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Note

The Wittig-cyclization procedure: acid promoted intramolecular formation of 3-C-branched-chain 3,6-anhydro furano sugars via 2′-oxopropylene derivatives

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Abstract—Some olefinic Wittig products, 3-deoxy-5,6-*O*-isopropylidene-3-*C*-(2′-oxopropylene)-1,2-*O*-alkylidene hexofuranose derivatives were converted to the branched-chain 3,6-anhydro-3-*C*-(2′-oxopropyl) derivatives on treatment with ion exchange resin Amberlite 120 (H^+) in methanol–water at room temperature. Hydrolysis of 5,6-isopropylidene groups and intramolecular ring-closures took place in one pot reactions.

Keywords: Branched-chain sugars; Anhydrosugars; Wittig-cyclization; Intramolecular ring-closure

Branched-chain sugar derivatives are important compounds as they are commonly found as the glycosidic components of substances having physiological activity, such as antibiotics and nucleotides.[1] The Wittig approach has been widely used in ring-closure reactions of both furanose and pyranose derivatives, to produce C-glycosides.[2–17] However, formation of anhydrosugar derivatives other than C-glycosides have not been widely studied especially under acidic conditions. Ethoxycarbonylmethylene derivatives of sugars have probably been the most widely used, ring-closures having been carried out under weakly basic conditions (Moffatt C-glycosidation).[2–8] When stabilized ylides are used for the formation of the Wittig products, subsequent cyclization of the unsaturated intermediate may occur by treatment with bases. This may occur spontaneously, if a free hydroxyl group is present at a suitable position. For instance, the reaction of 2,3-*O*-isopropylidene-D-ribofuranose with $Ph_3P{=}C(Me)CO_2Me$, $Ph_3P{=}C(Me)CN$ and $Ph_3P{=}CHCOMe$ gave olefinic Wittig products which, upon treatment with dilute base afforded the corresponding anhydrosugars as anomeric mixtures.[6]

The anomeric ratios were dependent on the structures of the ylides but the β-D-anomer usually dominated.[6] In related examples, 4,6-*O*-ethylidene-D-glucopyranose reacted with $Ph_3P{=}CHCOCH_2CO_2Et$ to afford directly a 1:1 anomeric mixture[6] and the same substrate reacted with a stabilized Wittig reagent to give *trans*-oct-2-enoate in excellent yield which was cyclized by treatment with dilute base to afford a 1:1 mixture of the α and β anomers of the C-glycoside.[5] When unstabilized ylides are used for the formation of Wittig products, cyclization can be obtained by halo-, seleno- or mercuri-electrophilic activation.[9–12]

Stereoselective routes for the *C*-α- and *C*-β-glycosyl compounds have also been reported by the use of promoters such as zinc powder[13] and iodine.[14] Sugar lactones have also been converted to C-glycosides using the Wittig-cyclization method.[15,16] More recently open-chain vinylsulfides, produced by the Wittig method from furano-type carbohydrates, were also successfully used as new substrates for regiocontrolled ring-closure reactions.[17]

Nonglycosidic branched-chain anhydrosugar derivatives are not widely found in the literature. One report

