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A Facile Preparation of 2′,3′-Unsaturated Nucleosides and Hexopyranosides from Acetylated Halohydrins by Reductive Elimination

BJÖRN CLASSON, PER J. GAREGG and BERTIL SAMUELSSON

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden

Reductive eliminations by treatment of acetylated halohydrins with zinc powder in ethanol containing acetic acid are described. The examples include a purine, a pyrimidine and a disaccharide derivative. The procedure allows facile access to 2,3-dideoxy-2-enoside derivatives.

Nucleosides containing unsaturation in the sugar moiety are found among naturally occurring antibiotics *e.g.* blasticidin S[1,2] and angustomycin.[3] Modified nucleosides are also of interest as potential enzyme inhibitors of viruses and malignant cells. Unsaturated sugar derivatives may further be used for synthetic manipulations.

Several routes to 2′,3′-unsaturated nucleosides have been described.[4–8] In one of these, 2′-deoxynucleosides are transformed *via* the 3′,5′-ditosylate into the 3′,5′-anhydrosugar with inverted configuration at C-3′. The latter, upon treatment with sodium hydroxide in hexamethylphosphoric triamide, gives 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-uracil and -thymine.[4] Another route, exemplified by the synthesis of a 2′,3′-unsaturated derivative from adenosine, proceeds *via* the intermediate 6-*N*-pivalamido-9-[3-deoxy-3-iodo-2-*O*-(4,4-dimethyl-3-pivaloxy-pent-2-enoyl)-5-*O*-pivalyl-β-D-xylofuranosyl]purine.[5,6] This route involves chromatographic separation of the desired intermediate from various other compounds formed simultaneously.[5,6] In two other methods, 2′(3′)-*O*-acyl-3′(2′)-deoxyhalonucleosides, readily obtained in a single reaction step from the parent ribonucleosides,[7] are subjected to reduction, either with chromium(II) acetate[7] and ethylene diamine or electrolytically.[8]

We now describe an improved, efficient reductive elimination of vicinal haloacetates producing unsaturation, applicable to nucleosides and hexopyranosides. In this method, zinc powder in ethanol containing acetic acid is used at room temperature. Three examples are given, comprising a purine and a pyrimidine nucleoside and a disaccharide derivative.

The crude 5′-*O*-substituted 2′(3′)-*O*-acetyl-3′(2′)-deoxyhalonucleosides *1*, *2* and *4* (Scheme 1) were synthesized as described by Moffatt and co-workers.[7] Attempted iodination of uridine according to procedure a, Scheme 1, failed, probably due to product decomposition. Treatment of *1*, *2* and *4* with zinc powder in ethanol containing acetic acid, followed by Zemplén deacylation afforded the product *3* and *5*, respectively, in the yields indicated.

9-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-adenine (*3*) and 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (*5*) have been tested for activity against *Herpes influenzae* virus. Compound *3* had general cell toxicity, while *5* was essentially inactive.

Ferrier and co-workers[9,10] have described the reaction of 3,4,6-tri-*O*-acetyl-D-glucal with alcohols in inert solvents in the presence of boron trifluoride to obtain 4,6-di-*O*-acetyl-α-D-*erythro*-hex-2-enopyranosides. The corresponding reaction starting from 3,4,6-tri-*O*-acetyl-D-galactal did not give the 4,6-di-*O*-acetyl-α-D-*threo*-hex-2-enopyranosides due to subsequent elimination reactions.[9,10] The use of tin(IV) chloride instead of boron trifluoride did, however, give the *threo*-isomers. Thus, the reaction of 3,4,6-tri-*O*-acetyl-D-galactal with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in 1,2-dichloromethane in the presence of tin(IV) chloride afforded 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactofuranose in a 56 % yield.[11]

