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Note

Glycosyl 1-piperidinecarbodithioates in the synthesis of glycosides

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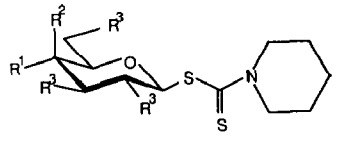
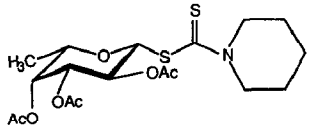
In glycosylation reactions, the classical glycosyl donors are glycosyl bromides or chlorides. These compounds are hygroscopic, unsuitable for transport, and are usually stored under vacuum over phosphorus pentaoxide.

The use of thioglycosides in oligosaccharide synthesis has attracted considerable attention[1]. We have found that acylated glycopyranosyl 1-piperidinecarbodithioates in the D-*gluco*, D-*galacto*, and L-*fuco* series are stable, crystalline, non-hygroscopic compounds that require no special care in storage or handling and are useful in 1,2-*trans*-glycosidation reactions. *S*-Glycosyl *N,N*-dialkyldithiocarbamates[2,3] react with methanol or *p*-nitrophenol in the presence of Hg(II) salts to yield glycosides[2].

When sodium hydride reacted with piperidine and the resulting salt was treated with carbon disulfide and then with the appropriate acylated D-gluco-, D-galacto-, or L-fuco-pyranosyl bromide, the resulting acylated *β*-glycopyranosyl 1-piperidinecarbodithioates (**1–3**, **5**) were isolated by direct crystallisation and without the need for chromatography.





3

1 $R^1 = R^3 = OAc$, $R^2 = H$
2 $R^1 = H$, $R^2 = R^3 = OAc$
4 $R^1 = R^3 = OH$, $R^2 = H$
5 $R^1 = R^3 = OBz$, $R^2 = H$

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TABLE I

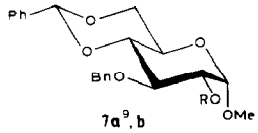
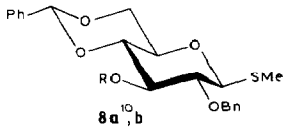
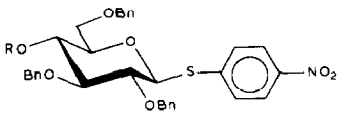
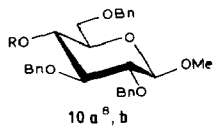
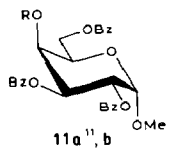
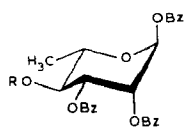
Reaction between **1** and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose to yield **6**

Promoter[a]	*Reaction time (min)*	*Yield of* **6** *(%)*
$MeOSO_2CF_3$	120	86
$[Me_2SSMe]^+OSO_2CF_3^-$	120	85
$AgOSO_2CF_3$	90	92
$SnCl_4$	180	79
$FeCl_3$	180	87

[a] 1 mol. equiv.

TABLE II

Reaction between 2,3,4,6-tetra-*O*-acyl-3- D-glucopyranosyl 1-piperidinecarbodithioate (**1**) and various acceptors

Acceptor[a]*/product*[b]	*Promotor*[c] *(Mol. eqiv.)*	*Reaction time (h)*	*Yield (%)*
 **7a**[9]**, b**	$MeOSO_2CF_3$ (4.5)	3	84
 **8a**[10]**, b**	$AgOSO_2CF_3$ (1.5+1)	16	79
 **9a, b**	$MeOSO_2CF_3$ (4.5)	4	85
 **10a**[8]**, b**	$MeOSO_2CF_3$ (4.5)	1.5	84
 **11a**[11]**, b**	$MeOSO_2CF_3$ (4.5)	16	41
 **12a**[12]**, b, c**	$MeOSO_2CF_3$ (4)	4	78 (**12b**)
	$MeOSO_2CF_3$ (4)	2	90 (**12c**)

[a] Series **a**, R = H. [b] Series **b**, R = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; **12c**, R = 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl. [c] 2,6-Di-*tert*-butylpyridine (0.9 mol. equiv.) was present in each reaction in Table II.

