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Synthesis of 4-thiofuranoid 1,2-glycals and their application to stereoselective synthesis of 4′-thionucleosides

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Abstract

Convenient one-pot procedures using iodine monochloride have been developed for the preparation of two 4-thio-1,2-glycals from readily available starting materials and for their β-anomer selective conversion into 2′-iodo-4′-thionucleosides. Conditions for the reductive de-iodination of these iodonucleosides have been established and hence routes to a range of 2′-deoxy-4′-thionucleosides become feasible.

Keywords: 4-thio-1,2-glycals; stereoselective addition; 2′-deoxy-4′-thionucleosides.

Over the last two decades or so, furanoid 1,2-glycals have emerged as synthetically accessible intermediates[1] and, subsequently, have been of value in stereoselective syntheses of nucleoside analogues.[2] For the preparation of conventional pyrimidine and purine nucleosides, the required regio- and stereoselective *trans*-addition to the double bond of the glycal is initiated by a soft electrophile and then completed via trapping, at the 1-position of the glycal, by a silylated base. The usefulness of glycals in anomer selective nucleoside synthesis is therefore dependent upon the facial selectivity of the addition, which, precedence suggests, is largely controlled by the ligands at C-3 and C-4.[3]

Another feature of recent nucleoside literature has been the renewed interest in 4′-thionucleosides,[4] particularly evident for the 2′-deoxy series. It therefore seemed apposite to study the generation of 4-thiofuranoid 1,2-glycals, then novel in the chemical literature, and hence investigate their application to stereoselective synthesis of 4′-thionucleosides. After our studies were initiated, examples of protected 4-thio-1,2-glycals were described by Swedish and Japanese groups.[5] A general synthesis of 1-substituted 4-thio-1,2-glycals has also appeared.[6] Here we report the synthesis of two 4-thio-1,2-glycals direct from readily available benzylthio glycosides,[7] and then their application to pyrimidine 4′-thionucleoside synthesis. Our synthesis, outlined in Scheme 1, uses the glycosides (**1**) and (**2**), each of which is an anomeric mixture, and can be conveniently prepared on the multi-gram scale.[7] For the generation of

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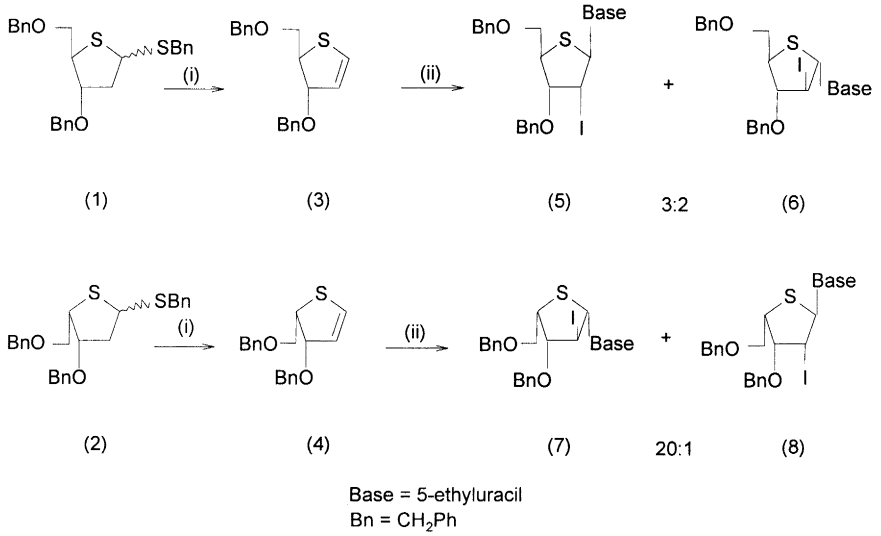
glycals (**3**) and (**4**), the preferred method uses iodine monochloride (ICl) in the presence of 2,6-di-*t*-butyl-4-methylpyridine, and routinely gives 60–70% yields. The expensive base appears to be desirable for reproducibility and ease of work-up, but, fortunately, it can be recovered and reused. Both (**3**) and (**4**) can be stored at −10°C under nitrogen, and are stable enough to be purified by rapid flash chromatography, although they are not stable enough to permit microanalysis, and (**4**), in particular, decomposes to 2-hydroxymethylthiophene upon standing in solution at room temperature.

