

exo-Glycals from glycosyl cyanides. First generation of C-glycosylmethylene carbenes from 2,5- and 2,6-anhydroaldose tosylhydrazones

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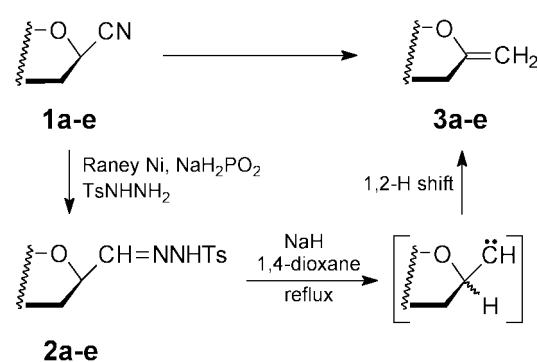
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In a one-pot reaction acylated glycosyl cyanides were transformed with Raney nickel–sodium hypophosphite into 2,5- and 2,6-anhydroaldose tosylhydrazones, which gave *exo*-glycals under Bamford–Stevens conditions.

exo-Glycals (2,5- or 2,6-anhydro-1-deoxy-hex- or -hept-1-enitols) are useful carbohydrate derivatives exemplified by their applications *e.g.* in syntheses¹ and biological investigations.²

Several synthetic protocols are known for the preparation of such compounds: olefination of sugar lactones by using the Tebbe reagent,³ dimethyltitanocene,^{1a} or the Wittig methodology;⁴ hydrogen halide eliminations from C-glycosyl-iodomethanes;⁵ other methods using glycosyl carbanions as intermediates have been reviewed recently.⁶

Here we report a novel method for the preparation of *exo*-glycals based on the generation of C-glycosylmethylene carbenes by application of the aprotic Bamford–Stevens reaction⁷ to tosylhydrazones of 2,5- and 2,6-anhydroaldose derivatives followed by their spontaneous rearrangement (Scheme 1). The reaction of acylated glycosyl cyanides⁸ (**1**) with Raney nickel–sodium hypophosphite in the presence of



Scheme 1

1.2–1.7 eq. of tosylhydrazine⁹ in acetic acid–water–pyridine solvent mixture proved to provide easy access to the previously unknown 2,5- and 2,6-anhydroaldose tosylhydrazones **2** (Table 1). With the exception of **2e**, one isomer was formed in

Table 1 Synthesis and selected data of 2,5- and 2,6-anhydroaldose tosylhydrazones **2** and *exo*-glycals **3**

1	2					3				
	Yield (%)	$[a]_D^b$ (c)	NMR ^a			Yield (%)	$[a]_D^b$ (c)	NMR ^a		
			H-1 ($J_{1,2}$) C-1	H-2 ($J_{2,3}$)	NH			H-1, H-1' C-1	C-2	
a 	64	+4 (1.00)	7.16 (6.3) 144.1	4.34 (9.5)	8.12	72	+43 (0.98)	4.70, 4.96 97.3	153.3	
b 	87	+6 (0.97)	7.00 ^c (6.7) 144.1	4.14 ^c (9.8)	11.6 ^c	82	+74 (1.45) Lit. ¹² +69 (1.00)	4.51, 4.82 96.1	154.1	
c 	73	–35 (2.03)	7.04 (6.8) 144.3	3.89 (9.5)	9.07	86	–94 (0.94)	4.49, 4.69 ^c 96.9	154.5	
d 	58	+65 (1.01)	7.10 ^c (5.5) 144.0	4.87 ^c (10.4)	11.48 ^c	74	+29 (1.08)	4.24, 4.80 95.7	151.9	
e 	Inseparable mixture (probably two diastereomers)					26 ^{d,e}	+24 (0.90)	4.44, 4.67 87.1	157.7	

^a For CDCl₃ solutions unless otherwise stated (δ /ppm, J /Hz). ^b Measured in CHCl₃ at room temperature. $[a]_D$ Values are given in 10^{–1} deg cm² g^{–1}. ^c For DMSO-*d*₆ solutions. ^d Overall yield for the two steps. ^e For deprotonation 2 eq. of NaH was used.

these transformations. These compounds are new representatives of the rather sparsely populated class of 2,5- and 2,6-anhydroaldimine derivatives.¹⁰

The tosylhydrazone salt formation and thermolysis were performed in one operation as suggested in the literature.^{7a} a solution of **2** in 1,4-dioxane was added dropwise to boiling 1,4-dioxane containing 10 eq. of sodium hydride. *exo*-Glycals **3** were isolated by column chromatography. The reactions were rather clean and highly selective in so far as no products of 1,2-C or 1,2-O shifts could be detected in the mixtures. This was the case even with the furanoid derivative **2e**, in contrast to the ring enlargement observed with tetrahydrofuran-2-yl-methylenes.¹¹

In summary, we have described a new route to *exo*-glycals from readily available glycosyl cyanides *via* 2,5- and 2,6-anhydroaldose tosylhydrazones. This method can be a useful alternative to the known procedures, especially for the preparation of acyl-protected derivatives.

Experimental

General procedure for the synthesis of 2,5- and 2,6-anhydroaldose tosylhydrazones (**2**)

Raney nickel (1.5 g, from an aqueous suspension, Merck) was added at room temperature to a vigorously stirred solution of pyridine (5.7 mL), acetic acid (3.4 mL), and water (3.4 mL). Then sodium hypophosphite (0.74 g, 8.4 mmol), tosylhydrazine (0.22–0.32 g, 1.2–1.7 mmol), and the corresponding glycosyl cyanide **1** (1 mmol) were added to the mixture. When the reaction was complete (TLC, eluent: ethyl acetate–hexane 1 : 1) the insoluble materials were filtered off with suction, and washed with dichloromethane (10 mL). The organic layer of the filtrate was separated, washed sequentially with water (3 mL), 10% aqueous hydrogen chloride solution (2 × 3 mL), cold, saturated sodium hydrogen carbonate solution (2 × 3 mL) and water (3 mL), and then dried on anhydrous magnesium sulfate. The solution was concentrated under reduced pressure, and traces of pyridine were removed by repeated co-evaporations with toluene. The residue was purified by column chromatography (eluent: ethyl acetate–hexane 1 : 1 or 1 : 2) to give syrupy **2a–d**.

General method for the synthesis of *exo*-glycals (**3**)

Sodium hydride (0.24 g, 10 mmol) was added to dry 1,4-dioxane (25 mL). The suspension was stirred and heated to reflux, and then a solution of a tosylhydrazone **2** (1 mmol) in dry 1,4-dioxane (25 mL) was added dropwise. When the reaction was complete (TLC, eluent: ethyl acetate–hexane 1 : 1), the mixture was cooled and the insoluble material filtered off. The solvent was removed under reduced pressure, and the resi-

due was purified by column chromatography (eluent: gradient of ethyl acetate–hexane 1 : 2 to 1 : 1) to give *exo*-glycals **3a–e**.

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