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Block synthesis of oligosaccharides. Part 1: Preparation of furanosyl-1-thiopyranosides

Jadwiga Bogusiak[a,*] and Wiesław Szeja[b]

[a]*Faculty of Pharmacy, Silesian Medical School, PL 41-200 Sosnowiec, Poland*
[b]*Department of Chemistry, Silesian Technical University, PL 44-100 Gliwice, Poland*

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Abstract—Condensation of fully benzylated pentafuranosyl dithiocarbamates **2a**–**c** with (5-nitro-2-pyridyl) 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside **1** under the agency of NIS/TfOH proceeds with high yields and good degrees of 1,2-*cis* stereoselectivity.

There is considerable interest in the synthesis of furanose oligosaccharides and related analogues that could act as either glycosyltransferase substrates or inhibitors.[1] Oligosaccharides containing furanose moieties are important constituents of a number of lower organisms (bacteria, parasites, fungi and plants). It is now well established that they are critical for the survival of mycobacteria and other pathogenic organisms, and because furanose oligosaccharides are unknown in humans, the enzymes that assemble them are ideal targets for drug action.

Many methods for the stereoselective synthesis of glycopyranosides have been reported, whereas there has been relatively little work directed toward stereoselective synthesis of glycofuranosides, which appears to be a more difficult problem. Remarkable contributions to stereoselective synthesis of ribofuranosides rely on in situ activation of 2,3,5-tri-*O*-benzyl-D-ribofuranose[2] or the application of 2,3,5-tri-*O*-benzyl-1-*O*-iodoacetyl-D-ribofuranose as glycosyl donor.[3] More recently Lowary et al.[1] reported the highly stereoselective synthesis of oligofuranosides from acetylated thiocresyl glycofuranosides.

As part of our programme directed at the synthesis of furanose oligosaccharides, we were interested in developing an efficient route to oligosaccharides with a terminal furanosyl moiety, which could be used directly in a convergent block synthesis of complex carbohydrates.

The key steps in building oligosaccharides are often the glycosylation steps. One of the most successful approaches has been the use of thioglycosides and other anomeric *S*-derivatives in combination with various promoters.

Recently we have reported that a stereocontrolled synthesis of 1,2-*trans* glycofuranosides had been achieved readily and efficiently by a coupling reaction of benzylated pentafuranosyl 1-dithiocarbonates with galactopyranosyl acceptors in toluene in the presence of silver triflate as a promoter.[4] A highly 1,2-*cis* selective glycosylation with these donors was effected under mild conditions by combined use of silver triflate and a stoichiometric amount of polar organic compounds.[5] In this communication we would like to present our study on the glycosylation reactions of pentafuranosyl dithiocarbamates with 1-thiopyranosyl acceptors.

In our initial attempts the glycosylation of *N*,*N*-diethyl *S*-(2,3,5-tri-*O*-benzyl-D-xylofuranosyl) dithiocarbamate **2a**[6] as a model glycosyl donor ('armed' donor) was examined with common 'armed' thiopyranosyl acceptors like methyl 2,3,5-tri-*O*-benzyl-1-thio-β-D-glucopyranoside and 4-nitrophenyl 2,3,5-tri-*O*-benzyl-1-thio-β-D-glucopyranoside by the method previously described.[4] In both cases the reaction mixture consisted almost exclusively of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranoside, undoubtedly resulting from cyclization of the acceptors. Less than 10% of the desired disaccharide was detected by ^{1}H NMR.

Keywords: oligosaccharides; glycosylation; glycofuranosyl donors; glycofuranosides; hetaryl thiopyranosyl acceptors.
* Corresponding author. Fax: 048 (032) 266 78 60; e-mail: jbogusiak@farmant.slam.katowice.pl

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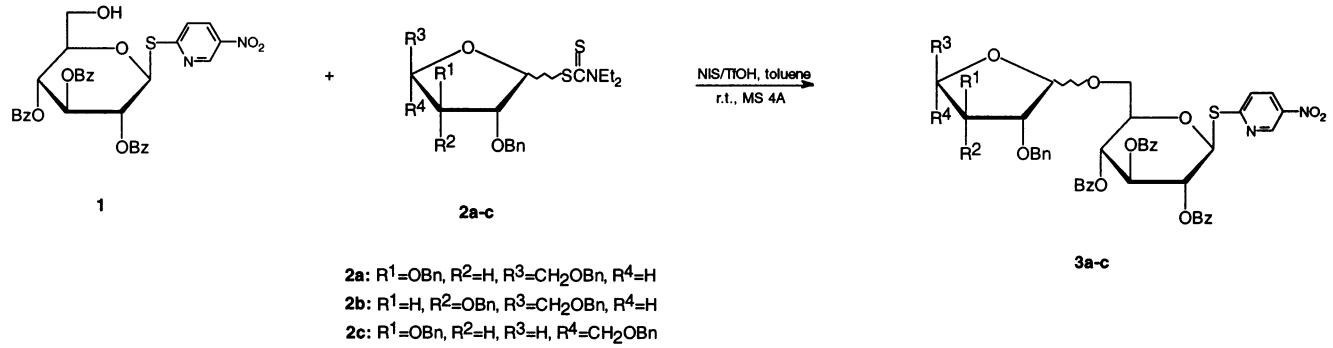

Scheme 1.

