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Coupling Reaction of 4-Chloro-7-H-Pyrrolo[2,3-d]Pyrimidine with 2,3,5-Tri-O-Acetyl-β-D-Ribofuranosyl Chloride

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Abstract: Coupling reaction of 4-chloro-7-H-pyrrolo[2,3-d]pyrimidine with 2,3,5-tri-O-acetyl -β -D-ribofuranosyl chloride under the basic condition was investigated. An abnormal coupling reaction, in which the heterocyclic base attacked at the carbon of 1,2-O-methylidene moiety instead of anomeric carbon of ribose was observed and the structure of products **5a**, **5b** were identified by NMR and X-Ray diffraction.

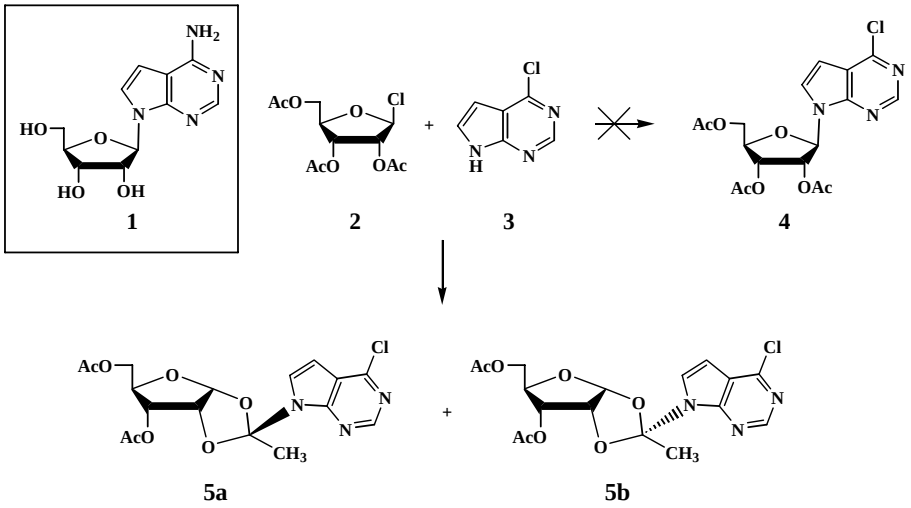
Keywords: 4-Chloropyrrolo[2,3-d]pyrimidine, 1-chloro-2,3,5-tri-O-acetyl-D-ribofuranose, neigh-boring participation effect, X-ray diffraction.

Tubercidin (4-amino-7- β -D-riobofuranosyl-7-H-pyrrolo[2,3-d]pyrimidine) **1**, an antibio-tic substance produced in the culture broth of *Streptomyces tubericidus*[1], is an adenosine analog in which N-7 is replaced by a carbon atom. It has attracted much attention due to the biological activities for the growth inhibition of certain tumors, and many derivatives of tubercidin have been synthesized[2-5].

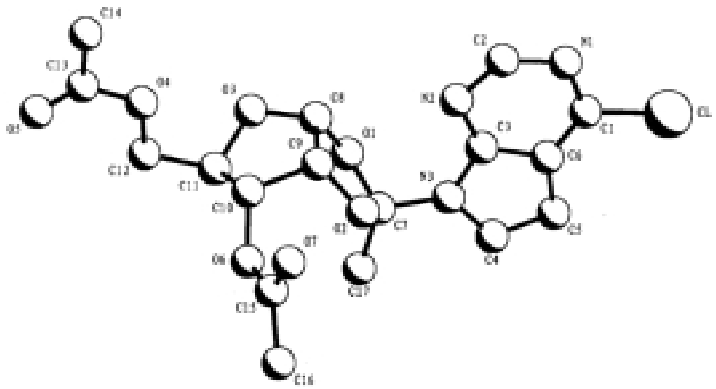
For the synthesis of tubercidin analogs, 4-chloro-7-H-pyrrolo[2,3-d]pyrimidine-2,3,5-tri-O-acetyl-β-D-ribofuranose **4** is a key intermediate. There are many methods for the synthesis of compound **4**, an often used way is the nucleophilic substitution at the C1 anomeric carbon of protected ribose. 2,3,5-Tri-O-acetyl- β -D-ribofuranosyl chloride **2** was reacted with 4-chloro-7-H-pyrrolo[2,3-d]pyrimidine **3** in dichloromethane solution at room temperature for 48 hr under the existence of NaH, after evaporation under reduced pressure and separation with silica gel column, two compounds were obtained with the yield of 41% **5a**[6] and 21% **5b**[7] respectively. NMR results demonstrated that neither **5a** nor **5b** were consistent with the expected product **4** (**Scheme 1**). ^{13}C NMR showed that only two carbonyl groups existed in both compounds and a new peak appeared at δ 114.9 (**5a**) or 115.8 (**5b**). HMBC and HMQC identified that this carbon was connected to a methyl group. After **5a** or **5b** was treated with saturated ammonia methanol solution, two signals of carbonyl groups disappeared in ^{13}C NMR but signal of 114.9 or 115.8 still existed in the deprotected product. All the spectrometric data of **5a** or **5b**

