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The Condensation of 2,6-Dichloroimidazo[1,2-a]pyridine with Ribonolactone Gives a Novel Imidazo[1,2-a]pyridine C-nucleoside with an Unexpected Site of Ribosylation.

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Abstract: A novel ribosylated imidazo[1,2-a]pyridine C-nucleoside was synthesized by condensing a lithiated 2,6-dichloroimidazo[1,2-a]pyridine (**1**) with a protected ribonolactone (**2**), followed by acetylation to give the intermediate nucleoside **4**. This intermediate was reductively deacetoxylated and deprotected to give what was determined to be the novel and unexpected 2,6-dichloro-5-(β-D-ribofuranosyl)imidazo[1,2-a]pyridine (**7**) and the corresponding α-product (**8**). The site of ribosylation was established with long range proton-carbon decoupling experiments. This ribosylation at C5 was entirely unexpected in view of previously reported condensations with lithiated imidazo[1,2-a]pyridines which occurred only at the C3 position. Copyright © 1996 Elsevier Science Ltd

Several C-nucleosides, both naturally occurring and synthetic, have significant antibacterial, antiviral and antitumor activities.[1] Since several polyhalogenated benzimidazole nucleosides,[2] e. g. 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole, have good antiviral activity against human cytomegalovirus, we became interested in the synthesis of polyhalogenated imidazo[1,2-a]pyridine C-nucleosides where the imidazo[1,2-a]pyridine heterocycle could be considered a benzimidazole analog. Recently the condensation of lithiated heterocycles with protected ribonolactones, followed by a reductive removal of the 1'-OH have been used to synthesize 3-pyridine,[3] benzamide[4] and thiazole[5] C-nucleosides. The literature further describes the synthesis of compounds such as 3-(1-hydroxycyclohexyl)imidazo[1,2-a]pyridine[6] and 2,6-dichloroimidazo[1,2-a]pyridine-3-sulfinic acid[7] from the corresponding lithiated heterocycles. We elected to investigate this approach for the synthesis of new imidazo[1,2-a]pyridine C-nucleosides, with the ribosyl moiety at C3.

To optimize reaction conditions for the condensation, we investigated the lithiation of 2,6-dichloroimidazo[1,2-a]pyridine (**1**),[7] followed by a reaction of this lithioderivative with protected ribonolactones. The initial investigation of this coupling reaction revealed that the choice of lithiation reagent, protecting groups for the lactone, reaction times and temperature were of great importance for obtaining good yields. Thus, when lithiated tetramethylpiperidine (LTMP) was used to lithiate **1**, higher yields (80 %) were obtained than when lithiated diisopropylamine (LDA) or phenyllithium (yields 70 % and 50 % respectively)

were used. Furthermore, 5-(tertbutyl(dimethyl)silyl)-2,3-O-isopropylidene-D-ribono-1,4-lactone (**2**)[8] was coupled with lithiated **1** to give a high yield of a C-nucleoside which we assumed to be the 3-ribosylated C-nucleoside, but was subsequently determined to be the 5-ribosylated C-nucleoside **3** based on NMR studies, while 2,3,5-tri-O-benzyl-D-ribono-1,4-lactone under the same reaction conditions gave mixtures of inseparable products. We found that the treatment of **1** with LTMP in THF at -78 °C, followed by the addition of **2** to the reaction mixture at -78 °C and quenching with an ammonium chloride buffer after 20-30 minutes gave the highest yields of the hemiacetal intermediate **3** (80 %). Longer reaction times and higher reaction temperatures gave lower yields. Several attempts to dehydroxylate **3** failed. We subsequently found that **3** could be acetylated to give **4** (98 % yield), which could then be reductively deacetoxylated using the conditions presented in Table 1. Compound **4** was also obtained directly from the hemiacetal **3** (70 - 80 % yield) by quenching the coupling reaction with acetic anhydride instead of with the ammonium chloride buffer. The deacetoxylation of **4** thus gave either 2,6-dichloro-5-[5-O-[tertbutyl)dimethylsilyl]-2,3-O-isopropylidene-β-D-ribofuranosyl]imidazo[1,2-a]pyridine (**5**) selectively or by using the conditions described in entry 3 in Table 1 a 1:1 mixture of the β-product **5** and the α-product **6**.

Table 1: Optimized conditions for reductive deacetoxylation of the 1'-acetoxy compound **4**.