Table 1. Glycosylation reactions of **2a**–**c** with **1**

Entry	Donor	Promoter	Reaction time (h)	Product	Yield (%)	Proportion of isomers α:β
1	**2a**	NIS/TfOH	2	**3a**	91	3:2
2	**2b**	NIS/TfOH	1	**3b**	87	6:1
3	**2b**	$BF_3{\cdot}Et_2O$	48	**3b**	68	1:5
4	**2c**	NIS/TfOH	2	**3c**	95	4:5

The powerful promoters *N*-iodosuccinimide/catalytic triflic acid (NIS/TfOH) and trimethylsilyl triflate (TMSOTf) in the presence of triethyl phosphite (TEP)[7] were also tried, but without success. Very similar results were observed when methyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside was used as acceptor ('disarmed' acceptor). No product formation was observed on TLC when 4-nitrophenyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside was used. These negative results prompted us to search for a glycosyl acceptor, which was sufficiently stable, but more reactive than 4-nitrophenyl 1-thioglycopyranoside (mentioned above). We have turned our attention to the heteroaromatic 1-thioglycosides. Recently, Szeja and co-workers[8] have found that readily available (5-nitro-2-pyridyl) 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside **1** can serve as a stable, effective 'latent' acceptor in several glycosylation procedures with 1-thioglycopyranosyl donors.

Glycosidation of the free 6-OH group in acceptor **1** with *N*,*N*-diethyl *S*-(2,3,5-tri-*O*-benzyl-D-ribofuranosyl) dithiocarbamate **2b**[6] proceeded smoothly at room temperature with high α-selectivity in toluene using the activating system NIS/TfOH (Scheme 1).

This methodology allows the coupling of **1** with fully benzylated dithiocarbamates derivatives of D-*xylo*-**2a** and L-arabinofuranose **2c**[6] within 2 h in very high yields and moderate 1,2-*cis* stereoselectivity (Table 1). The use of AgOTf and TMSOTf as catalysts was less successful.

Coupling of **1** with **2b** in the presence of boron trifluoride etherate ($BF_3{\cdot}Et_2O$) gave, after 2 days stirring, (5-nitro-2-pyridyl) 2,3,5-tri-*O*-benzyl-D-ribofuranosyl-(1→6)-2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranosides **3b**α and **3b**β in the ratio of 1:5.

In conclusion, the results presented in this paper show the usefulness of the 5-nitro-2-thiopyridyl anomeric substituent as a stable protecting group and, at the same time, the influence of the higher reactivity of the primary hydroxyl group at C-6. We have demonstrated the effectiveness of **1** as a glycosyl acceptor in NIS/TfOH mediated glycosylation with furanosyl dithiocarbamates **2**. Further investigations concerning the application of obtained precursors **3**[9] ('latent' donors) in blockwise oligosaccharide synthesis are now in progress.

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9. All new compounds gave satisfactory ^{1}H NMR (300 MHz) spectroscopic and elemental analytical data. Selected data: **3a**: *(5-nitro-2-pyridyl) 2,3,5-tri*-O-*benzyl*-D-*xylofuranosyl*-*(1→6)*-*2,3,4-tri*-O-*benzoyl*-*1*-*thio*-*β*-D-*glucopyranoside*: syrup, $[\alpha]=92.1$ (*c* 1.2, $CHCl_3$), ^{1}H NMR δ 3.21(dd, 1H,