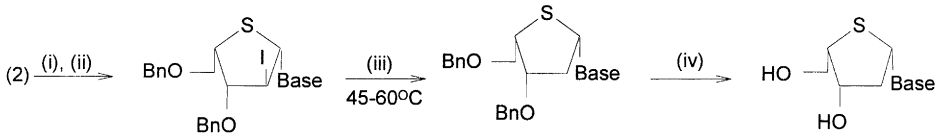


Scheme 1. *Reagents*: (i) ICl or NIS, 2,6-di-*t*-butyl-4-methylpyridine; (ii) 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine

Using additions to (**3**) and (**4**) as probes (see Scheme 1), it was found that *N*-iodosuccinimide (NIS) and ICl were preferred over other agents used previously[2] for nucleoside synthesis. One of our long-term targets was a β-selective synthesis of 2′-deoxy-4′-thionucleosides,[8] because normal coupling methodology produces at best a 3:2-ratio in favour of the α-anomer, and, moreover, anomer separation is exceedingly tedious. With thioglycal (**3**) and 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine, the anomer ratio (**5**):(**6**) was about 3:2 in favour of the β-isomer, the structure of which was confirmed by NOE difference spectroscopy. For example, for (**5**) it was shown that irradiation at H-6 enhanced the signals for H-3′ and H-2′, but not that for H-4′, thus confirming the β-configuration. With the L-xylothioglycal (**4**) a ratio of about 20:1 for (**7**):(**8**) was achieved. In (**4**), the presence of both the ligands on the same face of the thioglycal dictates that productive interaction with the iodine occurs largely on the opposite face, and, in turn, this controls the preference for β-nucleoside formation in the main product (**7**). By comparison, the di-benzylated oxygen glycal analogue of (**4**) gave a ratio of about 9:1 in favour of the β-isomer.[3]

The observation that ICl could replace NIS in the above additions suggested that a one-pot route from glycal precursor, e.g. (**2**), to iodonucleoside, e.g. (**7**), may be possible, and would have the merit of avoiding the need to handle sensitive glycal intermediates. As shown in Scheme 2, (**7**) was prepared in yields of about 70%, using 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine[8] as the trapping base. Initial attempts to de-iodinate the diastereomeric mixture of (**7**) and (**8**), using tributyltin hydride and azobis-isobutyronitrile at 80°C in toluene, resulted in predominant ring-opening by breaking the sulphur to anomeric carbon bond — a mode not seen in the oxygen series. We subsequently found that heating at 45–60°C in toluene led to good yields of (**9**), which was then debenzylated[9] to give (**10**). Stereochemical assignment to (**10**) was based on accepted NMR shift and coupling data,[10] and was confirmed by

NOE difference spectroscopy. These findings are entirely consistent with the only other report[5b] on the thioglycal addition route to β-2′-deoxy-4′-thionucleosides. Our use of ICl leads to a three-step sequence from (**2**), whereas the previous route[5b] requires seven steps from (**2**).



(7) (9) (10)

Base = 5-ethyluracil
Bn = CH_2Ph

Scheme 2. *Reagents*: (i) ICl, 2,6-di-*t*-butyl-4-methylpyridine; (ii) 2,4-bis-trimethylsilyloxy-5-ethylpyrimidine; (iii) Bu_3SnH, AIBN, toluene; (iv) BBr_3/CH_2Cl_2, −78°C

In principle, this type of sequence opens the way to anomer selective syntheses of a whole range of 4′-thionucleosides, which are of potential interest in the fields of anti-viral and anti-tumour chemotherapy.[4] Details of key experimental procedures are given below.

General procedure for the preparation of 4-thio-1,2-glycals. Compound (**3**): Thioglycoside (**1**) (0.5 g, 1.15 mmol) was dissolved in dry dichloromethane (5 ml) whilst stirring under nitrogen at 0°C. 2,6-Di-*t*-butyl-4-methylpyridine (0.47 g, 2.29 mmol) was added and the reaction mixture stirred for 10 min, before adding a solution of iodine monochloride (0.224 g, 1.38 mmol) in dichloromethane (2 ml) over 10 min. The mixture was allowed to warm up to room temperature and then stirred for a further 3 h, before quenching with a saturated solution of sodium thiosulphate and extracting with dichloromethane (3×10 ml). The combined extracts were washed with water, then with brine and dried over magnesium sulphate. After evaporating the solvent, the crude product was purified by flash chromatography. Elution with ethyl acetate:light petroleum (bp 40–60°C) (1:9) gave the desired glycal (**3**)[11] as a pure (TLC) oil (0.230 g, 64%).

Preferred one-pot procedure for the preparation of 2′-iodonucleosides. Compound (**7**): Thioglycoside (**2**) (0.436 g, 1.00 mmol) was dissolved in dry dichloromethane (20 ml) under nitrogen at 0°C, and 2,6-di-*t*-butyl-4-methylpyridine (0.41 g, 2.00 mmol) was added to the stirred solution. Iodine monochloride (0.195 g, 1.20 mmol) in dichloromethane (5 ml) was added dropwise over 10 min and the mixture stirred at 0°C until all of the thioglycoside starting material had been consumed (as shown by TLC). A solution of freshly prepared bis-silylated base made from 5-ethyluracil (0.288 g, 2.00 mmol) in dichloromethane (10 ml) was added at 0°C, followed by a solution of a further portion of iodine monochloride (0.195 g, 1.20 mmol) in dichloromethane (5 ml). The reaction mixture was allowed to warm to room temperature, and stirring was continued overnight. A saturated solution of sodium thiosulphate was added and the reaction mixture extracted with chloroform (3×20 ml), before drying the combined extracts over magnesium sulphate. ^1H NMR of the crude product showed the β:α-anomer ratio to be 20:1. The crude product was purified by flash chromatography. The iodonucleoside (**7**)[12] (0.404 g, 70%) was a white powder, mp 103–104°C.