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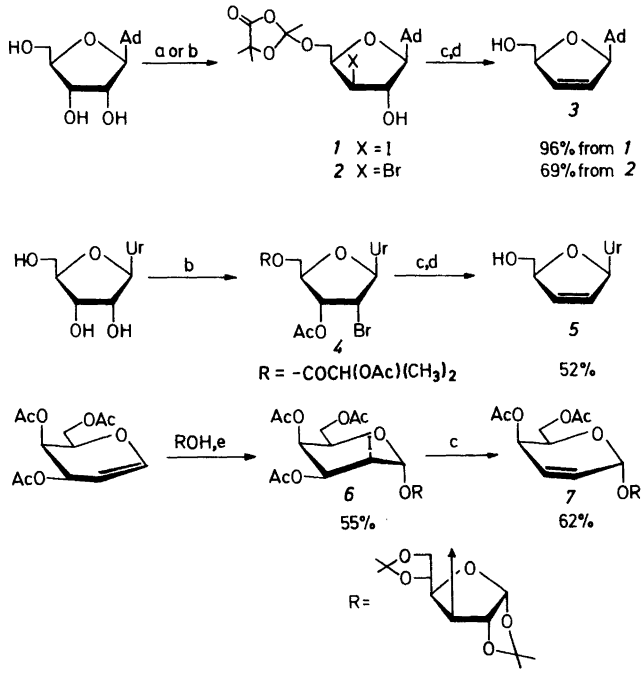

Scheme 1. a: $(CH_3)_2C(OAc)COCl$, NaI, CH_3CN; b: $(CH_3)_2C(OAc)COBr$, CH_3CN; c: Zn(powder), CH_3CO_2H, CH_3CH_2OH; d: $NaOCH_3$, CH_3OH; e: $ZnCl_2$ (or $HgCl_2$), I_2, silver imidazolate, CH_3CN.

In the present work, 1,2:5,6-di-*O*-isopropylidene-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-talopyranosyl)-α-D-glucofuranose (*6*) was obtained by the reaction of 3,4,6-tri-*O*-acetyl-D-galactal with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in acetonitrile in the presence of iodine, zinc chloride and silver imidazolate as previously described.[1,2] Treatment of *6* with zinc dust in ethanol containing acetic acid gave the disaccharide *7* containing a 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranosyl residue in a 62 % yield. The reductive elimination from *6* can conceivably follow two paths, *cis*-elimination yielding *7* and also *trans*-diaxial elimination yielding 3,4,6-tri-*O*-acetyl-D-galactal. The latter was indeed observed as a by-product. When better leaving groups than alkoxyls are positioned at C-1, the *trans*-diaxial elimination is favoured.[13]

EXPERIMENTAL

General methods were the same as those previously reported.[14] *9-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)adenine*[4,6,7] (*3*). Zinc powder (2.0 g, 30 mmol) and acetic acid (0.37 g, 6.2 mmol) were added with stirring at room temperature to a solution of 9-[2-*O*-acetyl-3-deoxy-3-iodo-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]adenine (*1*)[7] (1.7 g, 3.1 mmol) in ethanol (80 ml). After a reaction time of 15 min the mixture was filtered through Celite, concentrated to about 10 ml (at a bath temperature below 30 °C), diluted with ethyl acetate (100 ml) and transferred to a separating funnel. The solution was washed with aqueous sodium carbonate (3 × 20 ml) and then water (2 × 20 ml); dried ($MgSO_4$), filtered and concentrated to dryness. The residue was dissolved in 0.1 M sodium methoxide in methanol (40 ml) and allowed to stand for 10 min at room temperature. The solution was neutralized with acetic acid, concentrated to dryness and the product was purified by silica gel column chromatography (ethyl acetate – methanol – water 6:3:1) to yield *3* (695 mg, 96 %), $[\alpha]_D^{22}$ + 20° (*c* 0.25, methanol), m.p. 185 – 187 °C (from methanol) lit.[7] $[\alpha]_D$ + 23° (methanol), m.p. 194 – 195 °C], ^1H NMR shifts and coupling constants were in agreement with those published.[7]