$J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'a}$ = 3.9 Hz, H-5′a), 3.27 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'b}$ = 3.7 Hz, H-5′b), 3.63 (dd, 1H, $J_{6a,5}$ = 2.2 Hz, $J_{6,6a}$ = 11.5 Hz, H-6a), 3.65–3.74 (m, 1H, H-4′), 3.96 (dd, 1H, $J_{6a,6}$ = 11.5 Hz, $J_{6,5}$ = 4.9 Hz, H-6), 3.97–4.08 (m, 2H, H-2′,3′), 4.12–4.26 (m, 1H, H-5), 4.31–4.67 (m, 6H, C$\underline{H}_2$Ph), 4.89 (d, 1H, $J_{1',2'}$ = 4.2 Hz, H-1′α), 4.99 (bs, 1H, H-1′β), 5.67–5.79 (m, 2H, H-2,4), 6.03 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3α), 6.04 (dd, 1H $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3β), 6.13 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1α), 6.14 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1β), 7.09–7.45 (m, 31H, H_{ar}, H-3_{ar}), 7.78–7.96 (m, 6H, H_{ar}), 8.13 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 9.0 Hz, H-4_{ar} α), 8.22 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 8.8 Hz, H-4_{ar} β), 9.23 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar} α), 9.29 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar} β). **3b**α: *(5-nitro-2-pyridyl) 2,3,5-tri*-O-*benzyl*-α-D-*ribo-furanosyl-(1→6)-2,3,4-tri*-O-*benzoyl-1-thio-β-D-glucopyranoside*: syrup, [α] = 65.7 (*c* 0.6, $CHCl_3$), ^{1}H NMR δ 3.21 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'a}$ = 3.9 Hz, H-5′a), 3.27 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'b}$ = 3.7 Hz, H-5′b), 3.71 (dd, 1H, $J_{6a,5}$ = 2.2 Hz, $J_{6,6a}$ = 11.5 Hz, H-6a), 3.74 (dd, 1H, $J_{1',2'}$ = 3.9 Hz, $J_{2',3'}$ = 6.8 Hz, H-2′), 3.77 (dd, 1H, $J_{2',3'}$ = 6.8, $J_{3',4'}$ = 3.7 Hz, H-3′), 3.94 (dd, 1H, $J_{6a,6}$ = 11.5 Hz, $J_{6,5}$ = 6.0 Hz, H-6), 4.11–4.24 (m, 2H, H-4′, H-5), 4.28, 4.34 (AB, 2H, *J* = 12.1 Hz, C$\underline{H}_2$Ph), 4.44, 4.49 (AB, 2H, *J* = 12.3 Hz, C$\underline{H}_2$Ph), 4.51 (s, 2H, C$\underline{H}_2$Ph), 4.93 (d, 1H, $J_{1',2'}$ = 3.9 Hz, H-1′), 5.57 (dd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{3,4}$ = 9.8 Hz, H-4), 5.62 (dd, 1H, $J_{1,2}$ = 10.3 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 5.87 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 5.95 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 7.08–7.44 (m, 31H, H_{ar}, H-3_{ar}), 7.89–7.72 (m, 6H, H_{ar}), 8.05 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 8.8 Hz, H-4_{ar}), 9.02 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar}). **3b**β: *(5-nitro-2-pyridyl) 2,3,5-tri*-O-*benzyl-β-D-ribofuranosyl-(1→6)-2,3,4-tri*-O-*benzoyl-1-thio-β-D-glucopyranoside*: syrup, [α] = 40.7 (*c* 0.5, $CHCl_3$), ^{1}H NMR δ 3.43 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'a}$ = 5.9 Hz, H-5′a), 3.52 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4'5'b}$ = 3.2 Hz, H-5′b), 3.79 (d, 1H, $J_{2',3'}$ = 4.4 Hz, H-2′), 3.85 (dd, 1H, $J_{6a,5}$ = 2.2 Hz, $J_{6,6a}$ = 11.5 Hz, H-6a), 3.94–4.09 (m, 2H, H-3′,6), 4.11–4.26 (m, 2H, H-4′, H-5), 4.33, 4.44 (AB, 2H, *J* = 11.7 Hz, C$\underline{H}_2$Ph), 4.35 (s, 2H, C$\underline{H}_2$Ph), 4.42, 4.48 (AB, 2H, *J* = 12.1 Hz, C$\underline{H}_2$Ph), 4.89 (s, 1H, H-1′), 5.53 (dd, 1H, $J_{4,5}$ = $J_{3,4}$ = 9.8 Hz, H-4), 5.62 (dd, 1H, $J_{1,2}$ = 10.3 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 5.87 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 5.95 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 7.09–7.43 (m, 31H, H_{ar}, H-3_{ar}), 7.72–7.89 (m, 6H, H_{ar}), 8.03 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 8.8 Hz, H-4_{ar}), 9.15 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar}). **3c**: *(5-nitro-2-pyridyl) 2,3,5-tri*-O-*benzyl-L-arabinofuranosyl-(1→6)-2,3,4-tri*-O-*benzoyl-1-thio-β-D-glucopyranoside*: syrup, [α] = 63.6 (*c* 1.7, $CHCl_3$), ^{1}H NMR δ 3.45 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'}$ = 5.4 Hz, H-5′a,5′b β), 3.51 (dd, 1H, $J_{5'a,5'b}$ = 10.7 Hz, $J_{4',5'}$ = 3.7 Hz, H-5′a,5′b α), 3.68 (dd, 1H, $J_{6a,5}$ = 2.2 Hz, $J_{6,6a}$ = 11.7 Hz, H-6a), 3.76–4.02 (m, 3H, H-2′,3′,6), 4.11–4.55 (m, 8H, H-4′,5, C$\underline{H}_2$Ph), 4.77 (d, 1H, $J_{1',2'}$ = 4.2, H-1′β), 4.98 (bs, 1H, H-1′α), 5.52 (dd, 1H, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 5.65 (dd, 1H, $J_{1,2}$ = 10.3 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 5.94 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 5.95 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 7.08–7.48 (m, 31H, H_{ar}, H-3_{ar}), 7.72–7.89 (m, 6H, H_{ar}), 7.93 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 9.0 Hz, H-4_{ar} α), 8.05 (dd, 1H, $J_{4ar,6ar}$ = 2.7 Hz, $J_{3ar,4ar}$ = 9.0 Hz, H-4_{ar} β), 9.13 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar} α), 9.22 (d, 1H, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar} β).