Journal of the Chinese Chemical Society, 1997, *44*, 413-416

Improved Syntheses of Halofuranose Derivatives with the Desired α-Configuration

Tsung-Mei Chin*[a] (靳宗玫), Liang-Kuen Huang[a] (黃亮焜) and Lou-sing Kan[b] (甘魯生)
[a]*Institute of Applied Chemistry, Chinese Culture University, Taipei, Taiwan 11114, R.O.C.*
[b]*Institute of Chemistry, Academia Sinica, Taipei, Taiwan 11529, R.O.C.*

Chlorination of ribofuranose or 2-deoxyribofuranose derivatives was carried out in a 1,4-dioxane solution of hydrogen chloride. This improved procedure allowed the syntheses of 1-chloro-α-D-ribofuranose and 1-chloro-2-deoxy-α-D-ribofuranose derivatives and offered ease of handling, high yield, and the stereo-controlled α-configuration at C-1.

INTRODUCTION

Nucleoside analogs are of wide biological interest. They can be used for site-directed modification of DNA/RNA fragments with respect to the studies of structures and functions of nucleic acids.[1] Of paramount importance to the modified nucleoside synthesis is a preparation of the carbohydrate portion in a manner which allows stereoselective control at C-1 during glycosylation. According to studies in various laboratories,[2,3] in addition to the nature of the C-2 substituent, the anomeric disposition of the starting halogenose had an important bearing on the stereochemical outcome of the condensation reaction with a base. α-Halosugars under proper reaction conditions were converted via an S_N2 mechanism predominantly to β-nucleosides, which are of the natural configuration, while β-halosugars yielded both α- and β-nucleosides via an S_N2 mechanism and a passway of neighboring-group participation, respectively. These anomeric mixtures of nucleosides presented the difficulty of separation. In consequence, α-glycosyl halides with easily removable acyl protecting groups become vital intermediates in a variety of syntheses of N- or C-β-nucleosides. Here we report a practical and efficient method for stereo-controlled syntheses of 1-chloro-(2-deoxy-)α-D-ribofuranose derivatives.