The potential of these 1-piperidinecarbodithioates for the synthesis of glycosides was investigated with the β-D-*gluco* derivative **1**. Thus, **1** was reacted with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1 equiv.), using various promoters, to give 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (**6**). The results (Table I) show that, in addition to thiophilic promoters, silver triflate, tin(IV) chloride, and iron(III) chloride were also efficient activators for the glycosylation reaction. The last two salts are cheap and are of interest for large-scale glycosylations, although the work-up procedure was sometimes cumbersome when using iron(III) chloride. $HgBr_2$, used in the earlier publication[2], gave complexes with 1-piperidinecarbodithioates at room temperature, which could be transformed partially into the disaccharide derivative at elevated temperatures, but the other Lewis acids used gave better yields and cleaner reaction mixtures. In general, the thiophilic promoters or the less reactive silver triflate are preferred for laboratory-scale work.

Further examples of the use of **1** in syntheses of disaccharide derivatives are shown in Table II. Glycosyl acceptors with secondary hydroxyl groups in position 2, 3, or 4 each gave a disaccharide derivative in high yield, provided that the hydroxyl group was not flanked by a deactivating group, as illustrated in the preparation of disaccharide derivative **11b**.

Two of the glycosyl acceptors in Table II are thioglycosides that are potential glycosyl donors. However, under the conditions used, the thioglycoside bonds were quite stable.

EXPERIMENTAL

General methods. — These were the same as reported[4]; $[\alpha]_D$ values were measured at 20°. In the glycosylation reactions, dry solvents and glassware were used. Molecular sieves were not included in the reaction mixtures since they retard the rates of reaction considerably. The reason for this effect is not clear.

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl 1-piperidinecarbodithioate (**1**). — Piperidine (0.1 mol) was added to a stirred suspension of sodium hydride (0.1 mol) in *N,N*-dimethylformamide (100 mL) at 0°. After 10 min, carbon disulfide (0.12 mol) was added dropwise, and stirring was continued for 30 min. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.1 mol) in *N,N*-dimethylformamide (25 mL) was then added dropwise during 10 min, the mixture was allowed to warm up to room temperature, stirring was continued for 1 h, and the mixture was poured onto ice. The brown solid was collected and recrystallised from ethanol to give **1** (82%), m.p. 154–155°, $[\alpha]_D$ +30° (*c* 1.25, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.71 (bm, 6 H, piperidine), 2.02 (s, 3 H, Ac), 2.04 (s, 6 H, 2 Ac), 2.08 (s, 3 H, Ac), 3.82 (bm, 2 H, piperidine), 3.91 (ddd, 1 H, $J_{4,5}$ 10.1 Hz, H-5), 4.13 (dd, 1 H, $J_{5,6b}$ 2.1 Hz, H-6b), 4.28 (bm, 2 H, piperidine), 4.29 (dd, 1 H, $J_{5,6a}$ 4.7, $J_{6a,6b}$ 12.5 Hz, H-6a), 5.14 (m, 1 H), 5.40–5.29 (m, 2 H), 5.91 (d, 1 H, $J_{1,2}$ 10.2 Hz, H-1); ^{13}C, δ 20.7 (2 C), 20.8, 20.9 (CH_3CO), 24.2, 25.4, 26.2, 52.0, 53.5 (piperidine), 62.0 (C-6), 68.4, 68.8, 74.7, 76.5 (C-2,3,4,5), 87.4 (C-1), 170.2, 170.3, 170.7, 171.3 (4 C=O), 191.3 (C=S).

Anal. Calc. for $C_{20}H_{29}NO_9S_2$: C, 48.9; H, 5.9; N, 2.9. Found: C, 48.8; H, 6.0; N, 2.8.

2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl 1-piperidinecarbodithioate (**2**). — Prepared (80%) as described above for **1**, **2** had m.p. 198–200°, $[\alpha]_D$ +55° (*c* 1.2, chloroform).

Anal. Calc. for $C_{20}H_{29}NO_9S_2$: C, 48.9; H, 5.9; N, 2.9. Found: C, 48.6; H, 6.0; N, 2.9.

2,3,4-Tri-O-acetyl-β-L-fucopyranosyl 1-piperidinecarbodithioate (**3**). — Prepared (85%) as described above for **1**, **3** had m.p. 117–119°, $[\alpha]_D$ −78° (*c* 0.9, chloroform).