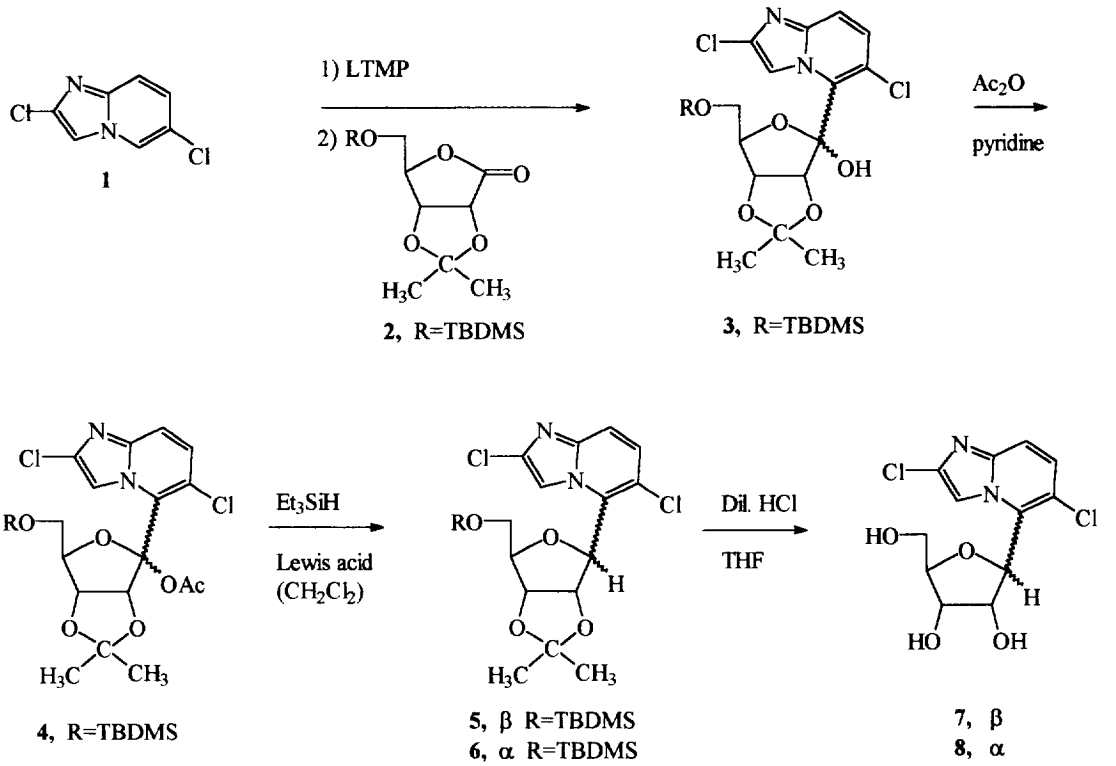
Entry[a]	Solvent	Lewis acid (equiv.)[b]	Reaction time (hours)	Yields (%)[c]	
				5	**6**
1	CH_2Cl_2	BF_3OEt_2 (2.5)	4	50	<3
2	CH_2Cl_2	TMSOTf (2.5)	0.5	78	<3
3	NONE	BF_3OEt_2 (2.5)	4	34	34

a) In a typical procedure the acetoxy compound **4** was placed in a dry flask to which solvent (if applicable) and excess Et_3SiH (10-20 equiv.) were added. This solution was cooled to 0°C in an ice bath and the Lewis acid (2.5 equiv.) was added. The reaction mixture was then allowed to warm to room temperature and stirred for the specified time. Saturated $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2, the organic phase dried, filtered and concentrated followed by purification of the resulting residue with column chromatography. b) A larger excess of the Lewis acid resulted in desilylation and formation of significant quantities of 1,5-anhydro-2,3-O-isopropylidene-1-C-(2,6-dichloroimidazo[1,2-a]pyridine-5-yl)-β-D-ribofuranose and other unidentified decomposition products. c) Isolated yields, the ratio of **5** to **6** (that is β to α) did not depend on the anomeric ratio of **4**, same ratio of **5** and **6** were obtained whether anomerically pure **4** or anomeric mixtures of **4** were used as starting material. This is consistent with a mechanism where the hydride delivery occurs cis to the adjacent oxygen (2'-O) of the presumed oxonium ion intermediate when the reaction was run in CH_2Cl_2. In the absence of solvent the large excess of Et_3SiH evidently results in a random delivery of the hydride from either side of the oxonium ion intermediate.

