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Palladium Catalyzed Coupling of 2,6-Dichloro-3-iodoimidazo[1,2-*a*]pyridine and 2,3-Dihydrofuran as an Approach to Novel Imidazo[1,2-*a*]pyridine C-nucleosides.

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Abstract: Palladium was used for a cross coupling of 2,6-dichloro-3-iodoimidazo[1,2-*a*]pyridine (**2**) to 2,3-dihydrofuran (**3**). Optimization of the coupling conditions have given exclusively (+/-)-2,6-dichloro-3-(2′,5′-dihydrofuran-2′-yl)imidazo[1,2-*a*]pyridine (**4**) in high yield. Compound **4** was dihydroxylated using a catalytic amount of osmium tetroxide to give the erythrofuranosyl C-nucleoside derivatives **6** and **7**. This is the first report of a C-nucleoside derivative containing a sugar moiety attached to the C3 position of an imidazo[1,2-*a*]pyridine heterocycle.

C-nucleosides differ from the more commonly occurring N-nucleosides by having their carbohydrate moiety and heterocycle linked via a hydrolytically resistant carbon-carbon bond instead of the more reactive aminal linkage. Several C-nucleosides, both naturally occurring and synthetic, have significant antibacterial, antiviral and antitumor activities.[1] Some of these biological activities have been postulated to depend on the resistance of the C-C linkage to hydrolytic or enzymatic cleavage.[2] C-nucleosides of several different heterocycles, such as purines, pyrimidines and pyridines, have been reported.[3] Since several halogenated benzimidazole nucleosides[4] have demonstrated significant antiviral activity against human cytomegalovirus, we became interested in the synthesis of halogenated imidazo[1,2-*a*]pyridine C-nucleosides that would be structurally related to the active benzimidazole nucleosides. This prompted us to explore the possibility of attaching a furanose moiety to the C3 position of a halogenated imidazo[1,2-*a*]pyridine. We now wish to report the synthesis of erythrofuranosyl C-nucleoside derivatives **6** and **7**.

Of the several literature methods available for the synthesis of C-nucleosides,[3] we opted to investigate the coupling of 2,3-dihydrofuran (**3**) to 2,6-dichloro-3-iodoimidazo[1,2-*a*]pyridine (**2**) using the palladium (0)-mediated cross coupling methodology.[5] 2,6-Dichloroimidazo[1,2-*a*]pyridine (**1**)[6] was iodinated using NIS in $CHCl_3$ to give **2**. Compound **2** was then coupled to **3** as outlined in Table 1 to give (+/-)-2,6-dichloro-3-(2′,5′-dihydrofuran-2′-yl)imidazo[1,2-*a*]pyridine (**4**) and (+/-)-2,6-dichloro-3-(2′,3′-dihydrofuran-2′-yl)-imidazo[1,2-*a*]pyridine (**5**).

Table 1: Coupling of 2,6-dichloro-3-iodoimidazo[1,2-*a*]pyridine (**2**) with 2,3-dihydrofuran (**3**).

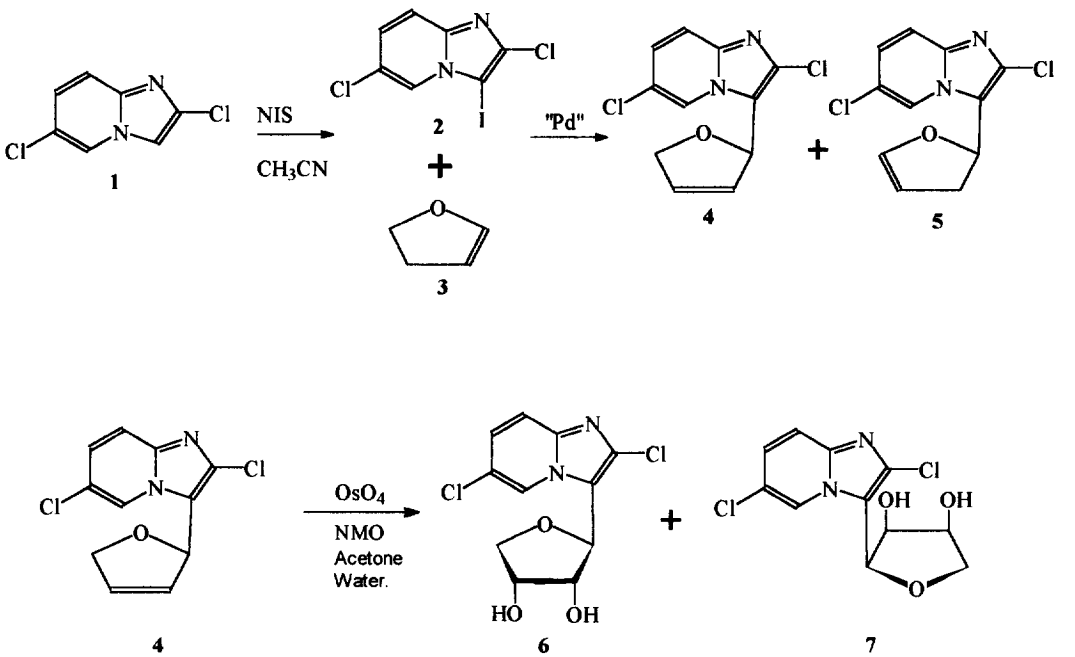
Entry[a]	Base (2 molar equiv)	Ligand (0.2 molar equiv)	Solvent	Ag_2CO_3 (2 molar equiv)	Temp (°C)	% Yields[b]	
						4	**5**
1[c]	Et_3N	Ph_3P	CH_3CN	-	25 °C	10	11
2[c]	Et_3N	Ph_3P	DMF	-	25 °C	20	10
3	Et_3N	Ph_3As	CH_3CN	-	25 °C	20	25
4	Et_3N	Ph_3As	CH_3CN	-	60 °C	15	30
5	Bu_3N	$P(o\text{-}tol)_3$	DMF	-	25 °C	30	15
6	Et_3N	Ph_3As	DMF	-	25 °C	55	35
7	Bu_3N	Ph_3As	DMF	-	25 °C	55	35
8[d]	Et_3N	Ph_3As	DMF	+	60 °C	60	25
9[d]	Et_3N	Ph_3As	DMF	+	45 °C	81	0

