Synthesis of 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl Cyanide by Phase Transfer Reaction

Kwangjun Lee, Byounghee Son, and Yonghan Kang*

Department of Chemistry, Hanyang University, Ansan 425-791, Korea
Received January 13, 2000

The potential antiviral, antibacterial, and antitumorous activities shown by *C*-nucleosides which have the carbon-carbon glycosidic bond have incited many attempts at the organic synthesis.[1-3] 2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**2**)[4,5] has been used as a potentially versatile intermediate for the synthesis of *C*-nucleoside derivatives. Ribofuranosyl cyanide **2** was prepared primarily from the reaction of 1-halo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose which was prepared from the reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) with mercuric cyanide.[4]

An efficient procedure for the synthesis of **2** was accomplished by the reaction of 1-*O*-acetate ribose **1** with cyanotrimethylsilane by Utimoto and Horiie.[6] Our synthetic approach was to prepare 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**3**) from the reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) with potassium cyanide instead of TMS-CN (Scheme 1) because potassium cyanide is cheaper and more easily commercially available than TMS-CN. Potassium cyanide could provide the cyanide ion in the presence of 18-crown-6 in nonpolar solvent, which is called phase transfer reaction.[7]

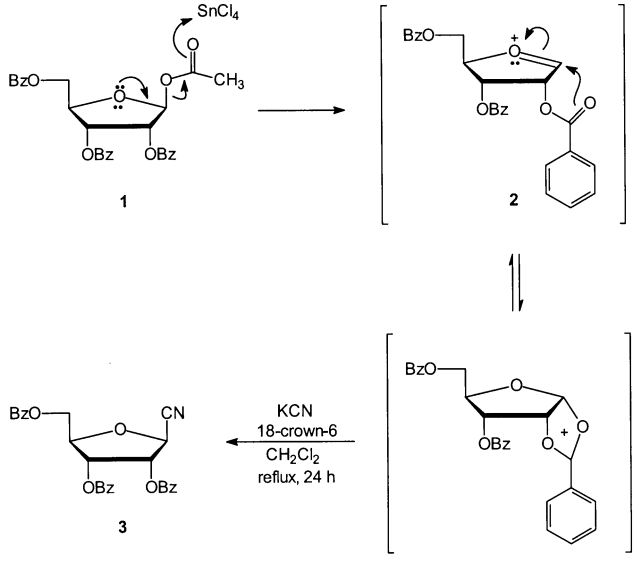
After 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) was dissolved in dry methylene chloride, stannic chloride, 18-crown-6, and potassium cyanide were added to the solution and then the reaction mixture was heated under reflux for 24 h. Ribofuranose **1** was converted to 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (**3**) *via* 1,2-acyloxonium intermediate **2** which allowed a naked cyanide ion to attact on the β-face. From the ^{1}H NMR spectrum of the obtained product **3**, the anomeric proton at C_1 was identified as a doublet at $\delta = 5.49$ ppm ($J_{12} = 4.0$ Hz).[6]

For an adequate choice of reagent ratio, several reactions were carried out. The optimized condition was obtained from the reaction with a molar ratio of compound **1**/KCN/stannic chloride/18-crown-6 = 1.0 : 2.0 : 1.5 : 0.15.

1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (**4**) was also tested under the phase transfer reaction condition to synthesize 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl cyanide. The reaction of **4** in the similar manner as compound **3** by using stannic chloride as a Lewis acid gave no desired product. On the contrary, the reaction of compound **4** in the presence of BF_3·OEt_2 provided two different products, **5** and **6**, separated by flash silica gel column chromatography (Scheme 2).

^{1}H NMR spectrum of the isolated product **5** showed two anomeric protons at 5.92 and 5.95 ($J_{12} = 3.9$ and 4.2 Hz). The separated product **5**, therefore, was expected to be a mixture of 3,5-di-*O*-acetyl-1,2-*O*-(1-endo-cyanoethylidene)-α-D-ribofuranose and its exo-isomer which could be also obtained from the reaction of 1-*O*-acetate **4** with TMS-CN in the presence of BF_3·OEt_2.[8]

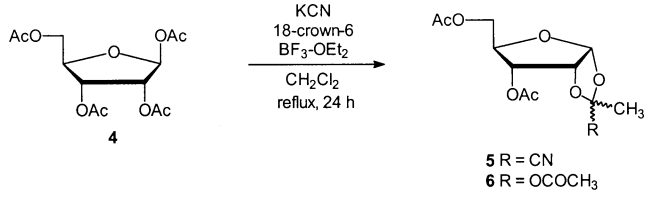
^{1}H NMR spectrum of product **6**, identified as a 3,5-di-*O*-acetyl-1,2-*O*-(1-endo or exo-acetoxy-ethylidene)-α-D-ribofuranose, presented four methyl groups at the range of δ = 2.02-2.07 ppm and a C_1 proton with a doublet at $\delta = 6.36$ ($J_{12} = 4.2$ Hz), whereas the starting material **4** showed a C_1 proton at $\delta = 6.09$ ppm.



