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(5-Nitro-2-pyridyl) 1-thio-β-D-glucopyranoside as a stable and reactive acceptor

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Abstract

The title compound was synthesised and studied in several glycosylation procedures as an acceptor. Presented experiments indicate its value as a very stable, effective 'latent' glycosylating agent.

Keywords: glycosidation; thioglycosides; dithiocarbamates of 2-deoxysugars.

Among many approaches described in carbohydrate chemistry, thioglycosides[1] are very useful glycosylating agents in oligosaccharide synthesis.[2] Frequent use of this class of compounds as donors and acceptors is due to their ease of preparation and availability of methods for their activation in the presence of a variety of promoters. To facilitate the synthesis of oligosaccharides, some new chemoselective glycosylation strategies, e.g. the 'one-pot sequential glycosylation'[3] and 'active and latent glycosylation',[4] have recently been developed.

The general concept used herein is based on the difference in reactivity of two anomeric centres of the glycosyl donor and acceptor. The more reactive thioglycoside is a donor. In our glycosylation strategy several protected thiosugars have been used as donors: methyl 1-thioglucosides (**4**, **5**) and 1-dithiocarbamates of 2-deoxy sugars (**6**, **7**). We looked for an anomeric substituent of a glycosyl acceptor that was sufficiently stable to withstand protecting group manipulations and, moreover, inert towards many activation methods, and we turned our attention to heteroaromatic 1-thioglycosides. Recently, we have reported a new and effective methodology for the synthesis of thioglycosides via aromatic nucleophilic substitution of halogen with 1-thiosugar derivatives.[5–7] We have found that hetaryl thioglycosides with electron withdrawing groups in the ring are very stable donors in most glycosylation conditions. Our initial experiments on the application of 4-nitrophenyl thioglucoside in a 'latent glycosylation' strategy show its moderate reactivity even if very reactive glycosyl donors were used. Searching

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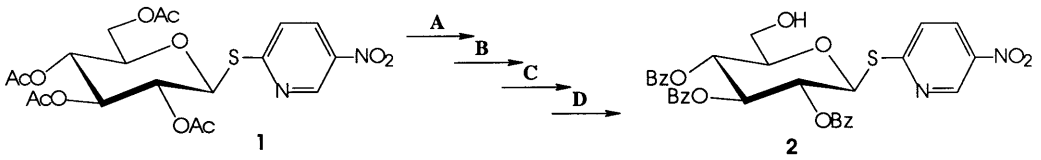
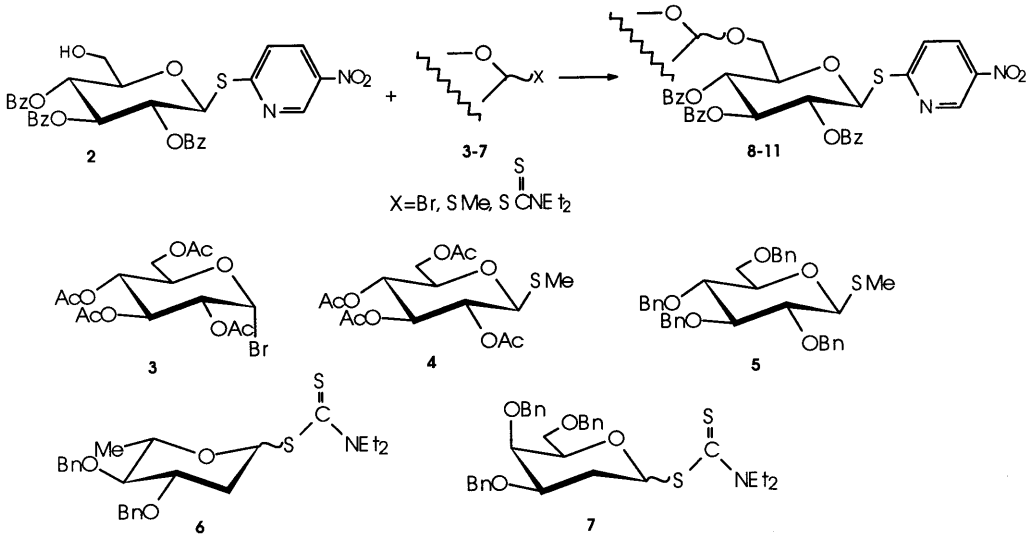
for a more suitable acceptor with a sufficiently reactive primary hydroxyl group, 5-nitro-2-pyridyl β-D-thioglucoside **2**[8] was synthesised in a four-step procedure (Scheme 1). Further investigations were directed in order to examine the limitations of this glycosylating agent.