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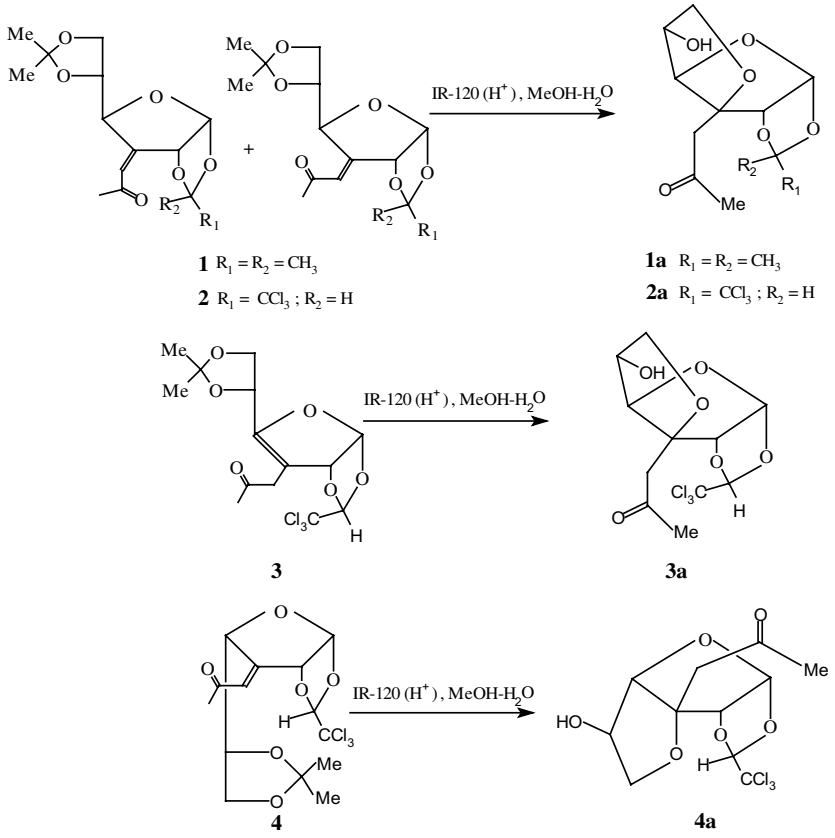
describes intramolecular cyclizations of 3-*C*-cyanomethylene and 3-*C*-(*p*-nitrophenyl)methylene derivatives of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose using an ion-exchange resin to form 3,6-anhydro derivatives.[18] Another example is 3,6-anhydro-5-azido-5-deoxy-3-*C*-ethoxycarbonylmethyl-1,2-*O*-isopropylidene-α-D-glucofuranose which is synthesized as an intermediate during the synthesis of 3-C-branched-chain analogous of 3,6-anhydrodeoxynojirimycin.[1]

Trichloroethylidene acetals are useful protecting groups since they are highly stable in acid media, thus, allowing acid catalyzed reactions to be carried out on parent compounds. Their removal is possible by hydrogenation with Raney nickel followed by acid hydrolysis.[19] They can be converted to dichloroethylidene ketene acetals[20] or to dichloroacetyl orthoesters[20,21] by their reaction with potassium *t*-butoxide. Dichloroacetyl orthoesters have found use in the formation of glycosides.[22] Trichloroethylidene acetals are potentially biologically active compounds; α-chloralose (1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose) is a hypnotic which is used as an animal anaesthetic.[23]

Our continuing interest in the formation of new compounds from trichloroethylidene acetal protected sugars prompted us to prepare new anhydro-sugar derivatives and now we wish to report some acid promoted ring-closure reactions using 2′-oxopropylene derivatives to form branched-chain 3,6-anhydro rings from some furanosugars.

Furanos-3-ulose derivatives were obtained by the oxidation of appropriate diacetals using a conventional PCC/MS 4 Å method[24] which were then reacted with acetylmethylenetriphenylphosphorane affording the Wittig products as a mixture of *E* and *Z* isomers in good yield, according to a previously reported method.[25] It is interesting to note that all furanos-3-ulose derivatives gave the expected olefinic Wittig products except 5,6-*O*-isopropylidene-1,2-*O*-(*R*)-trichloroethylidene hexofuranos-3-ulose. The reaction of this compound with acetylmethylenetriphenylphosphorane both in tetrahydrofuran and chloroform did not afford the expected Wittig product but instead gave only **3**, probably through allylic prototropy. Similar compounds could be obtained from the analogous Wittig products by heating them in a basic solvent such as pyridine or even in dimethyl sulfoxide.[25]

The Wittig products (**1**–**4**) were subjected to hydrolysis and subsequent ring-closure reactions in MeOH solution using acidic ion exchange resin Amberlite 120 (H^+) as a catalyst in one pot reactions to afford five-membered anhydro derivatives (**1a**–**4a**) (Scheme 1). Monitoring the reaction by TLC indicated that a single product had been formed which implies that the intramolecular closure of the ring takes place spon-



Scheme 1.