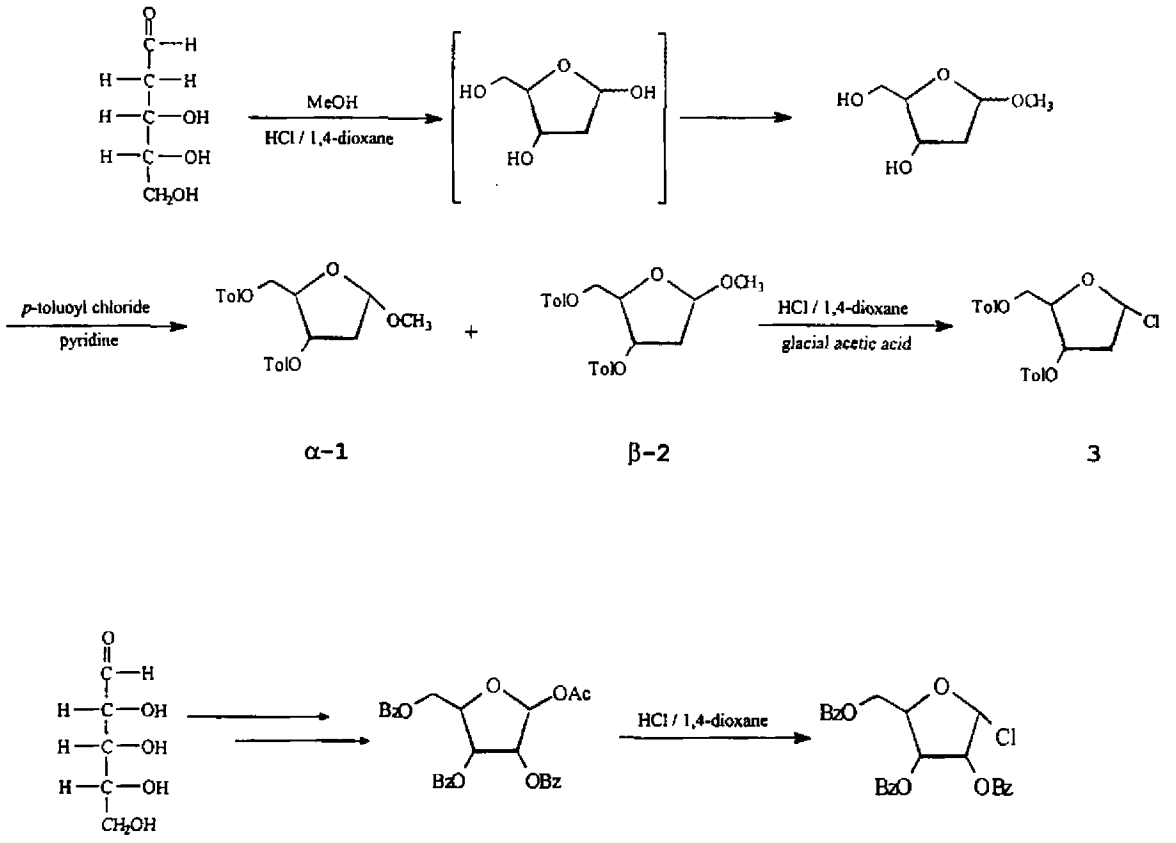
RESULTS AND DISCUSSION

Cyclization of (2-deoxy-)D-ribose and subsequent chlorination used to be performed by bubbling a stream of hydrogen chloride gas directly into a solution;[4] hence the acid concentration could not be controlled precisely. The considerable excess of hydrogen chloride was not only wasteful, but also caused side reactions and degradation. The approach presented herein avoids such problems by utilizing a commerically-available 4 M solution of hydrogen chloride in 1,4-dioxane in place of hydrogen chloride gas. In addition to its lower cost and to being more amenable to control, the 1,4-dioxane solvent seems to be an appropriate medium for the formation of halosugars with the desired α-configuration.

2-Deoxy-3,5-di-O-*p*-toluoyl-α-D-ribofuranosyl chloride **3** is a common starting material for most deoxyribonucleoside syntheses. The convenient synthetic procedure is shown in Scheme I. In order to cyclize 2-deoxy-D-ribose as a five-membered furanose ring, rather than a six-membered pyranose ring, the concentration of hydrogen chloride has to be controlled at 0.1% during the cyclization reaction.[5] From the 4 M solution of hydrogen chloride, a 0.1% concentration can be easily prepared by adding hydrogen chloride solution (0.25 mL) to anhydrous methanol (43 mL). 2-Deoxy-D-ribose was then cyclized in the methanolic solution of 0.1% hydrogen chloride, followed by toluoylation, and gave the anomeric products **α-1** and **β-2** in a total yield of 90%, which was much higher than that of the reported 70% with hydrogen chloride gas as a reagent.[6] The mixed anomers could be separated by column chromatography, then analyzed by the NMR and MS spectra. **α-1** revealed lower-field resonances of H-3 at 5.58 ppm and H-1 at 5.21 ppm than those of **β-2** with H-3 at 5.40 ppm and H-1 at 5.17 ppm. Even without chromatographing purification, the product from above was pure enough for the next reaction. After the mild chlorination by treating a 4 M solution of hydrogen chloride in 1,4-dioxane, the single α-anomer **3** was obtained in a yield of 70%. The structure was confirmed by NMR spectroscopic analyses. The characteristic signal of anomeric proton H-1 was assigned to a doublet centered at 6.45 ppm (J = 4.8 Hz), and identified as an absorbance of α-anomer.[3]

