Carbohydrate Research, 177 (1988) c13–c17
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Preliminary communication

Alkyl sulfenyl triflate as activator in the thioglycoside-mediated formation of β-glycosidic linkages during oligosaccharide synthesis*

FALGUNI DASGUPTA AND PER J. GAREGG†

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

(Received March 12th, 1988; accepted for publication, April 15th, 1988)

Thioglycosides have been used in glycosidation reactions and as donors in oligosaccharide synthesis[1–12]: (*a*) by conversion into glycosyl halides which can be isolated or used *in situ* for reaction, in the presence of a suitable halophilic promoter, with a hydroxylic acceptor; and (*b*) directly, in the presence of a thiophilic promoter. A participating 2-acyl substituent results in the formation of 1,2-*trans*-glycosides, and a non-participating 2-substituent promotes the formation of 1,2-*cis*-glycosides. In method (*b*), methyl trifluoromethanesulfonate (MT) and dimethyl(methylthio)-sulfonium trifluoromethanesulfone (DMTST) have emerged as powerful promoters. However, the former is a potential carcinogen, and although methylating agents other than MT may be used in the preparation of DMTST, which otherwise is a crystalline, easily handled compound, they are also carcinogenic.

In searching for alternative promoters more suitable for large-scale synthesis and routine handling, we have considered nitrosonium or alkyl sulfenyl cations. The NO^+ ion is a border-line acid according to Pearson's description of hard and soft Lewis acids[13] and $AlkS^+$ is a soft acid. The use of $NOBF_4$ has been reported[14], but, in our hands, $NOBF_4$ and N_2O_4 did not give consistent yields especially with acceptors that were comparatively unreactive (*e.g.*, the HO-4 hexopyranosides)[15]. The reaction of sulfenate esters as glycosyl acceptors with benzylated methyl or phenyl 1-thio-β-D-glucopyranoside carried out in the presence of Lewis acids ($CF_3SO_3SiMe_3$, $TrBF_4$, or $BF_3 \cdot Et_2O$) at −35° generally afforded αβ-mixtures[16]. We now report on the use of alkyl sulfenyl halides (triflates) as efficient activators of thioglycosides at room temperature during 1,2-*trans* glycosidation.

The results (Table I) show that alkyl sulfenyl cations, in general, can activate thioglycosides. Thus, methylsulfenyl bromide (MSB) and *o*-nitrobenzenesulfenyl chloride (NSC) were used for the activation of **1, 2,** and **4**. Both MSB (method *A*) and NSC (method *B*) promoted the coupling between **1, 2,** or **4** with **9**, in the presence of silver triflate (ST), to afford methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-

*Use of Sulfenyl Halides in Carbohydrate Reactions, Part I.

†Author for correspondence.

0008-6215/88/$ 03.50

TABLE I

YIELDS AND SELECTED PHYSICAL PROPERTIES OF β-D-LINKED DISACCHARIDES

Entry	*D/A*[a]	*Product*[d]	*Yield (%)*[e]*/Time (min)*			$[\alpha]_D^{25}$[f] (c)	*M.p. (degrees)*	*N.m.r. data for C-1 and C-1' (p.p.m.)*
			Method A	*Method B*	*Method C*			
1	**1/9**	**12**[b]	96/45	60–65/70	67/45	−24° (1.0)	179–180	98.8, 100.9
2	**2/9**	**13**[c]	94/40	85/90	79/70	−20° (1.65)	foam	98.86, 101.1
3	**4/9**	**14**	95/45	64/120	66/45	+12° (1.1)[g]	188–189[g]	98.68, 98.68
4	**2/7**	**15**[c] –	86/45			−2.5° (1.4)	syrup	102.7, 101.3
5	**2/8**	**16**[b,c]	97/45			+18° (1.6)	foam	100.3, 102.3
6	**6/10**	**17**[b]	77[h,i]/<120			−3° (1.65)	foam	98.5, 100.4
7	**2/11**	**18**[c]	82[h,i]/40			−20° (1.4)	foam	91.4, 101.4
8	**3/9**	**19**[c]	97/40			+3.5° (1.5)	foam	98.99, 101.1
9	**5**[b,j]**/9**	**20**[b]	88[k]/45			−11.5° (1.4)	219–220	98.64, 100.9