Scheme 1. (**A**) MeONa, MeOH, 95% yield. (**B**) *t*-Butyldimethylsilyl chloride, imidazole, DMF, 95% yield. (**C**) CH_2Cl_2, benzoyl chloride, pyridine, 81% yield. (**D**) Acetonitrile, HBF, 81% yield

In reactions with methanol or di-*O*-isopropylidene-α-D-galactopyranose as glycosyl acceptors, thioglycoside **2** was inert towards typical promoter systems: Ag_2O, silver triflate (AgOTf), trimethylsilyl triflate (TMSOTf), *N*-iodosuccinimide/catalytic triflic acid (NIS/TfOH) and di-*sym*-collidine perchlorate (IDCP). Next, coupling reactions of **2** with several glycosyl donors, presented in Scheme 2, were carried out using the above activators. In every case, the glycosylation reaction proceeded smoothly, affording the corresponding disaccharides **8**–**11**[12] in good yields with moderate to high stereoselectivity. Results of our experiments are collected in Table 1.



Scheme 2.

Donor **3**[9] was prepared to show the usefulness of acceptor **2** in a typical Koenigs–Knorr procedure, donors **4**[10] and **5**[11] show its application in the 'armed and disarmed' glycosylation method. Thus, treatment of per-*O*-acetylated donor **4** with acceptor **2** in the presence of appropriate promoter gave disaccharide **8**[12] as the β anomer, while reaction between **2** and **5** gave disaccharide **9**[12] as a mixture of anomers (Table 1, entry 2 and 3).

Table 1
Glycosylation reactions of **3**–**7** with **2**

Entry	Donor	Promoter	Reaction conditions solvent/temperature	Reaction time	Product	Yield (%)	α:β
1	**3**	Ag_2O	Toluene/rt	24 h	**8**	62	Only β
2	**4**	NIS/TfOH	Toluene/rt	2 h	**8**	82	Only β
3	**5**	NIS/TfOH	Toluene/rt	1 h	**9**	85	2:1
4	**6**	AgOTf	Toluene/rt	5 min	**10**	67	4:1
5	**6**	AgOTf	Toluene/−25°C	15 min	**10**	81	9:2
6	**6**	TMSOTf	Toluene/−25°C	15 min	**10**	78	5:1
7	**6**	$BF_3{\cdot}Et_2O$	Toluene/rt	1 h	**10**	94	6:1
8	**6**	NIS/TfOH	Toluene/rt	25 min	**10**	93	9:2
9	**6**	IDCP	Toluene/rt	50 min	**10**	92	3:2
10	**7**	AgOTf	Toluene/−25°C	25 min	**11**	71	15:1
11	**7**	TMSOTf	Toluene/−25°C	25 min	**11**	95	15:1
12	**7**	$BF_3{\cdot}Et_2O$	Toluene/rt	45 min	**11**	92	16.5:1

Other model donors, dithiocarbamates **6** and **7**,[13] were prepared to examine the effect of various promoters and temperature on stereoselectivity of the glycosylation reactions. The yields of the thiodisaccharides **10** and **11**[12] varied from 67 to 95% depending on the method applied. Decreasing temperature always gave better yields but did not interfere with the stereoselectivity. Concerning the effect of promoters, the best result was observed when $BF_3{\cdot}Et_2O$ was used. All examples collected in Table 1 confirm the extreme stability of acceptor **2** under the conditions tested.

Acknowledgements

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8. *(5-Nitro-2-pyridyl) 2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside* **2**: mp = 60–62°C; $[\alpha] = 132.7$ (*c* 0.6, $CHCl_3$), ^{1}H NMR (300 MHz) δ 1.22 (s, 1H, 6-OH), 3.73 (dd, 1H, $J_{6,5} = 4.6$ Hz, $J_{6,6a} = 12.9$ Hz, H-6), 3.86 (dd, 1H, $J_{6a,5} = 2.2$ Hz, $J_{6a,6} = 12.9$ Hz, H-6a), 4.03 (ddd, 1H, $J_{5,4} = 10.2$ Hz, $J_{5,6} = 4.6$ Hz, $J_{5,6a} = 2.2$ Hz, H-5), 5.59 (dd, 1H, $J_{4,3} = 9.8$ Hz, $J_{4,5} = 10.2$ Hz, H-4), 5.75 (dd, 1H, $J_{2,3} = 9.5$ Hz, $J_{2,1} = 10.5$ Hz, H-2), 6.13 (dd, 1H, $J_{3,2} = 9.5$ Hz,

