Tetrahedron Letters,Vol.27,No.33,pp 3919-3922,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHESIS OF 1,2-CIS-LINKED GLYCOSIDES USING DIMETHYL(METHYLTHIO)SULFONIUM TRIFLATE AS PROMOTER AND THIOGLYCOSIDES AS GLYCOSYL DONORS

Fredrik Andersson, Péter Fügedi*, Per J. Garegg and Mina Nashed**

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm, Sweden

Stereoselective, halide-assisted, 1,2-cis-glycosylations may be obtained using stable thioglycosides containing a non-participating 2-substituent as glycosyl donors, in the presence of dimethyl-(methythio)sulfonium triflate and tetrabutylammonium bromide as promoters.

In oligosaccharide synthesis, block condensation has the advantage over the stepwise addition of one monomer at a time of minimising protection group manipulation at the oligomeric level[1]. At the same time, however, it necessitates the conversion of oligosaccharides into donors, suitable for the construction of glycosidic bonds. By far the most widely used donors are glycosyl halides. The conversion of an oligosaccharide into a glycosyl halide may, however, meet with difficulties, resulting in diminished overall yields[2]. Thioglycosides have been advocated as a solution to this problem. They are stable to the synthetic manipulations usually found in carbohydrate synthesis and are convertible into glycosyl halides[3]. They may also be used directly as glycosyl donors. Their direct use for the synthesis of 1,2-cis[4] as well as 1,2-trans-glycosidic bonds[5] have been described using methyl triflate as promoter. Complete stereospecificity is only achieved for the 1,2-trans-bonds due to the use of neighbouring group participation from a 2-acyl substituent for controlling the steric outcome of the reaction.

We have previously described the use of dimethyl(methylthio)sulfonium triflate (DMTST) as a highly thiophilic promoter in the synthesis of 1,2-trans-glycosides using various thioglycosides with participating 2-substituents as glycosyl donors. Excellent yields are obtained and no O-alkylation is observed[6]. We now report an extension into the synthesis of 1,2-cis-glycosides.

---

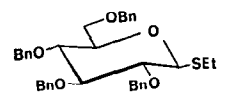
*On leave from: Institute of Biochemistry, L. Kossuth University, Debrecen 10, Hungary

**On leave from: Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt

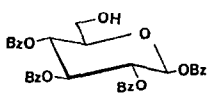
The thioglycoside donor 1[7] was reacted with the glycosyl acceptors 2[8] and 3[9] (molar ratio 1.2:1) in the presence of DMTST (4-5 molar equivalents) and 4 Å molecular sieves in either dichloromethane or acetonitrile. The results are shown in Table 1. The yields are high, but not the stereoselectivity, which follows the pattern previously observed with methyl triflate as promoter[4].

It is, however, possible to transfer these reactions into much slower, but highly stereoselective halide-assisted[10] glycosylation, as shown by entries 5-7. The normal halide-assisted reaction of the glycosyl bromide 7[10] with the acceptor 4[11] using an excess of tetrabutylammonium bromide as promoter gave an 85 % yield of the α-D-linked disaccharide 8a (entry 6). The corresponding β-anomer was not observed. Using the thioglycoside donor 1 with the same aglycone gave, as expected from entries 1-3, an α/β mixture (entry 5). When, however, this latter reaction was run in the presence of an excess tetrabutylammonium bromide (molar ratio 1:4:DMTST:Bu_4NBr 1.2:1:3:5), the thioglycoside 1 almost immediately disappeared from the reaction mixture (t.l.c.) and the glycosyl bromide 7 appeared. The only product subsequently isolated, in 83 % yield was 8a (entry 7).

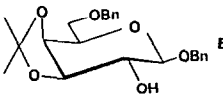
These model experiments show that thioglycosides may be used as glycosyl donors in stereoselective 1,2-cis-glycosylation reactions, using DMTST as a thiophilic glycosylation promoter in the presence of an excess of tetrabutylammonium bromide.