a) In a typical procedure $Pd(OAc)_2$ (0.1 molar equiv) and Ph_3As (Ph_3P or $P(o\text{-}tol)_3$) (0.2 molar equiv) were added to dry solvent (5 mL) and the resulting mixture stirred at room temperature for 30 min. Heterocycle **2** was then added along with Et_3N (Bu_3N) (2 molar equiv) and **3** (5 molar equiv). Once all of the heterocycle **2** had reacted as determined by TLC, EtOAc was added to the reaction mixture, the mixture filtered through Celite, evaporated to dryness and isomers **4** and **5** separated by column chromatography. $Pd(OAc)_2$ was used as the catalyst for all entries outlined in Table 1. Other Pd species did not improve the yields. b) Isolated yields. c) Increasing reaction temperature decreased reaction time but did not improve the yield. d) Other silver species such as $AgNO_3$ did not improve the yield.

Initial yields from the cross coupling reaction were low, but have been optimized. Variations in the use of ligands were based on the fact that triphenylarsine[7] and tri-o-tolylphosphine[8] had been reported to accelerate the rate of coupling over those rates obtained using triphenylphosphine. DMF proved to be a superior solvent to CH_3CN, presumably due to improved solubilization of salts formed during the reaction. Once an excellent combined yield of **4** and **5** had been obtained (entry 6 and 7 in Table 1), reaction conditions were optimized so as to give only **4** (entry 9 in Table 1). This was accomplished by adding silver salts to the reactions, as silver salts are known to prevent double bond migration in palladium reactions.[9] The incorporation of silver salts slowed the coupling reaction to such an extent that it was still not complete in several days at room temperature. This could be offset by increasing the reaction temperature. If the coupling reactions were run in the presence of a silver salt at 60 °C, the formation of significant quantities of **5** was still observed. However, by lowering the temperature to 45 °C, **4** was formed exclusively in good yield. Finally, dihydroxylation[10] of **4** using catalytic OsO_4 in the presence of N-methylmorpholine N-oxide (NMO) gave a 2:1

mixture of the erythrofuranosyl C-nucleosides **6** and **7**,[11] which were separated by column chromatography. While 2′,3′-dideoxy-2′,3′-didehydro ribose nucleoside derivatives have been hydroxylated selectively from the α-face,[12] it was not surprising that in this case a significant amount of **7** (resulting from hydroxylation on the β-face) was obtained since the absence of a 4′-substituent would result in a decrease in steric hindrance to hydroxylation from the β-face.

SCHEME I



To the best of our knowledge, C-nucleosides containing a sugar moiety (such as ribose or erythrose) at the C3 position of an imidazo[1,2-*a*]pyridine have not been reported and the synthesis of other imidazo[1,2-*a*]-pyridine C-nucleosides is being pursued in our laboratory. The biological activity of these compounds will be published elsewhere.

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11. Compounds **6** and **7** were obtained from racemic **4** and are both racemic: **6**: mp 180-181°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 8.49 (d, 1H, J= 2.0 Hz), 7.64 (d, 1H, J=9.6 Hz), 7.45 (dd, 1H, J=9.6 Hz, J= 2.0 Hz), 5.19 (d, 1H, J=6.3 Hz, D_2O exchangeable), 5.11 (broad s, 1H, D_2O exchangeable), 5.03 (d, 1H, J=9.03 Hz), 4.43 (m, 1H), 4.32 (m, 1H), 4.20 (m, 1H), 3.75 (m, 1H). MS (EI 70 eV with DCI probe): m/z, Calcd:288.0068, Found:288.0065. Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_3$ x1/4 H_2O : C, 45.00; H, 3.60; N, 9.54. Found:C, 45.06; H, 3.48; N, 9.32. **7** :mp 183°C; ^{1}H-NMR (360 MHz, DMSO-d_6): δ 8.83 (d, 1H, J= 2.0 Hz), 7.58 (d, 1H, J=9.6 Hz), 7.40 (dd, 1H, J=9.6 Hz, J= 2.0 Hz), 5.40 (d, 1H, J=4.2 Hz, D_2O exchangeable), 5.26 (m, 2H, simplifies to d, 1H, J=4.3 Hz upon D_2O wash), 4.40 (t, 1H, J=5.3 Hz), 4.26 (m, 1H), 3.82 (q, 1H), 3.89 (q, 1H). MS (EI 70 eV with DCI probe): m/z, Calcd:288.0068, Found:288.0079. Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_3$: C, 45.70; H, 3.49; N, 9.69. Found:C, 45.37; H, 3.39; N, 9.35. Satisfactory spectral and analytical data were also obtained for all other compounds.
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