were consistent with the structure in which the heterocyclic base was connected to the carbon of 1,2-O-ethylidene moiety of 3,5–diacetyl-ribose. A crystalline sample of **5a** was obtained from petroleum-dichloromethane solution, and its X-ray diffraction results confirmed the structure and showed that new chiral center, C-7 of **5a**, is in *S* configuration. Since the spectrometric data of **5b** was nearly identical to **5a**, it should be a stereo isomer of **5a** with *R* configuration of its C-7 (**Scheme 2**).

Scheme 1 Tubercidin and synthetic routine of its analogs



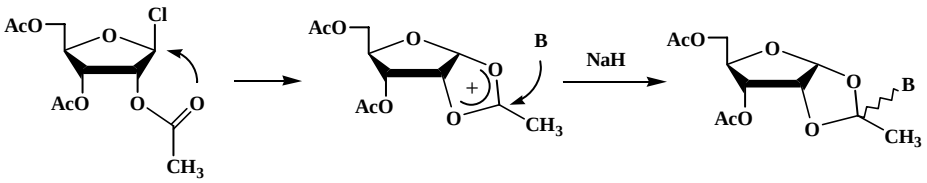
Scheme 2 X-ray crystal structure of **5a**



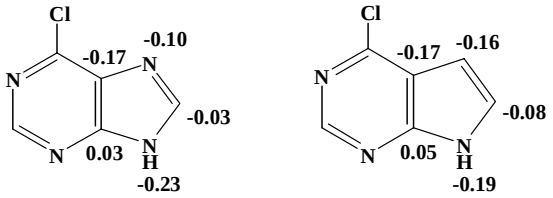
The formation of **5a** and **5b** could be explained by the neighboring participation effect of acetyl group as demonstrated in **Scheme 3**. The heterocyclic base attacked the carbon of the cation intermediate instead of the ribosyl C-1 carbon. Comparing the atomic electron density of 4-chloro-7-H-pyrrolo[2,3-d]pyrimidine with 4-chloro-adenine by using quantum mechanic MOPAC calculation, it was shown that the nucleophilicity of N-9 in the former was nearly 20% lower than in the latter (**Scheme 4**). The result

might explain the formation of the abnormal coupling structure **5a** and **5b**.

Scheme 3 The mechanism of the formation of compound **5a** and **5b**

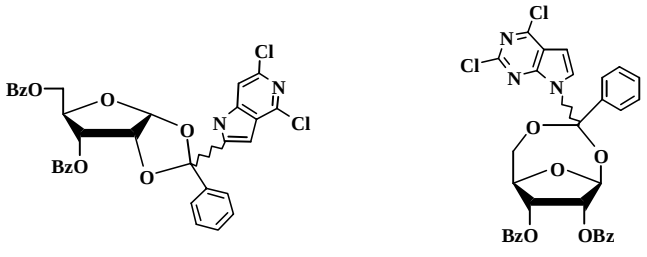


Scheme 4 Comparison of electrical density between 4-chloro-7H-pyrrolo[2,3-*d*]pyrimidine and 4-chloro-purine



Similar coupling results were reported by Gloria, *et al.*[8], in 1989. He obtained the similar structure **6** as shown in **Scheme 5**. But Serafinowski, *et al.*[9], proposed a different structure in 1995, after the coupling reaction of 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide with 2,4-di-chloro-7-H-pyrrolo[2,3-d]pyrimidine in the presence of NaH, and he suggested that the O-5 carbonyl group took part in the reaction. Our result was the first time to get a crystal structure from such abnormal coupling reaction and clarified the neighboring participation mechanism.

