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Carbohydrate Research 330 (2001) 141–144

CARBOHYDRATE RESEARCH

Note

Studies on the synthesis of 1,2-cis pentofuranosides from *S*-glycofuranosyl dithiocarbamates, dithiocarbonates and phosphorodithioates

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Received 16 March 1999; received in revised form 10 July 2000; accepted 16 July 2000

Abstract

The selectivity in the synthesis of 1,2-cis glycofuranosides from dithiocarbonates, dithiocarbamates and phosphorodithioates is improved by combined use of silver triflate and catalytic amount of hexamethylphosphoramide (HMPA) under mild conditions.

Keywords: Glycosylation; Glycofuranosyl donors; Glycofuranosides; Dithiocarbamates; Dithiocarbonates; Phosphorodithioates

Despite recent progress, the stereoselective synthesis of glycosides remains a major target in carbohydrate chemistry.[1] Since the discovery that glycofuranosyl dithiocarbonic[2] and dithiophosphoric[3] acid derivatives have glycosylating properties, our attention has focused on the possibility of using these classes of compounds in the stereoselective synthesis of 1,2-cis glycofuranosides under mild reaction conditions.

Recently, we have reported the synthesis of 1,2-trans glycofuranosides by reaction of benzylated pentofuranosyl 1-dithiocarbonates with galactopyranosyl acceptors in toluene in the presence of silver triflate as a promoter.[2] We furthermore established that the stereoselectivity in the formation of xylofuranosides can be controlled by the addition of a polar aprotic solvent tetramethylurea, dimethyl sulfoxide, hexamethylphosphoramide to the reaction.[4]

We have now applied this methodology to the synthesis of 1,2-cis glycofuranosides from dithiocarbamate,[5] dithiocarbonate[5] and dithiophosphate[3] derivatives of 2,3,5-tri-*O*-benzyl-D-xylo- (**1**), D-ribo (**2**) and L-arabino-furanose (**3**) (Scheme 1). Some representative results are summarized in Tables 1–3. Among the additives screened, hexamethylphosphoramide (HMPA) proved to be the best choice for allowing rapid and high-yielding 1,2-cis glycosidation, under the conditions where further anomerization can be excluded. The stereochemical results are practically independent of the compositions of the starting *S*-glycosyl esters and temperature.

It is generally acknowledged that the stereochemistry of a glycosylation reaction is solvent dependent. The differences in solvent polarity have already been exploited for the stereocon-

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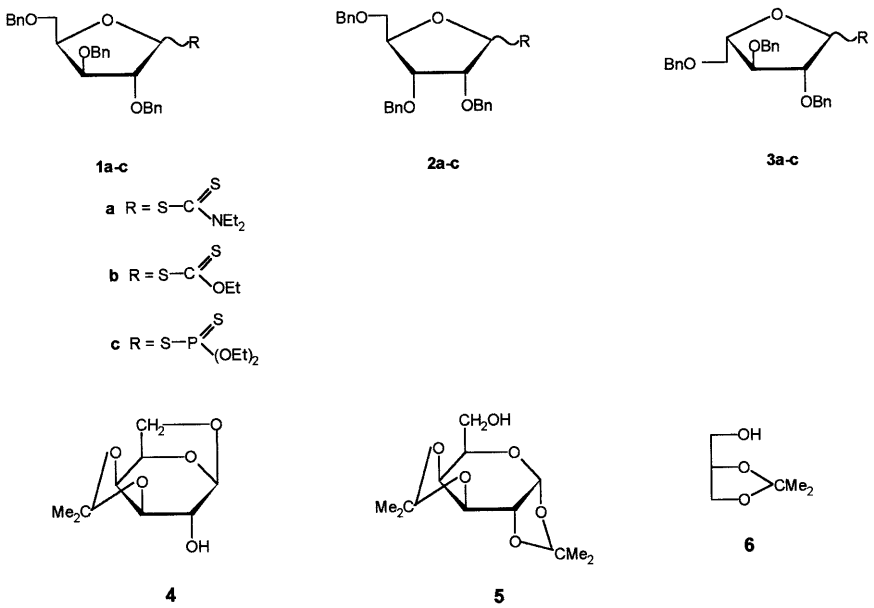
0008-6215/01/$ - see front matter
PII: S0008-6215(00)00220-2

trolled (α- or β-) synthesis of glycopyranosides. Particularly well documented is the significant effect of acetonitrile on stereoselectivities of glycosidation with benzyl-protected glycopyranosyl donors in favor of the predominant formation of β-glycosides.[6] Similar results were found for glycosidation reactions carried out in diethyl ether and with excess of tertiary amines.[5]. This effect was best explained by solvent participation at the anomeric center of the intermediate glycosyl cation.[6–8] In the course of our research on glycosylation reactions of 1-thioglycofuranose derivatives in acetonitrile, diethyl ether or THF in the presence of silver triflate, no significant change in the proportion of anomeric glycofuranosides compared with results in toluene was observed.