1-(2,3-Dideoxy-β-D-glycero-pent-2-enofuranosyl)-uracil[4,7] (*5*). Zinc powder (2.74 g, 41.9 mmol) and acetic acid (1.0 g, 16.7 mmol) were added with stirring at room temperature to 5′-*O*-(2-acetoxyisobutyryl)-3′-*O*-acetyl-2′-bromo-2′-deoxyuridine

(*4*)[7] (2.0 g, 4.2 mmol) in ethanol (300 ml). After a reaction time of 10 min the mixture was filtered through Celite. Triethylamine (1.0 ml) was added to the filtrate which was concentrated to 10 ml; 0.4 M sodium methoxide in methanol (50 ml) was added. After 30 min at room temperature the solution was neutralized with acetic acid and concentrated to dryness. The solid residue was extracted with boiling ethyl acetate, the combined extracts were concentrated to dryness and the product subjected to flash chromatography on silica gel[15] (chloroform–ethanol 95:5) to yield *5* (455 mg, 52 %), $[\alpha]_D^{22}$ −15° (*c* 0.2, methanol), m.p. 156–158 °C (from methanol) [lit.[7] $[\alpha]_D$ −15° (methanol), m.p. 155–156 °C]. ^{1}H NMR shifts and coupling constants were in agreement with those published.[7]

3-O-(3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-α-D-talopyranosyl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (*6*) was prepared as described before[12] except that dry zinc chloride[16] was used instead of mercury (II) chloride in the glycosidation step.

3-O-(4,6-Di-O-acetyl-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1,2:5,6-di-O-isopropylidene)-α-D-glucofuranose (*7*). Zinc powder (1.1 g, 16.8 mmol) was added to a solution of *6* (1.0 g, 1.52 mmol) in ethanol (50 ml) and then acetic acid (350 mg, 1.63 mmol) at room temperature with stirring. After a reaction time of 15 min, pyridine (1 ml) was added. The mixture was filtered through Celite, concentrated to about 5 ml, dissolved in toluene (200 ml) and transferred to a separating funnel. The solution was washed with aqueous sodium carbonate (4 × 75 ml), water (2 × 75 ml), dried ($MgSO_4$), filtered and concentrated to dryness. The product was purified by silica gel column chromatography (toluene–ethyl acetate 1:1 containing 0.5 % pyridine) to yield 7 (477 mg, 66 %). $[\alpha]_D^{22}$ −116° (*c* 1.0, chloroform). Anal. $C_{22}H_{32}O_{11}$: C, H. δ_{1H} (100 MHz, $CDCl_3$): 1.32 (s, 6 H, 2 CH_3), 1.41, 1.51 (2 s, each 3 H, 2 CH_3), 2.09, 2.12 (2 s, each 3 H, $COCH_3$), 4.00–4.37 (m, 8 H, H-3, H-4, H-5, H-6,6, H-5′, H-6′,6′), 4.62 (d, 1 H, H-2), 5.02 (dd, 1 H, H-4′), 5.35 (d, 1 H, H-1′), 5.89 (d, 1 H, H-1), 6.06 (d, 1 H, H-2′), 6.11 (d, 1 H, H-3′); $J_{1,2}$ 3.7 Hz, $J_{1',2'}$ 2.5 Hz, $J_{2',3'}$ ~0 Hz, $J_{3',4'}$ 5.2 Hz, $J_{4',5'}$ ~2 Hz, δ_{13C} (25 MHz, $CDCl_3$): 20.8, 20.9 (2 × $COCH_3$), 25.5, 26,6, 27.0, 27.1 (4 × CH_3), 62.9, 63.2, 67.3, 68.0, 72.8, 80.9, 81.4, 84.5 (C-2, C-3, C-4, C-5, C-6, C-4′, C-5′, C-6′), 95.0 (C-1′), 105.6 (C-1), 109.3, 112.1 [2 × C $(OR)_2$] 125.5, 130.1 (C-2′, C-3′), 170.4, 170.9 (2 × $COCH_3$).

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