Benzylthioethyl Group as a Base Stable/Base Removable Glycosidic Protecting Group in Oligosaccharide Synthesis

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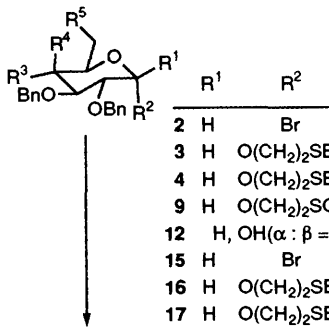
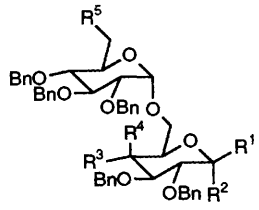
Benzylthioethyl can be used as a glycosidic protecting group and removed by oxidation with dimethyldioxirane followed by base treatment.

The efficient synthesis of oligosaccharides remains one of the major challenges of chemistry and biochemistry. Many recent advances have been made to address the questions of efficient coupling and stereochemical control in the glycosylation step.[1,2] Equally challenging is the need to differentiate the multiple hydroxy groups present in any carbohydrate moiety using protecting group chemistry. In this connection, the sensitivity of the glycosidic linkages in oligosaccharides to acidic conditions limits somewhat the type of hydroxy protecting groups that can be used. We report here the use of benzylthioethyl (BTE) as a base stable as well as base removable glycosyl protecting group in oligosaccharide synthesis.

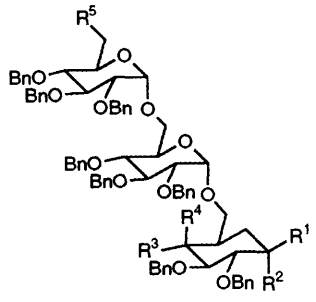
Benzylthioethanol **1** reacted with the glycosyl donor **2** in diisopropylethylamine (DIPEA)–CH_2Cl_2 at room temperature to give the benzylthioethyl (BTE) glucoside **3** {$[\alpha]_D$ = +50.6 (*c* 0.74, $CHCl_3$)} in 71% yield. ^1H and ^{13}C NMR showed that **3** was formed exclusively as the α-anomer. Base methanolysis of **3** under K_2CO_3–MeOH(aq) conditions deprotected the acetate ester function to give the glycosyl acceptor **4** in quantitative yield. Coupling of **2** and **4**, in DIPEA–CH_2Cl_2, gave the disaccharide **5** {$[\alpha]_D$ = + 62.8 (*c* 1.2, $CHCl_3$)} in 66% yield. Again, the coupling product **5** was obtained as the α-anomer. A similar cycle of deacetylation to give **6** and coupling with **2** gave the trisaccharide **7** {$[\alpha]_D$ = + 71.6° (*c* 6.2, $CHCl_3$)} (Scheme 1) in 56% yield, again with good stereoselection at the new anomeric centre. Removal of the BTE group can be achieved first by quantitative oxidation of the sulfide (**3**, **5** or **7**) wth dimethyldioxirane **8** in acetone at −80 °C, then gradually at room temperature for 2 h to the corresponding sulfone (**9**, **10** or **11** respectively).[3] Treatment of the sulfone with lithium diisopropylamide in tetrahydrofuran at room temperature–45 °C or sodium methoxide in methanol at 0 °C revealed the corresponding mono-, di- or



	R^1	R^2	R^3	R^4	R^5	$[\alpha]_D^{20}$ ($CHCl_3$)
2	H	Br	BnO	H	OAc	
3	H	$O(CH_2)_2SBn$	BnO	H	OAc	+50.6, *c* 0.74
4	H	$O(CH_2)_2SBn$	BnO	H	OH	+47.8, *c* 3.87
9	H	$O(CH_2)_2SO_2Bn$	BnO	H	OAc	+48.2, *c* 5.2
12	H, OH(α : β = 1:1)		BnO	H	OH	
15	H	Br	H	OBn	OAc	
16	H	$O(CH_2)_2SBn$	H	OBn	OAc	+20.0, *c* 3.75
17	H	$O(CH_2)_2SBn$	H	OBn	OH	+21.5, *c* 7.9



	R^1	R^2	R^3	R^4	R^5	$[\alpha]_D^{20}$ ($CHCl_3$)
5	H	$O(CH_2)_2SBn$	BnO	H	OAc	+62.8, *c* 1.2
6	H	$O(CH_2)_2SBn$	BnO	H	OH	+57.0, *c* 8.3
10	H	$O(CH_2)_2SO_2Bn$	BnO	H	OAc	+71.1, *c* 16.4
13	H, OH(α : β = 1:1)		BnO	H	OH	
18	H	$O(CH_2)_2SBn$	H	OBn	OAc	+50.0, *c* 4.0
19	H	$O(CH_2)_2SO_2Bn$	H	OBn	OAc	+54.0, *c* 3.9
20	H, OH(α : β = 1:1)		H	OBn	OH	



	R^1	R^2	R^3	R^4	R^5	$[\alpha]_D^{20}$ ($CHCl_3$)
7	H	$O(CH_2)_2SBn$	BnO	H	OAc	+71.6, *c* 6.2
11	H	$O(CH_2)_2SO_2Bn$	BnO	H	OAc	+77.6, *c* 2.3
14	H, OH(α : β = 1:1)		BnO	H	OH	

Scheme 1 (Bn = benzyl)

Table 1 Pyranose ring ^{13}C NMR of selected compounds ($CDCl_3$, in δ)

Compound	C-1	C-2	C-3	C-4	C-5	C-6
3	96.98	79.84	81.79	77.02	68.69	62.89
4	96.85	79.84	81.52	77.01	70.80	61.32
5	96.86	80.03	81.72	77.00	70.49	65.88
	96.74	79.81	81.49	77.49	68.53	62.84
7	97.17	81.93	80.30	77.16	70.77	65.91
	96.98	81.68	80.30	77.43	70.70	65.65
	96.98	81.58	80.04	77.70	68.70	62.99
9	97.71	79.89	81.87	77.02	69.23	62.75
10	97.55	80.04	81.86	77.01	70.90	65.70
	96.86	78.89	81.48	77.31	68.66	62.84
11	97.73	80.35	82.03	77.25	70.82	65.76
	97.12	80.28	81.63	77.43	68.76	65.67
	97.04	80.12	81.63	77.43	68.71	63.03

tri-saccharide (**12**, **13** and **14** respectively). In all cases, the ester function was deprotected at the same time to give the free hydroxy group.

A similar sequence of reactions with the galactosyl donor **15** gave the monosaccharide **16** and then the disaccharide **20** (*via* **17** → **18** → **19**). Again, deprotection of the BTE group was accomplished by the oxidation–base treatment.

These examples demonstrate that BTE can be a useful glycosyl protecting group in oligosaccharide synthesis. By being base stable, BTE is compatible with many hydroxy protecting groups which can be deprotected under basic conditions.

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