Our results show that stereoselectivity of the glycosidation reaction depends strongly on the nucleophilic properties of the electron pair donor (EPD) solvents, as quantified by the so-called donor number (DN) of Gutmann.[9] A correlation between DN and the content of 1,2-cis furanosides was observed, i.e., higher solvent DN favors the higher concentration of the 1,2-cis isomer in the final reaction mixture. From the reported data, acetonitrile (DN



Scheme 1.

Table 1
Synthesis of 2,3,5-tri-*O*-benzyl-D-xylofuranosides in the presence of polar additives (PA)

Donor	Acceptor	Yield (%)	PA	Proportions of isomers α:β	
				Without PA[2,3]	With PA
1a	**4**	78	TMU	2:3	3:1
1a	**4**	75	DMSO		3:1
1a	**4**	87	HMPA		10:1
1a	**4**	72	sulfolane		1:1
1a	**5**	69	TMU	1:1	4:1
1a	**6**	74	TMU	1:2	2:1
1b	**4**	83	HMPA	1:5	11:4
1b	**5**	88	HMPA	1:5	7:3
1b	**6**	86	HMPA	4:3	12:5
1c	**4**	87	HMPA	1:4	5:1
1c	**5**	85	HMPA	1:4	4:1

Table 2
Synthesis of 2,3,5-tri-*O*-benzyl-D-ribofuranosides in the presence of HMPA

Donor	Acceptor	Yield (%)	Proportion of isomers α:β	
			Without HMPA[2,3]	With HMPA
2a	**4**	82	β	11:5
2a	**5**	86	β	3:1
2a	**6**	89	1:15	13:5
2b	**4**	78	β	3:1
2b	**5**	72	2:3	3:1
2b	**6**	94	1:2	4:1
2c	**4**	84	1:5	5:1
2c	**5**	89	1:3	3:1

Table 3
Synthesis of 2,3,5-tri-*O*-benzyl-L-arabinofuranosides in the presence of HMPA

Donor	Acceptor	Yield (%)	Proportion of isomers α:β	
			Without HMPA[2,3]	With HMPA
3a	**6**	78	4:3	5:7
3b	**4**	80	3:1	1:3
3b	**6**	89	4:3	1:3
3c	**4**	86	4:1	1:2
3c	**5**	90	5:1	1:1

14.1) and sulfolane (DN 14.8) are weak donors, whereas HMPA (DN 38.8) is a very strong one.

The stereochemical outcome of the glycosidation in the presence of polar additives can be rationalized assuming that under the proposed reaction conditions, an interaction between the oxocarbenium ion intermediate and the EPD additive takes place. This results in the formation of 1,2-cis and 1,2-trans EPD adducts, which can react further with a glycosyl acceptor, probably in a synchronous manner.[10,11]

1. Experimental

General methods.—Optical rotations were measured at rt with a Perkin–Elmer 141 Polarimeter using a Na vapor lamp for solutions in $CHCl_3$. ^1H NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Varian (300 MHz) spectrometer. TLC was performed on precoated plates of Silica Gel G plates (E. Merck), using 8:1 benzene–EtOAc and detection by charring with sulfuric acid. Chromatographic purifications were performed with Silica Gel 60 (E. Merck) 0.063–0.2 mm. All glycosylation reactions were carried out in anhyd solvents. Organic soln were concd under reduced pressure at 40 °C. *S*-Glycofuranosyl *N*,*N*-diethyldithiocarbamates,[7] *O*-ethyl *S*-glycofuranosyl dithiocarbonates,[8] *S*-glycofuranosyl *O*,*O*-diethyl phosphorodithioates,[3] 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose(**4**),[12] 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranose (**5**)[13] were prepared according to the literature. 1,2-*O*-Isopropylidene-*sn*-glycerol (**6**), AgOTf and solvents were commercially available and were used without purification.

General procedure of glycoslyation.—A suspension of the donor (**1**–**3**, 0.2 mmol), acceptor (**4**–**6**, 0.2 mmol), polar additive (0.2 mmol) and molecular sieves 4 Å (40 mg) in toluene (10 mL) was treated with AgOTf (62 mg, 0.24 mmol). The resulting mixture was stirred at rt for about 10 min. After completion of the reaction, the mixture was filtered and diluted with toluene (10 mL). The filtrate was washed with an aq satd soln of $NaHCO_3$ ($\times 3$) and then with water, dried (Na_2SO_4) and concd under diminished pressure. The residue was purified by column chromatography on silica gel (9:1 hexane–EtOAc). Physical properties and spectral data of glycofuranosides were in accordance with published results.[2]

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