantage of being readily separable by simple column chromatography over silica gel. Attempted separation of the α and β anomers at later stages in this scheme proved much more tedious. With the pure β anomer of **8** in hand, conversion to the 5-[(trifluoromethanesulfonyl)oxy]pyrrolo[2,3-*d*]pyrimidine-2,4-dione **9** was performed in high yield using standard reaction conditions.[8a]

Representative reactions of pyrrole triflate **9**[15] using four major types of palladium-catalyzed carbon–carbon bond-forming reactions[16] are illustrated in eq 1 (Scheme 2). Thus, methoxycarbonylation of **9** was performed using the standard protocol of Ortar and co-workers[17a] and afforded ester **10a** in good yield. The Heck reaction with an electron deficient alkene, represented by ethyl acrylate, provided **10b** in respectable yield.[17b] The copper(I)-promoted coupling with *N*-(trifluoroacetyl)propargylamine, leading to **10c**, proceeded in high yield using reaction conditions which proved effective in related 5-iodopyrrolo[2,3-*d*]pyrimidine derivatives.[9] The Stille type coupling with a more demanding electron rich arylstannane was carried out using the modified reaction conditions developed by Farina and co-workers.[17c] The C-5 aryl substituted compound **10d** was isolated in a reasonable 71% yield.

Scheme 2



i Pd(OAc)$_2$, Ph$_3$P[b], CO, Et$_3$N, DMF, MeOH, 68 °C, 2 h
ii Pd(PPh$_3$)$_4$, CuI[c], Et$_3$N, DMF, HCCCH$_2$NHCOCF$_3$, 30 °C, 1 h
iii Pd(PPh$_3$)$_2$Cl$_2$, Et$_3$N, DMF, H$_2$C=CHCO$_2$Et, 90 °C, 17 h
iv Pd$_2$dba$_3$, (furyl)$_3$P[d], ArSn(*n*-Bu)$_3$, NMP, 55 °C, 16 h

[a] All reactions used 10 mol % palladium catalyst. [b] Metal to ligand ratio (1:3). [c] 20 mol % CuI used. [d] Metal to ligand ratio (1:2).

This reactivity study demonstrates the range of palladium-catalyzed carbon–carbon bond-forming reactions that can be realized for the 5-[(trifluoromethanesulfonyl)oxy]pyrrolo[2,3-*d*]pyrimidine-2,4-dione **9**. Since no optimization of reaction conditions were required, i.e., variation of ligand, solvent, catalyst, and additives, it can be expected that **9** will reveal general reactivity toward other coupling partners used in these palladium-catalyzed reactions.[16] The further conversion of compounds **10a–c** into 2-amino-4-oxo-, 4-oxo-, and 4-aminopyrrolo[2,3-*d*]pyrimidines (7-deazaguanosines, 7-deazainosines, 7-deazaadenosines, respectively) is currently under investigation.[18] These represent the most common base portions found in naturally occurring and nonnatural pyrrolo[2,3-*d*]pyrimidine nucleoside analogues.

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Supplementary Material Available: Experimental procedures and characterization data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) The ratio of α:β anomers was determined by integration of the respective OAc signals in a ^{1}H NMR spectrum of the crude reaction mixture. The assignment of the β-anomeric configuration for compound **7** was based on comparison of the C-1′ methine hydrogen coupling contants with the adjacent C-2′ protons, i.e., (CDCl$_3$) δ 6.77 (dd, J = 5.9, 7.3 Hz). This compares with the literature values reported for closely related compounds [β-2′-dideoxyribosyl-1,3-dimethylpyrrolo-[2,3-*d*]pyrimidine-2,4-dione, (DMSO-d_6) δ 6.63 (apparent t, J = 6.0 Hz) and β-2′-deoxyribosyl-2-amino-4-chloropyrrolo[2,3-*d*]pyrimidine, (DMSO-d_6) δ 6.54 (dd, J = 5.8, 8.7 Hz)]. By way of comparison, the α-anomer of **7** had data for H-1′ of (CDCl$_3$) δ 6.84 (dd, J = 2.2, 7.7 Hz) as compared to α-2′-deoxyribosyl-1,3-dimethylpyrrolo[2,3-*d*]pyrimidin-2,4-dione, (DMSO-d_6) δ 6.63 (dd, J_{total} = 10.0 Hz); see refs 5c and 5f.

(14) With an electron-withdrawing methoxycarbonyl group at C-5, the α:β ratio was determined to be 1:1. The bulky *N*-1 alkyl substituent is also a factor influencing the stereochemical outcome for these reactions.

(15) For related Heck coupling reactions using an indole-3-triflate, see: Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129.

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