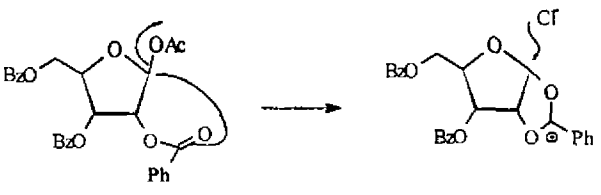
The 2,3,5-trisubstituted ribofuranosyl halides were to be prepared in a similar way. However, it was shown that

Scheme I



the chlorination of 2,3,5-trisubstituted ribofuranoses under various conditions produced halogenoses predominantly, if not exclusively, with β-configuration due to the steric hindrance and/or the neighboring-group participation of C-2 substituent.[2,7] The α/β ratio of chlorides increased as the polarity of reaction environments decreased. The most effective α/β ratio was 1/4.[8] We carried out the chlorination of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose[9,10] in a solvent of 1,4-dioxane at 0 °C for 4-7 days. Only one anomer was observed on TLC plates during the interval. After purification by flash chromatography, the ^{1}H NMR spectrum of the isolated product displayed the signal of H-1 as a doublet (J = 4.5 Hz) at 6.63 ppm. The chloride **4**, assigned as the α-configuration, exhibited a coupling typical of an anomeric proton vicinal-cis to proton H-2.[11] This phenomenon of the conformational preference may be explained by the domination of anomeric effect.[12] This effect varies inversely with the dielectric constant of the solvent, and is greater if effective charge density on the substituent atom attached directly to C-1 is higher. In addition, the population of the ionic intermediate **5** for the formation of β-anomer (shown in Scheme II) could not exist in a significant amount in such a low polarity solvent as 1,4-dioxane. This reaction unusually resulting in a smooth conversion to an α-halogenose paved a way to the synthesis of a non-natural β-nucleoside.

Scheme II



5

The approach herein to the chlorination of furanose derivatives by employing a 4 M solution of hydrogen chloride in 1,4-dioxane provides the following advantages: reduced costs for industrial applications, ease of the control of acid concentration in order to avoid side reactions and degradation, and most importantly, production of halogenoses with the desired α-configuration.

EXPERIMENTAL SECTION

General Methods

Infrared (IR) spectra were recorded on a Perkin-Elmer 882 spectrophotometer. Standard spectra were regularly obtained for polystyrene to verify accuracy. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker AC-200 and AC-300 instruments. ^{1}H NMR and ^{13}C NMR spectra were acquired using deuterochloroform ($CDCl_3$) solvent and tetramethylsilane (TMS) internal reference assigned 0.00 ppm. Mass spectra were measured with a VG Analytical Model 70-250 s/se spectrometer. All reagents were used as obtained commerically.

