Synthesis of *S*-Glycosyl *N,N*-Diethyldithiocarbamates from Protected, Reducing Monosaccharides Under Phase-Transfer Conditions

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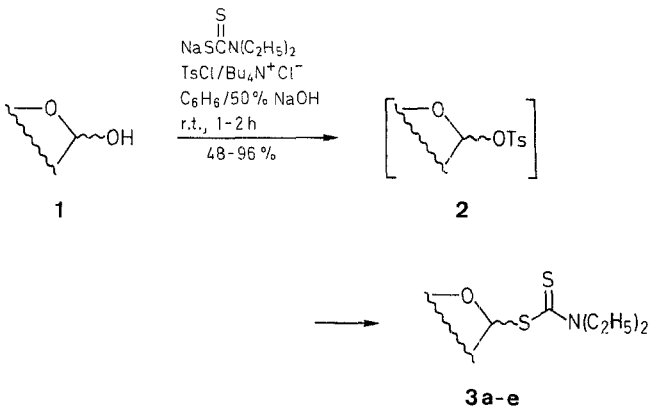
S-Glycosyl *N,N*-diethyldithiocarbamates can be conveniently prepared by treatment of reducing monosaccharides with *p*-toluenesulfonyl chloride and sodium diethyldithiocarbamate under phase-transfer conditions.

Sugar *N,N*-dialkyldithiocarbamates **3** are starting materials for the synthesis of the thiosugars.[1] Salts of dialkyldithiocarbamatic acids have been used as fungicides and insecticides.[2] Diethyldithiocarbamates prevent hepatic necrosis induced by methylformamide[3] and they are active antimalarial agents *in vitro*.[4] We therefore expected that the *S*-glycosyl *N,N*-diethyldithiocarbamates **3** might have some physiological activities and we looked for a convenient method for their synthesis.

Compounds **3** could be obtained from glycosyl bromides and sodium dialkyldithiocarbamates.[1] This method requires activation of the anomeric center by introduction of a leaving group; it is not suitable for sugar derivatives containing acid-labile acetal protective groups. On the other hand, the generation of glycosyl halides from sugars protected as benzyl ethers is laborious.[5] In reported reactions of glycosyl halides, exclusion of moisture is essential.

A good leaving group can be generated from a hydroxy group by treatment with a sulfonyl chloride under phase-transfer conditions.[6,7] We now report an application of this method to the synthesis of *S*-glycosyl *N,N*-diethyldithiocarbamates (**3**) by intermolecular nucleophilic substitution of intermediate glycosyl tosylates (**2**).



Thus, treatment of the protected reducing monosaccharide **1** with tosyl chloride and sodium diethyldithiocarbamate under phase-transfer conditions using conc. aqueous sodium hydroxide and tetrabutylammonium chloride, gives the glycosyl *N,N*-diethyldithiocarbamates **3** in good to excellent yields. Under these conditions, the initially formed glycosyl 1-*O*-sulfonate **2** can react with the hydroxy group of the pyranose or with dithiocarbamate ion present in the organic phase, forming trehalose or the glycosyl dithiocarbamate, respectively. The formation of disaccharides was not detected and side reactions (hydrolysis, degradation) are unimportant under the conditions employed.

The stereoselectivity of the reaction depends on the substrate used. Tetra-*O*-benzyl-D-gluco- (**1a**) and -D-galactopyranose (**1b**) formed only one product, with β-D-configuration, whereas tetra-*O*-benzyl-D-mannopyranose (**1c**), 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**1d**), and tri-*O*-benzyl-D-xylopyranose (**1e**) gave a mixture of anomeric dithiocarbamates.

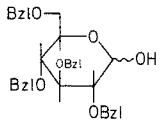
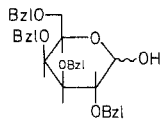
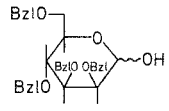
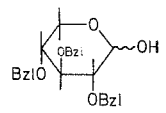
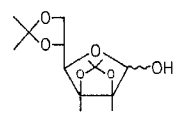
It is difficult to rationalize the influence of the substrate structure on the stereochemical results of the presented reactions, since the stereochemical course of reaction depends on the relative rates of the anomerization[8] α-D-glucosyl$^+$ tosylate$^-$ ⇆ β-D-glucosyl$^+$ tosylate$^-$ and of the subsequent reactions with the substrate.

Due to the anomeric effect, the α-forms of glucopyranose and galactopyranose are thermodynamically more stable. If the different reactivity of the α-D- and β-D-ion pair is a decisive factor in the reaction with the reactive, bulky dithiocarbamate anion the equatorially oriented β-anomer should be the main product. The preference for β-esterification has also been observed in reaction of tetra-*O*-benzyl-D-glucopyranosyl bromide with dithiocarbonates.[9]

Due to its simplicity and the good yields, the present method is an attractive one-pot procedure for the preparation of thiosugar precursors from reducing carbohydrate derivatives. It is worthy of note that sugar derivatives containing the somewhat acid-labile acetal protective groups can also be used as substrate.