Compounds **5** and **6** were deprotected under acidic conditions to give 2,6-dichloro-5-(β-D-ribofuranosyl)imidazo[1,2-a]pyridine (**7**)[9] and the α-product **8** respectively with the site of ribosylation being

determined by the following NMR studies. The heterocyclic part of the proton spectrum of **7** and its precursors did not show the expected splitting pattern for a 2,6-dichloroimidazo[1,2-a]pyridine with a ribose moiety at C3 and protons at C5, C7 and C8 (signals were expected to be a q, dd and dd, respectively). Signals assigned to protons at C7 and C8 were doublets, but did not show any coupling with the third heterocyclic proton. As spectral data, analysis and mass spectrum showed that neither chlorine had been replaced, the observed splitting pattern indicated that coupling had occurred at C5 rather than at C3. Furthermore, the full assignment of the ^{13}C-NMR of **7**, based on fully coupled spectra and partially decoupled spectra as well as chemical shift trends, followed by selective decoupling experiments showed the 1'-H to be three bond coupled to C6 and the 2'-H to be three bond coupled to C5 thus unambiguously showing that ribosylation had occurred at C5.

SCHEME I



The anomeric assignment of **7** as the β-anomer and **8** as the α-anomer was based partially on the well known upfield shift of the 1'-H signal for the β-anomer compared to the α-anomer[10], and was further supported by positive NOEs between the 1'-H and the 4'-H for **7**. Finally this assignment was consistent with an examination of the ^{1}H-NMR spectra of the 2,3-O-isopropylidene derivatives **5** and **6** where the $\Delta\delta$ CH_3 was

larger for **5** (0.30 ppm) than for **6** (0,01 ppm). This is consistent with the fact that for pairs of anomeric C-nucleosides, the $\Delta\delta$ CH_3 for the α-anomer is generally smaller than the corresponding value for the β-anomer[10].

Further investigations of similar coupling reactions is being pursued in our laboratory. The biological activity of these compounds will be published elsewhere.

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References and Notes.

1. (a)Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1-65; (b) Daves, G. D., Jr.; Cheng, C. C. *Prog. Med. Chem.* **1976**, *13*, 303-349.
2. (a)Revankar, G. R., Townsend, L. B. *Chem. Rev.* **1970**, *70*, 389-438; (b) Revankar, G. R., Townsend, L. B. *J. Heterocyclic Chem.* **1968**, *5*, 477-483. (c) Devivar, R. V.; Kawashima, E.; Revenkar, G. R.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1994**, *37*, 2942-2949. (d) Townsend, L. B., Devivar, R. V., Turk, S. R., Nassiri, M. R., Drach, J. C. *J. Med. Chem.* **1995**, *38*, 4098-4106.
3. Piccirilli, J. A.; Krauch, T.; MacPherson, L. J.; Benner, S. A. *Helv. Chim. Acta.* **1991**, *74*, 397-406.
4. Krohn, K.; Heins, H.; Wielckens, K. *J. Med. Chem.* **1992**, *35*, 511-517.
5. Donadoni, A; Scherrmann, M-C. *J. Org. Chem.* **1994**, *59*, 6404-6412.
6. Paudler, W. H.; Shin, H. G. *J. Org. Chem.* **1968**, *33*, 1638-1639.
7. Ishida, Y.; Ohta, K.; Nakahama, T.; Yoshikawa, H. European Patent no 0 238 070 A2, **1987**.
8. Cheng, J. C.; Hacksell, U.; Daves, G. D., Jr. *J. Org. Chem.* **1985**, *50*, 2778-2780.
9. For Compound **7**: Mp 232-233 °C; ^{1}H-NMR (DMSO-d_6, 360 MHz): δ 8.80 (s, 1H), 7.60 (d, 1H, J=9.5 Hz), 7.44 (d, 1H, J=9.5 Hz), 5.43 (m, 2H, simplifies on D_2O exchange to d, 1H, 1'-H, J=9.0 Hz), 5.21 (d, 1H, D_2O exchangeable), 5.14 (d, 1H, D_2O exchangeable), 4.38 (m, 1H), 4.16 (m, 1H), 3.97 (m, 1H), 3.71 (m, 2H); ^{13}C-NMR (DMSO-d_6, 90.556 MHz): δ 142.53 (C8a), 134.73 (C2), 131.35 (C5), 127.19 (C7), 121.07 (C6), 116.87 (C8), 111.12 (C3), 87.41, 77.97, 70.32, 69.80, 60.66; MS (EI 70 eV with DCI probe): m/z, Calcd: 318.0174, Found: 318.0169; Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_4$: C, 45.16; H, 3.79; N, 8.78; Found: C, 45.06; H, 3.87; N, 8.39. Satisfactory spectral and analytical data was also obtained for all other compounds.
10. (a)Tam, S. Y-K.; Klein, R. S.; de las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854-4862. (b)Sokolova, T. N.; Yartseva, I. V.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1981**, *93*, 19-34. (c)MacCross, M.; Robins, M. J.; Rayner, B.; Imbach, J.-L. *Carbohydr. Res.* **1977**, *59*, 575-579.

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