Procedure for reductive de-iodination and debenzylation. Compounds (**9**) and (**10**): Iodonucleoside (**7**) (1.0 g, 1.73 mmol) and azobis-isobutyronitrile (100 mg) were dissolved in dry toluene (10 ml) and this solution was added dropwise over 20 min to a solution of tributyltin hydride (1.4 ml, 5.2 mmol) in dry toluene (30 ml) stirred under argon at 45°C. The temperature was gradually raised to 60°C and stirring maintained until reduction was complete (4–5 h). After cooling to room temperature, a saturated solution of ammonium chloride (50 ml) was added and the mixture extracted with ethyl acetate (3×3 ml). The organic phase was washed with brine and dried over magnesium sulphate. After removal of the

solvents, the crude reaction product was purified by flash chromatography, eluting with ethyl acetate:light petroleum (40–60°C) (1:1) to give nucleoside (**9**)[13] (0.6 g), as a thick syrup. This was then debenzylated using a solution of boron tribromide (1.73 g, 4 mol equiv.) in dichloromethane at −78°C.[9] After flash column chromatography with chloroform:methanol (1:1) and then recrystallization from aqueous methanol, nucleoside (**10**)[14] (0.272 g, 58%) was isolated as a white solid, mp 189.5–191°C.

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11. Thioglycal (**3**): ^{1}H NMR ($CDCl_3$) δ 3.42 (dd appearing as t, *J*=4 Hz, 1H, 5′-C*H*OCH_2Ph) and 3.58 (dd, *J*=4 and 3 Hz, 1H, 5′-C*H*OCH_2Ph), 3.95 (m, 1H, 4′-C*H*S), 4.55 (m, 4H, 2×PhCH_2O), 4.90 (bs, 1H, 3′-C*H*OCH_2Ph), 5.70 (dd, 1H, *H*C=C), 6.45 (d, *J*=3 Hz, 1H, SC*H*=C), 7.30 (m, 10H, 2×Ph). MS (*m/z*) 312 $(M)^+$, 221 $(M-CH_2Ph)^+$, 204 $(M-HOCH_2Ph)^+$. $C_{19}H_{20}O_2S$ requires: 312.
12. β-Iodonucleoside (**7**): ^{1}H NMR ($CDCl_3$) δ 0.9 (t, *J*=7 Hz, 3H, CH_3CH$_2$-), 1.9–2.2 (m, 2H, CH$_3$CH_2-), 3.8 (m, 3H, 5′-CH_2 and 4′-C*H*S), 4.25 (dd, appears as t, *J*=6 Hz, 1H, 2′-C*H*I), 4.55 (m, 4H, 2×OCH_2Ph), 4.7 (dd, appears as t, *J*=6 Hz, 1H, 3′-C*H*OCH_2Ph), 6.28 (d, *J*=6 Hz, 1H, 1′-C*H*), 7.25–7.4 (m, 10H, 2×Ph), 7.65 (s, 1H, 6-H), 9.75 (bs, 1H, NH). MS (*m/z*) 578 $(M)^+$. Anal ($C_{25}H_{27}O_4N_2SI$): C, H, N.
13. β-Nucleoside (**9**): ^{1}H NMR ($CDCl_3$) δ 0.9 (t, *J*=7 Hz, 3H, CH_3CH$_2$-), 2.0–2.2 (m, 2H, CH$_3$ CH_2-), 2.3–2.6 (m, 2H, 2′-CH_2), 3.8–4.1 (m, 3H, 5′-CH_2 and 4′-C*H*S), 4.8 (dd appears as t, *J*=6 Hz, 1H, 3′-C*H*OCH_2Ph), 4.48 and 4.62 (two s, 4H, 2×OCH_2Ph), 6.35 (dd, *J*=6 Hz, 4Hz, 1H, 1′-C*H*), 7.2–7.4 (m, 10H, 2×Ph), 7.98 (s, 1H, C-6 C*H*), 9.0 (bs, 1H, N*H*).
14. β-Nucleoside (**10**): ^{1}H NMR ($CDCl_3$) δ 1.1 (t, *J*=7 Hz, 3H CH_3CH$_2$-), 2.2–2.6 (m, 4H, CH$_3$CH_2- and 2′-CH_2), 3.7 (m, 1H, 4′-C*H*), 3.9 and 4.05 (dd, *J*=11, 7 Hz, 2H, 5′-CH_2OH), 4.5 (m, 1H, 3′-C*H*), 4.7 (bs, 2H, two O*H*), 6.28 (dd, *J*=7, 3 Hz, 1H, 1′-C*H*), 8.33 (s, 1H, C-6 CH). MS (*m/z*) 272 (M^+). Anal ($C_{11}H_{16}N_2O_4S$): C, H, N.