[a]D, thioglycoside; A, acceptor. [b]Gave correct elemental analysis. [c]Gave correct molecular ion (M + 1$^+$) and/or (M + 18$^+$) in f.a.b.-m.s. [d]Small quantities of D and A could be isolated. [e]Based on the acceptor. [f]Measured in chloroform. [g]Matched the reported[18] value. [h]Based on the acceptor used. [i]Better yield on addition of fresh ST, donor, and MSB in quick succession. [j]Made from the corresponding β-D-tetra-acetate precursor, using a known method[19], m.p. 197–198°, $[\alpha]_D^{25}$ −24° (*c* 1.7, chloroform). [k]Same result on carrying out the reaction at 0°.

O-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**12**), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**13**), and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-α-D-glucopyranoside (**14**), respectively. The yields were poorer with NSC probably due to its highly hygroscopic nature and lower reactivity. The reactive species in these reactions are methyl sulfenyl triflate (MST) and *o*-nitrobenzenesulfenyl triflate (NST) since no reaction took place in the absence of ST. Reactions were also carried out after the prior preparation of the triflate (MST, method *C*), to give **12–14**, but 6–10 mol of the reagent were necessary. Dichloromethane was a better solvent than acetonitrile in these reactions.

Comparison of methods *A–C* (Table I, entries 1–3) indicated that method *A* was superior in promoting the formation of 1,2-*trans* linkages. Using method *A*, the reactions between **2** and **7, 2** and **8, 6** and **10, 2** and **11, 3** and **9**, and **5** and **9** (ratio of thioglycoside to alcohol, 1.2:1) afforded benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-galactopyranoside (**15**), methyl

OAc
SEt
AcO
AcO
OAc
1
OBz
SMe
BzO
BzO
OBz
2
OBz
SPh
BzO
BzO
OBz
3
OAc
SEt
AcO
AcO
NPhth
4
OBz
SEt
AcO
AcO
NHCOCH2Cl
5
OBz
SEt
BzO
BzO
OBz
6
OH
OBn
BnO
BnO
OBn
7
OMe
HO
BnO
Ph
8
OBn
OMe
HO
BnO
BnO
10
OMe
BnO
HO
Ph
9
OBz
OBz
H3C
OBz
HO
11

3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**16**), methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**17**), 1,2,3-tri-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-α-L-rhamnopyranose (**18**), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-α-D-glucopyranoside (**19**), and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(3,4,6-tri-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranosyl)-α-D-glucopyranoside (**20**), respectively (Table I, entries 4–9). Each reaction (except entry 6) was complete within 30–60 min (t.l.c.) and gave β-linked products. The acetylated thioglycoside **1** gave more side products and poorer yields than the benzoylated donors **2, 3,** and **6**, which corroborates previous observations[17]. Although the chloroacetamido donor **5** showed a clean reaction (t.l.c.), a larger proportion was needed than for the corresponding phthalimido donor **4** in order to afford comparable yields of **14** and **20**.

MSB was prepared by mixing equimolar quantities of dimethyl disulfide and bromine in 1,2-dichloroethane at room temperature and stirring the solution in the dark under nitrogen for 2–4 h. This solution can be preserved effectively for almost a week. Calculated volumes were used in the coupling reactions.

MST was prepared by injecting MSB (1 equiv.) through a septum into a flask which was protected from light and contained silver triflate (1.05 equiv.) dispersed in dry 1,2-dichloroethane. The solution was stirred for 15–30 min, the precipitate was allowed to settle, and a calculated volume of the supernatant solution was used directly in method *C*.