Anal. Calc. for $C_{18}H_{27}NO_7S_2$: C, 49.9; H, 6.3; N, 3.2. Found: C, 49.4; H, 6.3; N, 3.2.

β-D-Glucopyranosyl 1-piperidinecarbodithioate (**4**). — To a solution of **1** (2.46 g) in methanol (20 mL) was added methanolic M sodium methoxide (0.2 mL). The mixture was stirred overnight, neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated to give **4** (1.61 g, 99.5%). Recrystallisation from methanol–ether gave **4**, m.p. 152–153° (dec.), $[\alpha]_D$ −38° (*c* 1.2, water). N.m.r. data (D_2O): ^1H, δ 1.67 (bs, 6 H, piperidine), 3.44–3.67 (m, 4 H, H-2,3,4,5), 3.73 (dd, 1 H, $J_{5,6b}$ 5.3 Hz, H-6b), 3.89 (dd, 1 H, $J_{5,6a}$ 2.1, $J_{6a,6b}$ 12.4 Hz, H-6a), 3.96 (bm, 2 H, piperidine), 4.27 (bm, 2 H, piperidine), 5.74 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1); ^{13}C, δ 24.2, 26.0, 26.6, 53.5, 54.8 (piperidine), 61.5 (C-6), 70.1, 71.5, 78.5, 81.1 (C-2,3,4,5), 90.2 (C-1), 192.2 (C=S).

2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyl 1-piperidinecarbodithioate (**5**). — (*a*) 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (32.9 g) was treated with carbon disulfide (4.8 mL) and piperidine (6.9 mL), as described for **1**. Recrystallisation of the product from ethyl acetate–hexane gave **5** (31.4 g, 85%), m.p. 178–179° (sintering from 162°), $[\alpha]_D$ +110° (*c* 1.2, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 1.62 (bs, 6 H, piperidine), 3.77 (bs, 2 H, piperidine), 4.23 (bs, 2 H, piperidine), 4.39 (ddd, 1 H, $J_{4,5}$ 9.7 Hz, H-5), 4.47 (dd, 1 H, $J_{5,6b}$ 5.4 Hz, H-6b), 4.59 (dd, 1 H, $J_{5,6a}$ 2.6, $J_{6a,6b}$ 12.1 Hz, H-6a), 5.74, 5.85, 6.09 (3 t, each 1 H, H-2,3,4), 6.34 (d, 1 H, $J_{1,2}$ 10.7 Hz, H-1), 7.2–8.1 (m, 20 H, 4 Ph); ^{13}C, δ 24.2, 25.3, 26.0, 52.0, 53.6 (piperidine), 63.4 (C-6), 69.7, 69.8, 74.9, 77.0 (C-2,3,4,5), 88.0 (C-1), 165.8, 166.0, 166.3, 166.8 (4 C=O), 191.3 (C=S).

(*b*) A solution of **1** (5 g) in methanol (50 mL) was deacylated with methanolic M sodium methoxide (1 mL) as described for **4**. A solution of the crude product in pyridine (20 mL) was treated with benzoyl chloride (6 mL) for 2 h at 0°. Conventional work-up followed by crystallisation from ethyl acetate–hexane gave **5** (5.7 g, 76%).

p-*Nitrophenyl 2,3,6-tri-O-benzyl-1-thio-β-D-glucopyranoside* (**9a**). — *p*-Nitrophenyl 1-thio-β-D-glucopyranoside[5] was benzylidenated with benzaldehyde–formic acid[6] and the product was benzylated with sodium hydride and benzyl bromide in *N,N*-dimethylformamide[7] to give *p*-nitrophenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside, which was dissolved in tetrahydrofuran and treated with sodium cyanoborohydride and ethereal hydrogen chloride[8] to give **9a**, m.p. 132°, $[\alpha]_D$ −44° (*c* 1, chloroform).

Anal. Calc. for $C_{33}H_{33}NO_7S$: C, 67.4; H, 5.6. Found: C, 66.7; H, 5.6.

Glycosylation procedure. — Promoter (Tables I and II) was added to a stirred solution of 2,3,4,6-tetra-*O*-acyl-β-D-glucopyranosyl 1-piperidinecarbodithioate (0.01 mol) and the acceptor (Tables I and II, 0.01 mol) in dichloromethane (25 mL) at room temperature. After an appropriate time (Tables I and II), triethylamine (0.2 mL) was

added, and the mixture was stirred for 5 min, then concentrated. Column chromatography (toluene–ethyl acetate) of the residue on silica gel afforded the disaccharide derivative.