1-O-Methyl-2-deoxy-3,5-di-O-*p*-toluoyl-D-ribofuranoses, α-1 and β-2

A stock solution of 1% hydrogen chloride can be easily prepared from the 4 M solution (0.25 mL) combining anhydrous methanol (4.3 mL). 2-Deoxy-D-ribose (1 g) was dissolved in dry methanol (18 mL) and treated with a 1% solution of hydrogen chloride (2 mL). After stirring for 15 min at room temperature, the reaction mixture was evaporated *in vacuo*. A small amount of dry pyridine was added and concentrated. This procedure was repeated twice. The residue was then diluted with pyridine (5.9 mL), cooled to 0 °C, and treated dropwise with *p*-toluoyl chloride (4 mL). The resulting solution was maintained at 40-50 °C for 2 hours, then stirred overnight at room temperature. After the reaction was complete, the solution was acidified, and partitioned between ether and water. The organic phase was collected, washed with 5% sodium bicarbonate and water, then dried over magnesium sulfate. The mixture of 1-O-methyl-2-deoxy-3,5-di-O-*p*-toluoyl-D-ribofuranoses, α-1 and β-2, was separated by chromatography with benzene/ether (30/1) as an eluent. Both anomers were obtained in a total yield of 90%. α-1: IR ($CDCl_3$) 3002, 2958, 2930, 1720, 1615, 1450, 1275, 1180, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.26-2.57 (8H, m, H-2,2′, Ar-CH_3), 3.34 (3H, s, OCH_3), 4.43-4.56 (3H, m, H-4,5,5′), 5.21 (1H, dd, H-1, $J_{1,2}$ = 5.4 Hz, $J_{1,2'}$ = 2.2 Hz), 5.58 (1 H, m, H-3), 7.17-7.23 (4H, m, Ar-H), 7.88-7.98 (4H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.6, 39.2, 55.1, 64.3, 74.6, 80.9, 105.0, 127.0, 127.1, 129.1, 129.7, 129.8, 143.8, 143.9, 166.2, 166.5; MS (rel intensity) *m/z* 385 (MH^+), 353 (30), 154 (10), 137 (15), 119 (100); HRMS (FAB) for $C_{22}H_{25}O_6$ (MH^+): calcd. 385.1644, found 385.1651. β-2: IR ($CDCl_3$) 3030, 2926, 1715, 1641, 1451, 1272, 1180, 1109, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.13-2.53 (8H, m, H-2,2′, Ar-CH_3), 3.40 (3H, s, OCH_3), 4.49-4.64 (3H, m, H-4,5,5′), 5.17 (1H, br. d, H-1, $J_{1,2}$ = 4.6 Hz), 5.40 (1H, m, H-3), 7.18-7.24 (4H, m, Ar-H), 7.88-7.94 (4H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.6, 39.2, 55.1, 65.1, 75.3, 81.8, 105.5, 126.8, 127.2, 128.2, 129.0, 129.6, 143.6, 143.9, 166.0, 166.2; MS (rel intensity) *m/z* 385 (MH^+), 383 (5), 353 (40), 154 (10), 137 (15), 119 (100); HRMS (FAB): the same as α-1.

2-Deoxy-3,5-di-O-*p*-toluoyl-α-D-ribofuranosyl Chloride 3

The pre-purified product from above was dissolved in glacial acetic acid (4.30 mL) in an ice bath, and treated with 4 M solution of hydrogen chloride in 1,4-dioxane (5.74 mL). The reaction was traced by TLC. After the starting material was almost consumed, a little more glacial acetic acid was added. The solution was placed in a freezer for a couple of hours. The product was then collected by suction on a sintered glass funnel and washed with cold ether. The crude product, 2-deoxy-3,5-di-O-*p*-toluoyl-α-D-ribofuranosyl chloride 3, could be purified by crystallization from carbon tetrachloride. α-Anomer was obtained in a yield of 70%. IR ($CDCl_3$) 3030, 2945, 1725, 1615, 1273, 1180, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.39 (3H, s, Ar-CH_3), 2.40 (3H, s, Ar-CH_3), 2.67-2.93 (2H, m, H-2,2′), 4.57 (1H, dd, H-5, $J_{4,5}$ = 4.3 Hz, $J_{5,5'}$ = 12.1 Hz), 4.67 (1H, dd, H-5′, $J_{4,5'}$ = 3.2 Hz, $J_{5,5'}$ = 12.1 Hz), 4.84 (1H, m, H-4), 5.54 (1H, m, H-3), 6.45 (1H, d, H-1, $J_{1,2}$ = 4.8 Hz), 7.20-7.26 (4H, m, Ar-H), 7.85-8.00 (4H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.7, 44.5, 63.5, 73.5, 84.7, 95.3, 126.8, 129.2, 129.7, 129.9, 144.3, 166.1; MS (rel intensity) *m/z* 391 (MH^+ for ^{37}Cl), 389 (MH^+ for ^{35}Cl), 355 (10), 353 (30), 154 (25), 136 (40), 119 (100); HRMS (FAB) for $C_{21}H_{22}O_5Cl$ (MH^+): calcd. 389.1150 and 391.1120, found 389.1156 and 391.1136 (ratio 100:36).