Table 1. ^{1}H NMR chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in $CDCl_3$, for 3,6-anhydrosugars

Compound	H-1	$J_{1,2}$	H-2	H-4	$J_{4,5}$	H-5	$J_{5,6a}$	$J_{5,6b}$	H-6a	H-6b	$J_{6a,6b}$	H-1′a, H-1′b	$J_{1'a,1'b}$	OH	J_{OH}	$HCCl_3$	Ac	CH_3
1a	5.88 d	3.2	4.66 d	4.55 d	4.4	4.42 ddd	7.4	8.6	4.08 dd	3.43 dd	8.6	3.01 d, 2.77 d	16.4	—	—	—	2.12 s	1.50–1.35 s
2a	6.21 d	4.0	4.80 d	4.99 d	3.2	4.45 ddd	8.6	8.6	4.09 dd	3.48 dd	8.8	2.90 s	—	2.26 d	10.8	5.52 s	2.23 s	—
3a	6.11 d	3.9	4.70 d	5.04 d	3.9	4.45 ddd	7.4	8.6	4.11 dd	3.47 dd	8.6	3.12 d, 2.80 d	16.8	2.25 d	10.5	5.44 s	2.20 s	—
4a	6.12 d	4.3	4.90 d	4.50 s	0.0	4.45 d	3.5	0.0	4.14 dd	4.02 d	10.0	3.21 d, 3.14 d	18.5	—	—	5.65 s	2.20 s	—

Table 2. ^{13}C NMR chemical shifts (δ ppm) for 3,6-anhydrosugars

Compound	C=O	C-1, $C(CH_3)_2$	C-1, $CHCCCl_3$	CCl_3	C-2, C-3, C-4, C-5, C-6	C-1′	CH_3 (Ac)	CH_3 (i.p.)
1a	205.5	113.7, 102.6	—	—	85.3, 87.1, 90.6, 72.3, 72.6	45.4	31.8	27.8–27.2
3a	205.4	—	108.0, 107.8	98.5	90.2, 88.1, 87.6, 71.5, 70.8	45.2	31.9	—
2a	205.5	—	107.8, 107.7	99.6	90.2, 88.1, 86.4, 71.4, 70.6	45.3	31.9	—
4a	207.4	—	110.5, 107.2	99.2	93.2, 87.9, 86.6, 77.1, 75.7	49.0	31.0	—

Table 3. ^{1}H NMR chemical shifts (δ ppm) and $J_{H,H}$ values (Hz) in $CDCl_3$, for 5-O-acetylated-3,6-anhydrosugars

Compound	H-1	$J_{1,2}$	H-2	H-4	$J_{4,5}$	H-5	$J_{5,6a}$	$J_{5,6b}$	H-6a	H-6b	$J_{6a,6b}$	H-1′a, H-1′b	$J_{1'a,1'b}$	$HCCl_3$	$COCH_3$	Ac	CH_3 (i.p.)
1b	5.92 d	3.5	4.71 d	4.70 d	4.3	5.19 ddd	7.4	8.6	4.17 dd	3.71 dd	8.6	3.91 d, 2.77 d	16.8	—	2.20 s	2.10 s	1.48–1.34 s
2b	6.21 d	4.0	5.00 d	4.96 d	3.9	5.24 ddd	7.4	7.4	4.18 dd	3.72 dd	8.5	2.90 s	—	5.48 s	2.23 s	2.11 s	—
3b	6.14 d	3.9	5.07 d	4.85 d	3.9	5.20 ddd	7.4	8.6	4.19 dd	3.73 dd	8.6	3.14 d, 2.80 d	17.2	5.40 s	2.20 s	2.10 s	—
4b	6.18 d	3.9	4.92 d	4.52 s	0.0	5.27 d	3.5	0.0	4.19 dd	4.05 d	10.5	3.25 d, 2.94 d	18.0	5.67 s	2.21 s	2.07 s	—