$J_{3,4}$ = 9.8 Hz, H-3), 6.26 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 7.25–7.61 (m, 10H, Ph, H-3_{ar}), 7.82–7.92 (m, 6H, Ph), 8.25 (dd, 1H, $J_{4ar,6ar}$ = 2.6 Hz, $J_{4ar,3ar}$ = 8.8 Hz, H-4_{ar}), 9.28 (d, 1H, H-6_{ar}).

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12. All new compounds gave satisfactory ^{1}H NMR (300 MHz) spectroscopic and elemental analytical data. Selected data: **8**: *(5-Nitro-2-pyridyl) 2,3,4,6-tetra-O-acetyl-β-D-glucopiranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside*: syrup, [α] = 97.8 (*c* 0.3, $CHCl_3$), ^{1}H NMR δ 1.95, 1.97, 1.98, 2.01 (4s, 12H, 4×CH_3CO), 3.52 (m, 1H, H-5′), 3.78 (dd, 1H, $J_{6,5}$ = 6.3 Hz, $J_{6,6a}$ = 11.5 Hz, H-6), 4.01 (dd, 1H, $J_{6a,5}$ = 1.7 Hz, $J_{6a,6}$ = 11.5 Hz, H-6a), 4.03 (dd, 1H, $J_{6a',5'}$ = 2.2 Hz, $J_{6a',6'}$ = 12.2 Hz, H-6a′), 4.17 (dd, 1H, $J_{6',5'}$ = 4.9 Hz, $J_{6',6a'}$ = 12.2 Hz, H-6′), 4.23 (m, 1H, H-5), 4.54 (d, 1H, $J_{1',2'}$ = 7.3 Hz, H-1′), 4.89–5.0 (m, 3H, H-2′, H-3′, H-4′), 5.49 (dd, 1H, $J_{4,5}$ = 9.8 Hz, $J_{4,3}$ = 9.8 Hz, H-4), 5.69 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{2,1}$ = 9.8 Hz, H-2), 6.02 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 9.8 Hz, H-3), 6.16 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.25–7.57 (m, 9H, Ph, H-3_{ar}), 7.79–7.94 (m, 7H, Ph, H-3_{ar}), 8.31 (dd, 1H, $J_{4ar,6ar}$ = 2.6 Hz, $J_{4ar,3ar}$ = 8.8 Hz, H-4_{ar}), 9.31 (d, 1H, H-6_{ar}). **9:** *(5-Nitro-2-pyridyl) 2,3,4,6-tetra-O-benzyl-D-glucopiranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside*: syrup, ^{1}H NMR (α anomer) δ 3.44–3.51 (m, 4H, H-2′, H-5′, H-6, H-6′), 3.64 (dd, 1H, $J_{6a,5}$ = 2.4 Hz, $J_{6a,6}$ = 11.2 Hz, H-6a), 3.66–3.75 (m, 2H, H-5, H-6a′), 3.86 (dd, 1H, $J_{4',5'}$ = 8.1 Hz, $J_{4',3'}$ = 8.2 Hz, H-4′), 4.33 (dd, 1H, $J_{3',2'}$ = 8.2 Hz, $J_{3',4'}$ = 8.2 Hz, H-3′), 4.25, 4.52 (AB, 2H, *J* = 10.5 Hz, CH_2Ph), 4.41, 4.60 (AB, 2H, *J* = 12.0 Hz, CH_2Ph), 4.61, 4.76 (AB, 2H, *J* = 12.2 Hz, CH_2Ph), 4.70, 4.93 (AB, 2H, *J* = 10.7 Hz, CH_2Ph), 4.65 (d, 1H, $J_{1',2'}$ = 3.7 Hz, H-1′), 5.51 (dd, 1H, $J_{4,5}$ = 9.8 Hz, $J_{4,3}$ = 9.3 Hz, H-4), 5.67 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{2,1}$ = 10.5 Hz, H-2), 6.03 (dd, 1H, $J_{3,4}$ = 9.3 Hz, $J_{3,2}$ = 9.5 Hz, H-3), 6.04 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 6.87–6.90 (m, 2H, Ph), 6.99 (d, 1H, $J_{3ar,4ar}$ = 8.8 Hz, H-3_{ar}), 7.18–7.39 (m, 28H, Ph), 7.79–7.97 (m, 6H, Ph, H-4_{ar}), 9.17 (d, 1H, $J_{6ar,4ar}$ = 2.4 Hz, H-6_{ar}). (β anomer) δ 3.31–3.39 (m, 2H, H-2′, H-5′), 3.45–3.60 (m, 5H, H-5, H-6, H-6′, H-6a, H-6a′), 3.82 (dd, 1H, $J_{4',5'}$ = 8.2 Hz, $J_{4',3'}$ = 8.1 Hz, H-4′), 4.15 (d, 1H, $J_{1',2'}$ = 10.9 Hz, H-1′), 4.26, 4.42 (AB, 2H, *J* = 10.5 Hz, CH_2Ph), 4.36, 4.47 (AB, 2H, *J* = 12.2 Hz, CH_2Ph), 4.38 (dd, 1H, $J_{3',4'}$ = 8.1 Hz, $J_{3',2'}$ = 8.1 Hz, H-3′), 4.62, 4.77 (AB, 2H, *J* = 10.7 Hz, CH_2Ph), 4.64, 4.75 (AB, 2H, *J* = 10.7 Hz, CH_2Ph), 5.51 (dd, 1H, $J_{4,5}$ = 9.8 Hz, $J_{4,3}$ = 9.4 Hz, H-4), 5.73 (dd, 1H, $J_{2,3}$ = 9.4 Hz, $J_{2,1}$ = 10.5 Hz, H-2), 6.07 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{3,2}$ = 9.4 Hz, H-3), 6.23 (d, 1H, $J_{1,2}$ = 10.5 Hz, H-1), 6.91–7.01 (m, 3H, Ph), 7.10–7.45 (m, 25H, Ph, H-3_{ar}), 7.79–7.95 (m, 9H, Ph, H-4_{ar}), 9.04 (d, 1H, $J_{6ar,4ar}$ = 2.4 Hz, H-6_{ar}). **10**: *(5-Nitro-2-pyridyl) 2-deoxy-3,4-di-O-benzyl-L-rhamnopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside*: syrup, ^{1}H NMR δ 1.09 (d, *J* = 6.2 Hz, CH_3(H-6′β)), 1.15 (d, *J* = 6.0 Hz, CH_3(H-6′α)), 1.39 (m, H-$2'_{ax}$β), 1.56 (ddd, $J_{2'ax,2'eq}$ = 12.9 Hz, $J_{2'ax,3'}$ = 10.0 Hz, H-$2'_{ax}$α), 2.04 (m, H-$2'_{eq}$β), 2.29 (ddd, $J_{2'eq,3'}$ = 4.9 Hz, H-$2'_{eq}$α), 2.99 (dd, $J_{4',5'}$ = 9.0 Hz, H-4′β), 3.07 (dd, $J_{4',5'}$ = 9.2 Hz, $J_{4',3'}$ = 4.6 Hz, H-4′α), 3.19 (dd, $J_{6,5}$ = 6.4 Hz, $J_{6,6a}$ = 9.5 Hz, H-6β), 3.43–3.54 (m, H-5′β, H-6aβ), 3.61 (dd, $J_{6,6a}$ = 12.0 Hz, $J_{6,5}$ = 5.6 Hz, H-6α), 3.70 (dq, $J_{5',4'}$ = 9.3 Hz, H-5′α), 3.80 (dd, $J_{6a,5}$ = 2.4 Hz, $J_{6a,6}$ = 12.0 Hz, H-6aα), 3.88 (ddd, $J_{3',4'}$ = 4.6 Hz, H-3′α), 4.01 (m, H-3′β), 4.13 (m, H-5β), 4.15 (ddd, $J_{5,6a}$ = 2.4 Hz, $J_{5,6}$ = 5.6 Hz, $J_{5,4}$ = 10.0 Hz, H-5α), 4.34 (dd, $J_{1'2'eq}$ = 0.8 Hz, $J_{1'2'ax}$ = 8.3 Hz, H-1′β), 4.43, 4.50 (AB, *J* = 12.0 Hz, CH_2Phβ), 4.55, 4.59 (AB, *J* = 11.4 Hz, CH_2Phα), 4.57, 4.88 (AB, *J* = 10.7 Hz, CH_2Phβ), 6.63, 4.94 (AB, *J* = 11.4 Hz, CH_2Phα), 4.75 (d, $J_{1',2'ax}$ = 2.9 Hz, H-1′α), 5.65 (dd, $J_{4,5}$ = 10.0 Hz, $J_{4,3}$ = 9.5 Hz, H-4α), 5.66 (dd, $J_{4,5}$ = 10.0 Hz, $J_{4,3}$ = 9.3 Hz, H-4β), 5.72 (dd, $J_{2,3}$ = 9.9 Hz, $J_{2,1}$ = 10.6 Hz, H-2β), 5.74 (dd, $J_{2,3}$ = 9.5 Hz, $J_{2,1}$ = 10.5 Hz, H-2α), 6.02 (dd, $J_{3,4}$ = 9.3 Hz, $J_{3,2}$ = 9.9 Hz, H-3β), 6.03 (dd, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 9.5 Hz, H-3α), 6.18 (d, $J_{1,2}$ = 10.5 Hz, H-1α), 6.22 (d, $J_{1,2}$ = 10.6 Hz, H-1β), 7.32–7.95 (m, Ph, H-3_{ar}α, H-3_{ar}β), 7.81–7.95 (m, Ph), 8.19 (dd, $J_{4ar,3ar}$ = 8.7 Hz, $J_{4ar,6ar}$ = 2.4 Hz, H-4_{ar}β), 8.20 (dd, $J_{4ar,6ar}$ = 2.4 Hz, $J_{4ar,3ar}$ = 8.7 Hz, H-4_{ar}α), 9.28 (d, $J_{4ar,6ar}$ = 2.7 Hz, H-6_{ar}β), 9.32 (d, H-6_{ar}α). **11**: *(5-Nitro-2-pyridyl) 2-deoxy-3,4,6-tri-O-benzyl-D-galactopyranosyl-(1→6)-2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside:* syrup, ^{1}H NMR δ 1.86 (ddd, 1H, $J_{2'eq,1'} \approx 0$ Hz, $J_{2'eq,3'}$ = 4.6 Hz, $J_{2'eq,2'ax}$ = 12.4 Hz, H-$2'_{eq}$), 2.12 (ddd, 1H, $J_{2'ax,3'}$ = 12.0 Hz, $J_{2'ax,2'eq}$ = 12.4 Hz, $J_{2'ax,1'}$ = 3.4 Hz, H-$2'_{ax}$), 3.34–3.36 (m, 2H, H-6, H-5′), 3.66 (dd, 1H, $J_{6a,5}$ = 3.1 Hz, $J_{6a,6}$ = 11.3 Hz, H-6a), 3.70–3.89 (m, 4H, H-4′, H-5, H-6′, H-6a′), 4.17 (m, 1H, H-3′), 4.20, 4.26 (AB, 2H, *J* = 11.9 Hz, CH_2Ph), 4.51 (s, 2H, CH_2Ph), 4.53, 4.86 (AB, 2H, *J* = 11.5 Hz, CH_2Ph), 4.96 (d, 1H, $J_{1',2'ax}$ = 3.4 Hz, H-1′), 5.74 (dd, 1H, $J_{2,3}$ = 9.8 Hz, $J_{2,1}$ = 10.4 Hz, H-2), 5.75 (dd, 1H, $J_{4,5}$ = 10.4 Hz, $J_{4,3}$ = 9.5 Hz, H-4), 6.03 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{3,2}$ = 9.8 Hz, H-3), 6.20 (d, 1H, $J_{1,2}$ = 10.4 Hz, H-1), 7.14–7.38 (m, 25H, Ph, H-3_{ar}), 7.82–7.85 (m, 6H, Ph), 8.10 (dd, 1H, $J_{4ar,3ar}$ = 8.7 Hz, $J_{4ar,6ar}$ = 2.4 Hz, H-4_{ar}), 9.23 (d, 1H, $J_{6ar,4ar}$ = 2.4 Hz, H-6_{ar}).
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