Method *A*: a solution of the donor **1** (80 mg, 0.2 mmol) and the acceptor **9** (63 mg, 0.17 mmol) in dichloromethane (3 mL) was stirred (40 min) in the presence of powdered molecular sieve (4 Å, 0.5 g). ST (71 mg, 0.28 mmol) was added and a septum was attached. MSB (0.24 mL = 30.5 mg, 0.24 mmol) was injected in two equal portions at an interval of 30 min. All operations were carried out under a positive pressure of nitrogen. T.l.c. (15:1 toluene–acetone) after 45 min indicated major conversion into one product. The mixture was neutralized with triethylamine and filtered through Celite, and the flask and Celite were washed with dichloromethane (5 mL). The combined filtrate and the washings were washed with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated *in vacuo*, and the residue was subjected to chromatography on silica gel.

Method *B*: the reaction between **1** and **9** was carried out essentially as in method *A*, but using NSC instead of MSB.

Method *C*: freshly prepared MST (6–10 molar excess) was injected slowly (20–30 min) through a septum into a flask containing **1, 9,** ST (same proportion as in method *A*), and molecular sieve (4 Å) in dichloromethane (kept under N_2). The mixture was stirred for 30 min and then worked-up as in method *A*.

After completion of this work, benzeneselenyl triflate was described as a promoter for glycosidations using thioglycosides[20].

REFERENCES

1 P. FÜGEDI, P. J. GAREGG, H. LÖNN, AND T. NORBERG, *Glycoconjugate J.*, 4 (1987) 97–108.
2 P. FÜGEDI, W. BIRBERG, P. J. GAREGG, AND Å. PILOTTI, *Carbohydr. Res.*, 164 (1987) 297–312.
3 P. FÜGEDI AND P. J. GAREGG, *Carbohydr. Res.*, 149 (1986) c9–c12.
4 F. ANDERSSON, P. FÜGEDI, P. J. GAREGG, AND M. A. NASHED, *Tetrahedron Lett.*, 27 (1986) 3919–3922.
5 S. SATO, M. MORI, Y. ITO, AND T. OGAWA, *Carbohydr. Res.*, 155 (1986) c6–c10.
6 H. LÖNN, *Carbohydr. Res.*, 139 (1985) 105–113, 115–121.
7 P. J. GAREGG, C. HENRICHSON, AND T. NORBERG, *Carbohydr. Res.*, 116 (1983) 162–165.
8 K. C. NICOLAOU, S. P. SEITZ, AND D. P. PAPAHATJIS, *J. Am. Chem. Soc.*, 105 (1983) 2430–2434.
9 S. HANESSIAN, C. BACQUET, AND N. LEHONG, *Carbohydr. Res.*, 80 (1980) c17–c22.
10 J. W. VAN CLEVE, *Carbohydr. Res.*, 70 (1979) 161–164.
11 T. MUKAYAMA, T. NAKATSUKA, AND S. SHODA, *Chem. Lett.*, (1979) 487–490.
12 R. J. FERRIER, R. W. HAY, AND N. VETHAVIYASAR, *Carbohydr. Res.*, 27 (1973) 55–61.
13 R. G. PEARSON, *J. Am. Chem. Soc.*, 85 (1963) 3533–3539.
14 V. POZSGAY AND H. J. JENNINGS, *J. Org. Chem.*, 52 (1987) 4635–4637.
15 F. DASGUPTA, P. FÜGEDI, AND P. J. GAREGG, unpublished data.
16 Y. ITO AND T. OGAWA, *Tetrahedron Lett.*, 28 (1987) 4701–4704.
17 P. J. GAREGG, P. KONRADSSON, I. KVARNSTRÖM, T. NORBERG, S. C. T. SVENSSON, AND B. WIGILIUS, *Acta Chem. Scand., Ser. B*, 39 (1985) 569–577.
18 F. DASGUPTA AND P. J. GAREGG, *J. Carbohydr. Chem.*, in press.
19 M. KISO AND L. ANDERSON, *Carbohydr. Res.*, 72 (1979) c12–c14.
20 Y. ITO AND T. OGAWA, *Tetrahedron Lett.*, 29 (1988) 1061–1064.