A related synthesis of alkyl α-D-glucopyranosides has been described in our foregoing communication.[13]

Table. *S*-Glycosyl *N,N*-Diethyldithiocarbamates **3** from Reducing Monosaccharides **1**

Substrate	Reaction Time (h)	Product	Yield (%)	$[\alpha]_D^{20}$ ($CHCl_3$)[a] (*c*: g/100 mL)	Ratio of Isomers[b] $\alpha:\beta$	Molecular Formula[c]	UV (MeOH)[d] λ_{max} (nm) (log ε)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J*(Hz)
1a 	2	**3a**	90	+48.9 (0.9)	only β	$C_{39}H_{45}NO_5S_2$ (671.9)	246 (3.99), 282 (3.91)	1.19 [t, 6H, *J* = 7, $N(CH_2CH_3)_2$]; 3.70–5.07 [m, 18H, H-2, 3, 4, 5, 6, $ArCH_2$, $N(CH_2CH_3)_2$]; 5.70 (d, 1H, *J* = 9, H-1 β); 7.13–7.29 (m, $20H_{arom}$)
1b 	2	**3b**	48	+76.0 (0.3)	only β	$C_{39}H_{45}NO_5S_2$ (671.9)	246 (3.99), 282 (3.95)	1.17 [t, 6H, *J* = 7, $N(CH_2CH_3)_2$]; 3.45–5.00 [m, 18H, H-2, 3, 4, 5, 6, $ArCH_2$, $N(CH_2CH_3)_2$]; 5.70 (d, 1H, *J* = 10, H-1 β); 7.11–7.30 (m, $20H_{arom}$)
1c 	2	**3c**	56	+35.5 (1.0)	70 : 30	$C_{39}H_{45}NO_5S_2$ (671.9)	246 (4.07), 282 (3.95)	1.18 [t, 6H, *J* = 7, $N(CH_2CH_3)_2$]; 3.45–4.95 [m, 18H, H-2, 3, 4, 5, 6, $ArCH_2$, $N(CH_2CH_3)_2$]; 5.04 (d, 1H, *J* = 1.5, H-1α); 5.76 (s, 1H, H-1β); 7.10–7.30 (m, $20H_{arom}$)
1d 	1	**3d**	86	+47.0 (1.0)	40 : 60	$C_{31}H_{37}NO_4S_2$ (551.8)	246 (3.99), 282 (3.98)	1.20 [t, 6H, *J* = 7, $N(CH_2CH_3)_2$]; 3.17–5.02 (m, 15H, H-2, 3, 4, 5, $ArCH_2$, $N(CH_2CH_3)_2$]; 5.76 (d, 1H, *J* = 8.4, H-1β); 6.30 (d, 1H, *J* = 5, H-1α); 7.14–7.30 (m, $15H_{arom}$)
1e 	1.5	**3e**	96	+21.5 (1.0)	70 : 30	$C_{17}H_{29}NO_5S_2$ (391.5)	246 (3.82), 282 (3.83)	1.18 [t, 6H, *J* = 7, $N(CH_2CH_3)_2$]; 1.40, 1.45, 1.50, 1.55 [4s, 12H, $C(CH_3)_2$]; 3.50–5.15 [m, 10H, H-2, 3, 4, 5, 6, $N(CH_2CH_3)_2$]; 6.07 (d, 1H, *J* = 3, H-1α); 6.30 (s, 1H, H-1β)

[a] Measured using a Polamat A automatic polarimeter (Zeiss-Jena).
[b] Estimated from ^{1}H-NMR spectra.
[c] Satisfactory microanalyses obtained: C ±0.43, H ±0.12, N ±0.23, S ±0.39.
[d] Measured using a UV-VIS spectrophotometer (Zeiss-Jena).
[e] Obtained on a Brucker (100 MHz) spectrometer.

TLC was carried out on silica gel G (Merck), using benzene/EtOAc (2:1 or 8:1) and detection by charring with sulfuric acid. Column chromatography was done on silica gel 60 (Merck) 0.063–0.2 mm. All organic solutions were concentrated under reduced pressure at 40 °C.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose,[10] -D-galactopyranose,[10] -D-mannopyranose,[10] 2,3,4-tri-*O*-benzyl-D-xylopyranose,[11] and 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose[12] were prepared as described in the literature.

Sodium diethyldithiocarbamate, tetrabutylammonium chloride, and *p*-toluenesulfonyl chloride (tosyl chloride) were commercially available (Fluka, Reachim).

S-Glycosyl *N,N*-Diethyldithiocarbamates (3); General Procedure:

A mixture of the reducing sugar derivative (**1**; 0.5 mmol) in benzene (15 mL), tetrabutylammonium chloride (35 mg, 0.125 mmol), tosyl chloride (133 mg, 0.7 mmol), and the trihydrate of sodium diethyldithiocarbamate (113 mg, 0.5 mmol) is stirred with aqueous 50% NaOH (5 mL) at room temperature for 1–2 h. The organic layer is separated, washed with H_2O (3 × 10 mL), dried (Na_2SO_4), and concentrated. The syrupy product is purified by column chromatography on silica gel (eluent: benzene/Et_2O 25:1 v/v).

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