Table 4. ^{13}C NMR chemical shifts (δ ppm) for 5-O-acetylated-3,6-anhydrosugars

Compound	C=O	C=O (Ac)	C-1, $C(CH_3)_2$	C-1, $CHCCCl_3$	CCl_3	C-2, C-3, C-4, C-5, C-6	C-1′	CH_3	CH_3 (i.p.)	CH_3 (Ac)
1b	205.6	170.7	112.8, 106.9	—	—	91.8, 85.9, 83.8, 73.8, 68.9	44.8	31.2	27.9–27.6	21.1
2b	205.4	170.6	—	107.7, 107.7	99.4	84.1, 90.7, 87.6, 73.6, 68.6	44.4	31.8	—	21.1
3b	205.3	170.6	—	108.1, 107.9	98.4	90.7, 87.6, 85.5, 73.5, 68.8	44.2	31.8	—	21.0
4b	206.6	169.7	—	110.6, 107.7	99.1	90.7, 88.2, 86.3, 78.4, 73.2	48.8	31.0	—	21.1

taneously. The reactions are stereospecific due to the stereochemistry of the starting sugar derivatives. Therefore, usually a mixture of *E* and *Z* isomers was used in the ring-closure reactions to give a single product. Epimerized product (**3**) also gave the ring-closure reaction to afford **3a**, most probably after its re-epimerization to the usual Wittig product. The ^{1}H and ^{13}C NMR data were consistent with the proposed structures (Tables 1 and 2). Positive polarity APCI mass spectra (70 eV) of **1a**–**4a** also supported the proposed structures.

On acetylation, **1a**–**4a** gave their monoacetate derivatives (**1b**–**4b**). This can be considered as confirmation of the presence of a single free hydroxyl group. The ^{1}H and ^{13}C NMR data of **1b**–**4b** were consistent with their structures (Tables 3 and 4).

1. Experimental

1.1. General methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Varian AS 400 NMR spectrometer. APCI positive polarity (70 eV) mass spectra were recorded on Agilent 1100 (LC–MSD) mass spectrometer. IR spectra were recorded on Perkin–Elmer Spectrum 100 FTIR Spectrometer. Optical rotation measurements were carried out on a Schimidt–Haensch Polartronic E polarimeter. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel G-60 (Merck 7734), respectively. All solvent removals were carried out under reduced pressure.

1.2. 3,6-Anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (1a)

A solution of a mixture of *E* and *Z* isomers of **1** (0.77 g, 0.0026 mol) in methanol (20 mL) was stirred with amberlite (120 H^+) resin (8 mL) and H_2O (distilled, 3 mL) at room temperature for 24 h. TLC (toluene–methanol, 9:1) showed a single product. The resin was filtered off and the filtrate was neutralized with sodium bicarbonate. The solvent was removed and the residue was extracted with boiling dichloromethane (3×100 mL), filtered and dried to give a syrup which was crystallized and recrystallized from hexane to give

the pure **1a** (0.38 g, 57%) mp 75–76 °C, $[\alpha]_D^{22}$ +40.0 (*c* 0.1, CH_2Cl_2). MS *m/z* 201 [(M+1)−acetone, 18%] (201−H_2O, 100%).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.77; H, 6.91.

1.3. 5-*O*-Acetyl-3,6-anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (1b)

A solution of **1a** (0.35 g, 0.0014 mol) in pyridine (5 mL) was acetylated with acetic anhydride (1.5 mL, 0.0162 mol) at room temperature for 24 h. The usual work up procedure and purification on a silica gel column eluting with dichloromethane–methanol (100:1) gave the monoacetate as a colourless syrup (0.34 g, 81%), $[\alpha]_D^{23}$ +73.9 (*c* 0.17, CH_2Cl_2). MS *m/z* 243 [(M+1)−acetone, 26%], 225 [(M^+−Me)−AcOH, 40%], 165 (9%), 137 (100%).

Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 55.33; H, 6.57.