Scheme 5 Previously proposed abnormal coupling structures



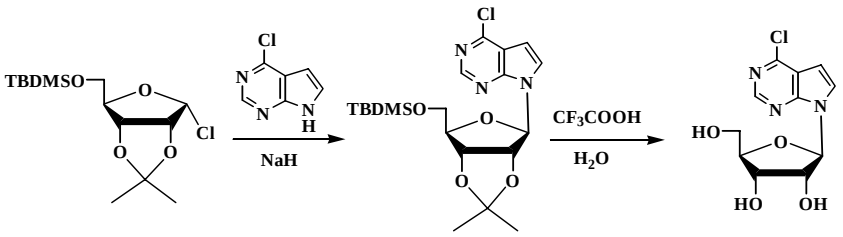
6 **7**

Compound **5a** and **5b** were not stable in acidic condition due to their acetal structure. Their acetyl groups could be removed under basic condition. Two deprotected compounds were obtained after treatment of **5a** or **5b** with NH_3/CH_3OH or K_2CO_3 /CH_3OH respectively. But in K_2CO_3/CH_3OH condition not only two acetyl groups were removed but also the chloro group was substituted by methoxy group.

When 5-O-TBDMS-2,3-isopropylidene-1-α-D-chloro-ribofuranose **8** was reacted with 4-chloro-7H-pyrrolo[2,3-d]pyrimidine in acetonitrile at room temperature for 24 hr

in the presence of NaH, 5'-O-TBDMS-2',3'-isopropylidene-1'-β-D-4-chloro-7-β-D-ribofuranosyl-7H-pyrrolo-[2,3-d]pyrimidine **9** was obtained in 60% yield. After the treatment with CF_3COOH, deprotected product **4** was obtained almost quantitatively (**Scheme 6**).

Scheme 6 Preparation of 4-chloro-7-H-pyrrolo[2,3-d]pyrimidine-2,3,5-tri-O-acetyl-β-D-ribofuranose



8 **9** **4**

Acknowledgments

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6. Compound **5a**. m.p. 115-117°C (dec.); $[\alpha]_D^{19}$ (c 0.175, MeOH) +70.8; UV (MeOH): λ_{max} 268 nm (ε 6200); FAB-MS (*m/z*): 412 $[M + H]^+$; ^{1}H NMR (300 MHz, DMSO-d_6, δ_{ppm}): 8.69 (s, 1H, H-2), 7.79 (d, 1H, $J_{6,5}$ 2.8 Hz, H-6), 6.66 (d, 1H, $J_{5,6}$ 2.8 Hz, H-5), 6.21 (d, 1H, $J_{1',2'}$ 4.2 Hz, H-1'), 4.93 (m, 1H, H-2'), 4.83 (m, 1H, H-3'), 4.33 (m, 2H, H-4', H-5'), 4.13 (m, 1H, H-5'), 2.22 (s, 3H, -CH_3), 2.11 (s, 3H, -CH_3), 0.98 (s, 3H, -CH_3); ^{13}C NMR (DMSO-d_6, δ_{ppm}): 170.1, 169.6, 150.9, 150.4, 149.4, 128.1, 118.4, 114.9, 105.2, 98.6, 78.0, 76.0, 62.0, 24.6, 20.5, 20.4. Anal. Calcd. for $C_{17}H_{18}ClN_3O_7$: C 49.58, H 4.41, N 10.20; Found: C 50.00, H 4.44, N 10.26.
7. Compound **5b**. Syrup; $[\alpha]_D^{19}$ (c 0.210, MeOH) +109.5; UV (MeOH): λ_{max} 269 nm (ε 4200); ^{1}H NMR (300 MHz, DMSO-d_6, δ_{ppm}): 8.73 (s, 1H, H-2), 7.78 (d, 1H, $J_{6,5}$ 3.9 Hz, H-6), 6.71 (d, 1H, $J_{5,6}$ 3.6 Hz, H-5), 6.24 (d, 1H, $J_{1',2'}$ 4.2 Hz, H-1'), 5.18 (m, 1H, H-2'), 4.68 (m, 1H, H-3'), 3.95 (m, 3H, H-4', H-5'), 2.00 (s, 3H, -CH_3), 1.98 (s, 3H, -CH_3), 1.73 (s, 3H, -CH_3); ^{13}C NMR (DMSO-d_6, δ_{ppm}): 169.9, 169.3, 150.9, 150.6, 149.8, 127.8, 118.3, 115.8, 106.3, 98.5, 79.2, 77.9, 71.7, 62.8, 26.4, 20.5, 19.9; HR-MS /FAB (*m/z*): 412.0898 $[M + H]^+$.
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