2,3,5-Tri-O-benzoyl-α-D-ribofuranosyl Chloride 4

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (300 mg) was added into a 4 M hydrogen chloride solution in 1,4-dioxane (0.8 mL) at 0 °C for 4-7 days. After the reaction was complete, dichloromethane was added. The solution was washed with 5% sodium bicarbonate and water, then dried over magnesium sulfate. The residue was purified by flash chromatography with chloroform as an eluent. IR ($CDCl_3$) 3069, 2930, 1731, 1605, 1454, 1268, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.66 (1H, dd, H-5, $J_{4,5}$ = 3.8 Hz, $J_{5,5'}$ = 12.3 Hz), 4.78 (1H, dd, H-5′, $J_{4,5'}$ = 2.9 Hz, $J_{5,5'}$ = 12.3 Hz), 4.90 (1H, m, H-4), 5.53 (1H, dd, H-2, $J_{1,2}$ = 4.5 Hz, $J_{2,3}$ = 6.9 Hz), 5.83 (1H, dd, H-3, $J_{2,3}$ = 6.9 Hz, $J_{3,4}$ = 2.9 Hz), 6.63 (1H, d, H-1, $J_{1,2}$ = 4.5 Hz), 7.27-7.59 (9H, m, Ar-H), 7.90-8.13 (6H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 63.3, 69.8, 72.7, 82.8, 93.8, 128.5, 128.6, 129.1, 129.3, 129.7, 129.9, 130.0, 133.4, 133.7, 165.0, 165.8, 166.0; MS (rel intensity) *m/z* 482 (M^+ for ^{37}Cl), 480 (M^+ for ^{35}Cl), 329 (10), 307 (25), 289 (15), 176 (20), 154 (100), 136 (75), 107 (30); HRMS (FAB) for

$C_{26}H_{22}O_7Cl$ (MH^+): calcd. 481.1048 and 483.1018, found 481.1073 and 483.1060 (ratio 100:39).

ACKNOWLEDGMENT

We thank the National Science Council for financial support (NSC 86-2113-M-001-011) of this work.

Received December 20, 1996.

Key Words

1-Chloro-(2-deoxy-)α-D-ribofuranose derivative; Chlorination; Stereo-control; α-Configuration.

REFERENCES

1. Montgomery, J. A. in *Nucleosides, Nucleotides, and Their Biological Applications*, Rideout, J. L.; Henry, D. W.; Becham, L. M., III, Eds., Academic Press: New York, **1983**, pp 19-46.
2. Watanabe, K. A.; Hollenberg, D. H.; Fox, J. J. *J. Carbohydrates·Nucleosides·Nucleotides* **1974**, *1*, 1.
3. Hubbard, A. J.; Jones, A. S.; Walker, R. T. *Nucleic Acids Research* **1984**, *12*, 6827.
4. Koh, J. S.; Dervan, P. B. *J. Amer. Chem. Soc.* **1992**, *114*, 1470.
5. Deriaz, R. E.; Overend, W. G.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2836.
6. Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777.
7. Brodfuehrer, P. R.; Sapino, C., Jr.; Howell, H. G. *J. Org. Chem.* **1985**, *50*, 2597.
8. Hanessian, S.; Pernet, A. G. *Can. J. Chem.* **1974**, *52*, 1280.
9. Howell, H. G.; Brodfuehrer, P. R.; Brundidge, S. P.; Benigni, D. A.; Sapino, C., Jr. *J. Org. Chem.* **1988**, *53*, 85.
10. Popsavin, M.; Popsavin, V.; Vukojevic, N.; Milikovic, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1884.
11. Stevens, J. D.; Ness, R. K.; Fletcher, H. G., Jr. *J. Org. Chem.* **1968**, *33*, 1806.
12. Angyal, S. J. *Angew. Chem. Internat. Edit.* **1969**, *8*, 157.