1.4. 3,6-Anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-glucofuranose (2a)

A mixture of *E* and *Z* isomers of **2** (0.71 g, 0.0018 mol) was used and the procedure described in Section 1.1 was applied. The resultant syrupy product was crystallized from dichloromethane–hexane (0.34 g, 54%), mp 154–156 °C, $[\alpha]_D^{22}$ +44.2 (*c* 0.10, CH_2Cl_2). MS *m/z* 347 (M+1), 2%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−H_2O, 17%], 183 (329−chloral, 100%).

Anal. Calcd for $C_{11}H_{13}Cl_3O_6$: C, 38.01; H, 3.77. Found: C, 38.08; H, 3.73.

1.5. 5-*O*-Acetyl-3,6-anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-glucofuranose (2b)

A solution of **2a** (0.47 g, 0.0014 mol) was acetylated as in Section 1.1. The yield of the syrupy monoacetate was 0.5 g (91%), $[\alpha]_D^{22}$ +73.3 (*c* 0.11, CH_2Cl_2). MS *m/z* 389 (M+1), 83%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−AcOH, 100%], 243 [(M+1)−chloral, 38%], 183 [(M^+−AcOH)−chloral, 25%].

Anal. Calcd for $C_{13}H_{15}Cl_3O_7$: C, 40.08; H, 3.88. Found: C, 39.53; H, 3.88.

1.6. 3,6-Anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (3a)

A solution of **3** (0.35 g, 0.0009 mol) was reacted as in Section 1.1. The syrupy product was crystallized from dichloromethane–hexane (0.18 g, 58%), mp 95–96 °C, $[\alpha]_D^{22}$ +53.1 (*c* 0.10, CH_2Cl_2). MS *m/z* 347 (M+1), 1%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−H_2O, 16%], 183 (329−chloral, 100%).

Anal. Calcd for $C_{11}H_{13}Cl_3O_6$: C, 38.01; H, 3.77. Found: C, 38.14; H, 3.88.

1.7. 5-*O*-Acetyl-3,6-anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*R*)-trichloroethylidene-α-D-glucofuranose (3b)

A solution of **3a** (0.21 g, 0.0006 mol) was acetylated as in Section 1.1. The yield of the syrupy monoacetate was 0.2 g (90%), $[\alpha]_D^{22}$ +88.5 (*c* 0.11, CH_2Cl_2). MS *m/z* 389 (M+1), 44%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−AcOH, 62%], 243 [(M+1)−chloral, 100%], 183 [(M^+−AcOH)−chloral, 76%].

Anal. Calcd for $C_{13}H_{15}Cl_3O_7$: C, 40.08; H, 3.88. Found: C, 40.53; H, 3.95.

1.8. 3,6-Anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-gulofuranose (4a)

A solution of **4** (0.76 g, 0.002 mol) was reacted as in Section 1.1. The product was obtained as a colourless syrup (0.41 g, 59%), $[\alpha]_D^{22}$ +23.9 (*c* 0.105, CH_2Cl_2). MS *m/z* 347 (M+1), 2%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−H_2O, 18%], 183 (329−chloral, 100%).

Anal. Calcd for $C_{11}H_{13}Cl_3O_6$: C, 38.01; H, 3.77. Found: C, 38.21; H, 3.92.

1.9. 5-*O*-Acetyl-3,6-anhydro-3-*C*-(2′-oxopropyl)-1,2-*O*-(*S*)-trichloroethylidene-α-D-gulofuranose (4b)

A solution of **4a** (0.41 g, 0.0012 mol) was acetylated as in Section 1.1. The yield of the syrupy monoacetate was 0.43 g (92%), $[\alpha]_D^{22}$ −22.3 (*c* 0.11, CH_2Cl_2). MS *m/z* 389 (M+1), 3%, 329–331–333 (3 × chlorine isotopic pattern) [(M+1)−AcOH, 4%], 243 [(M+1)−chloral, 1%], 183 [(M^+−AcOH)−chloral, 100%].

Anal. Calcd for $C_{13}H_{15}Cl_3O_7$: C, 40.08; H, 3.88. Found: C, 39.82; H, 3.76.

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