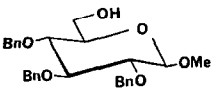
1



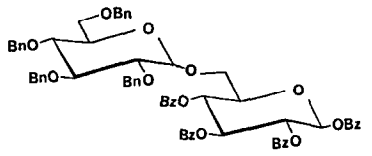
2



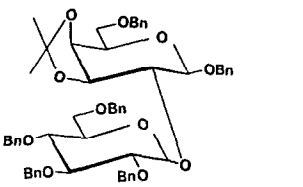
3



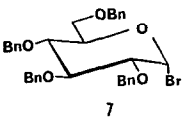
4



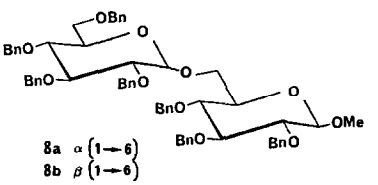
5a α(1→6)
5b β(1→6)



6a α(1→2)
6b β(1→2)



7



8a α(1→6)
8b β(1→6)

Table 1

Entry	Donor	Acceptor	Solvent	Reaction time[a]	Product	Yield (%)
1	1	2	CH_2Cl_2	5 min	5a[b]	59
					5b[c]	36
2	1	3	CH_2Cl_2	5 min	6a[d]	54
					6b[e]	33
3	1	2	CH_3CN	5 min	5a[b]	22
					5b[c]	74
4	1	2	CH_3CN	5 min	5a[b]	6
				-30°	5b[c]	85
5	1	4	CH_2Cl_2	2 days[f]	8a[g]	50[i]
					8b[g]	30[i]
6	7	4	CH_2Cl_2	1.5 weeks	8a[h]	85
					8b	-
7	1	4	CH_2Cl_2	1.5 weeks	8a[h]	83
					8b	-

[a]At room temperature unless otherwise stated. [b]Syrup, $[\alpha]_D^{20}$ +38° (c 1.0, $CHCl_3$), δ_C ($CDCl_3$) 92.8 p.p.m., $J_{C-1,H-1}$ 168 Hz (C-1), 97.4, $J_{C-1',H-1'}$ 167 Hz (C-1'). [c]M.p. 152-153 °C, $[\alpha]_D^{20}$ +15° (c 1.0, $CHCl_3$), δ_C ($CDCl_3$) 92.6 p.p.m., $J_{C-1,H-1}$ 168 Hz (C-1), 103.8, $J_{C-1',H-1'}$ 159 Hz (C-1'), Calc. for $C_{66}H_{62}O_{15}$, C 73.0, H 5.58. Found, C 73.0, H 5.58. [d]Syrup, $[\alpha]_D^{20}$ +37° (c 1.0, $CHCl_3$), δ_C ($CDCl_3$) 101.9 p.p.m., $J_{C-1,H-1}$ 159 Hz (C-1), 96.1, $J_{C-1',H-1'}$ 172 Hz (C-1'). [e]Syrup, $[\alpha]_D^{20}$ +9° (c 1.0, $CHCl_3$), δ_C 101.8 p.p.m., $J_{C-1,H-1}$ 160 Hz (C-1), 100.4, $J_{C-1',H-1'}$ 160 Hz (C-1'). [f]The reaction time most probably is excessive. [g]The total yield was 80 %. The α/β ratio was estimated from n.m.r. data. [h]Syrup, $[\alpha]_D^{20}$ +30° (c 1.0, $CHCl_3$), δ_C ($CDCl_3$) 104.4 p.p.m., $J_{C-1,H-1}$ 161 Hz, 96.7, $J_{C-1',H-1'}$ 167 Hz.

ACKNOWLEDGEMENTS

We are indebted to Professor Bengt Lindberg for his interest, to the Swedish Natural Science Research Council and the Swedish National Board for Technical Development for financial support.

REFERENCES

1. H. Paulsen, Angew. Chem. Int. Ed. Engl., 21, 155 (1982).
2. P. Ossowski, Å. Pilotti, P. J. Garegg, and B. Lindberg, Angew. Chem. Int. Ed. Engl., 22, 793 (1983); J. Biol. Chem., 259, 11337 (1984).
3. K. C. Nicolaou, R. E. Dolle, D. P. Papahatjis, and J. L. Randall, J. Amer. Chem. Soc., 106, 4189 (1984).
4. H. Lönn, Chem. Commun. Univ. Stockholm No 2, 1984.
5. H. Lönn, Carbohydr. Res. 139, 105, 115 (1985).
6. P. Fügedi and P. J. Garegg, Carbohydr. Res. in press.
7. F. Weygand and H. Ziemann, Liebigs Ann., 657, 179 (1962).
8. M.p. 179-181 °C, $[\alpha]_D^{20}$ -15° ($CHCl_3$), W. Birberg, P. Fügedi, P. J. Garegg and, Å. Pilotti, to be published.
9. S. David, A. Thieffrey, and A. Veyrières, J. Chem. Soc. Perkin Trans. I, 1981, 1796.
10. R. U. Lemieux, K. B. Hendricks, R. V. Stick, and K. James, J. Amer. Chem. Soc., 97, 4056 (1975).
11. D. Keglević and D. Ljevaković, Carbohydr. Res., 64, 319 (1978).

(Received in UK 12 May 1986)