Work-up with iron(III) chloride as promoter. — The brownish solution was poured into water (green precipitate) and extracted with dichloromethane, and the extract was washed with water, dried (Na_2SO_4), filtered, and concentrated. The product was purified by silica gel chromatography as described above.

Products. — 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (**6**) had m.p. 134–137°, $[\alpha]_D$ −51° (*c* 1.8, chloroform); lit.[13] m.p. 140–141° $[\alpha]_D$ −50° (chloroform).

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O* acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**7b**) had m.p. 183–185°, $[\alpha]_D$ −1° (*c* 1, chloroform).

Anal. Calc. for $C_{35}H_{42}O_{15}$: C, 59.8; H, 6.0. Found: C, 59.9; H, 6.0.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (**8b**) had $[\alpha]_D$ −28° (*c* 1, chloroform).

Anal. Calc. for $C_{35}H_{42}O_{14}S$: C, 58.5; H, 5.9. Found: C, 58.5; H, 6.1.

p-Nitrophenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (**9b**) had m.p. 149–151°, $[\alpha]_D$ −39° (*c* 1, chloroform).

Anal. Calc. for $C_{47}H_{51}NO_{16}S$: C, 61.5; H, 5.6. Found: C, 61.5; H, 5.7.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-β-D-glucopyranoside (**10b**) had $[\alpha]_D$ −5° (*c* 1, chloroform).

Anal. Calc. for $C_{42}H_{50}O_{15}$: C, 63.5; H, 6.3. Found: C, 63.4; H, 6.4.

Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (**11b**) had $[\alpha]_D$ +73° (*c* 1.2, chloroform); lit.[13] $[\alpha]_D$ +57° (chloroform).

1,2,3-Tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-L-rhamnopyranose (**12b**) had $[\alpha]_D$ −33° (*c* 1.1, chloroform).

Anal. Calc. for $C_{41}H_{42}O_{17}$: C, 61.0; H, 5.5. Found: C, 61.1; H, 5.2.

1,2,3-Tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-L-rhamnopyranose (**12c**) had $[\alpha]_D$ −13° (*c* 1.4, chloroform).

Anal. Calc. for $C_{61}H_{50}O_{17}$: C, 69.4; H, 4.8. Found: C, 69.5; H, 4.8.

All n.m.r. data on the disaccharide derivatives were in agreement with the structures postulated.

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REFERENCES

1 P. Fügedi, P. J. Garegg, H. Lönn, and T. Norberg, *Glycoconjugate J.*, 4 (1987) 97–108, and references therein.
2 S. Tejima and S. Ishiguro, *Chem. Pharm. Bull.*, 15 (1967) 255–263.

3 W. Szeja and J. Bogusiak, *Synthesis*, (1988) 224–225.
4 F. Dasgupta and P. J. Garegg, *Carbohydr. Res.*, 202 (1990) 225–238.
5 M. Blanc-Muesser, J. Defaye, and H. Driguez, *Carbohydr. Res.*, 67 (1978) 305–328.
6 J. G. Buchanan and J. C. P. Schwarz, *J. Chem. Soc.*, (1962) 4770–4777.
7 J. S. Brimacombe, *Methods Carbohydr. Chem*, 6 (1972) 376–378.
8 P. J. Garegg, H. Hultberg, and S. Wallin, *Carbohydr. Res.*, 108 (1982) 97–101.
9 P. J. Garegg, T. Iversen, and S. Oscarson, *Carbohydr. Res.*, 50 (1976) c12–c14.
10 T. Norberg and H. Ritzén, *Glycoconjugate J.*, 3 (1986) 135–142.
11 E. J. Reist, R. R. Spencer, D. F. Calkins, and L. Goodman, *J. Org. Chem.*, 30 (1965) 2312–2317.
12 R. K. Ness, H. G. Fletcher, and C. S. Hudson, *J. Am. Chem. Soc.*, 73 (1951) 296–300.
13 S. Hanessian and J. Banoub, *Methods Carbohydr. Chem.*, 8 (1980) 247–250.