Scheme 1

Experimental Section

General procedures. All chemicals used were purchased from commercial sources with an analytical grade. The solvents were purified by distillation and the other reagents were used without further purification. ^{1}H-NMR spectra were measured at 300 MHz using a Varian Unity Plus 300 spectrometer. The chemical shift values were reported as δ downfield from TMS as an internal standard. Melting points were determined on a Büchi 530 melting point apparatus and are uncorrected. Elemental analyses were performed by Fisons



Scheme 2

EA 1108.

2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl cyanide (3). Stannic chloride (3.5 mL, 30 mmol) was added to a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) (10 g, 20 mmol) in dry dichloromethane (100 mL) in an argon atmosphere. After being stirred for 10 min at room temperature, potassium cyanide (1.3 g, 20 mmol) and 18-crown-6 (0.8 g, 3.0 mmol) were added to the reaction mixture. The solution was heated under reflux for 24 h and cooled to room temperature. The organic layer was washed with 5% $NaHCO_3$ solution and water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The remaining residue was recrystallized from ethanol to provide **3** (7.1 g, 75%) as a colorless needle, mp 78-79 °C (lit., 78.5-80 °C[4] and 77.5-78.0 °C[6]). ^{1}H NMR ($CDCl_3$) δ 4.62 (m, 2H, C_5H), 4.79 (m, 1H, C_4H), 4.99 (d, 1H, J_{12} = 4.0 Hz, C_1H), 5.87 (t, J = 5.3 Hz, 1H, C_3H), 6.02 (t, J = 4.8 Hz, 1H, C_2H), 7.35-8.15 (m, 15H, phenyl).

3,5-Di-*O*-acetyl-1,2-*O*-(1-endo- and exo-cyanoethylidene)-α-D-ribofuranose (5) and 3,5-di-*O*-acetyl-1,2-*O*-(1-endo- or exo-acetoxyethylidene)-α-D-ribofuranose (6). BF_3·OEt_2 (3.8 mL, 30 mmol) was added to a solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**4**) (6.4 g, 20 mmol) in dry dichloromethane (100 mL) in an argon atmosphere. After being stirred for 10 min at room temperature, potassium cyanide (1.3 g, 20 mmol) and 18-crown-6 (0.8 g, 3 mmol) were added to the reaction mixture. The reaction mixture was heated under reflux for 24 h and cooled to room temperature. The organic layer was washed with 5% $NaHCO_3$ solution and water successively and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with methylene chloride/methanol (100 : 1, v/v) gave endo and exo mixture of **5** (2.9 g, 51%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.09 and 2.13 (2s, 3H, endo and exo-CH_3), 4.06-4.98 (m, 5H, C_2H, C_3H, C_4H, $2C_5H$), 5.92 and 5.95 (2d, 1H, J_{12} = 3.9 and 4.2 Hz, C_1H).[8]

Further elution with methylene chloride/methanol (20 : 1, v/v) yielded **6** (1.6 g, 25%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.02, 2.04, 2.06 and 2.07 (4s, 12H, 4 x CH_3), 4.11-5.18 (m, 5H, C_2H, C_3H, C_4H, $2C_5H$), 6.36 (d, 1H, J_{12} = 4.2 Hz, C_1H). Anal. Calcd for $C_{13}H_{18}O_9$: C, 49.06; H, 5.70. Found: C, 48.83; H, 5.87.

Acknowledgment. The author wishes to acknowledge the financial support of Hanyang University, Korea, made in the program year of 1998.

References

1. Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem. Biochem.* **1976**, *133*, 111.
2. Buchanan, J. G.; Moorhouse, S. J.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2258.
3. Cornia, M.; Casiraghi, G.; Zetta, L. *J. Org. Chem.* **1991**, *56*, 5466.
4. Bobek, M.; Farkas, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 247.
5. Kunsten, J. S.; Judkins, B. D.; Mitchell, W. L.; Newton, R. F.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 229.
6. Utimoto, K.; Horiie, T. *Tetrahedron Lett.* **1982**, 237.
7. Zubrick, J. W.; Dunber, B. I.; Durst, H. D. *Tetrahedron Lett.* **1975**, 71.
8. Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967.