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COMPARISON OF CATALYSTS IN α-GLUCOSYLATION REACTIONS AND IDENTIFICATION OF TRIFLIC ANHYDRIDE AS A NEW REACTIVE PROMOTER.

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Summary - Triflic anhydride is shown to be a highly reactive promoter in the *cis*-glycosylation reaction of 2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl fluoride with an unreactive glycosyl acceptor.

For the stereospecific synthesis of *cis*-glycosides various methods are known employing halides, imidates, thioglycosides or others as glycosyl donors.[1] The choice of the most promising method for a given problem is not obvious because very few direct comparisons are described in the literature. It was therefore desirable to study the available glycosylation methods with regard to their efficacy in glycosylation especially of unreactive glycosyl acceptors.

Due to our interest in substructures of trestatin A,[2] we embarked on the synthesis of α(1 → 4)-linked trehalose glycosides.To this end, we investigated the use of 2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl trichloroacetimidate (**1**)[3] and fluoride (**2**).[4] Both donors had been employed successfully in α-glycosylations of relatively unreactive hydroxyl components. One of the trehalose glycosyl acceptors we have used is **4**,[5] readily prepared from known[7] diol **3** ($(Bu_3Sn)_2O$, toluene, reflux, 4 h; then BnBr, Bn_4NBr, 80 °C, 7 d, 60%). In all glycosylation reactions dry ether was used as a solvent, which is generally known to favour the formation of *cis*-glycosides. With glucoside donor **1** trimethylsilyl triflate was used which is described to be the most active catalyst for the imidate method;[3] using the fluoride **2**, the catalysts trimethylsilyl triflate,[8] stannous chloride / silver triflate,[9] and titanium tetrafluoride[10] were compared in the synthesis of trisaccharide **5**.[5] The reaction conditions were very similar to those used by the corresponding authors, results are recorded in Table 1.

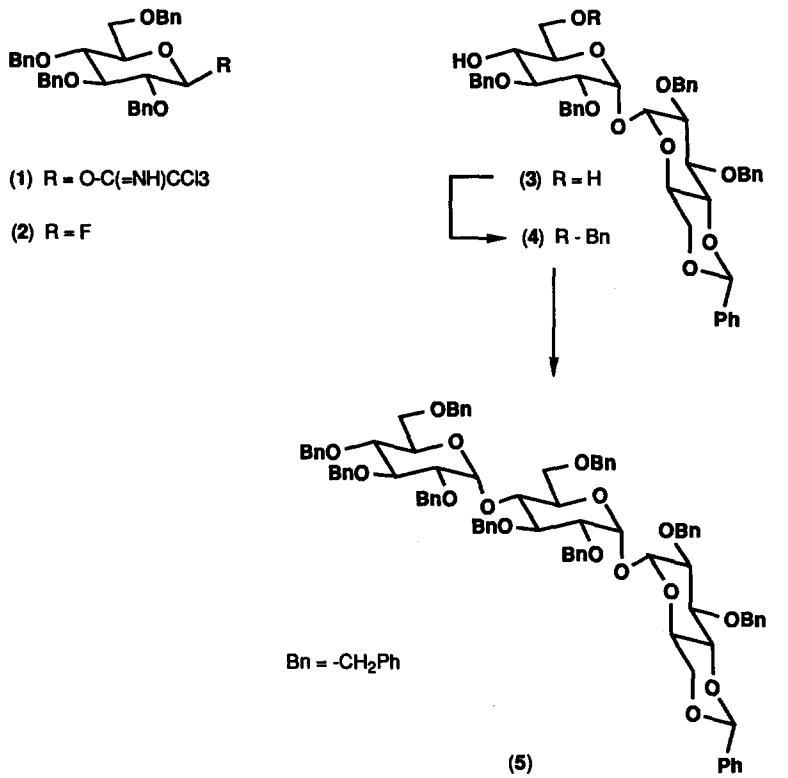

Table 1: Comparison of promoters in syntheses of trisaccharide **5** from **4**[a].

Entry	Donor	Equivalents	Promoter	Yield[b] [%]
1	(1)	9	TMSOTf	51
2	(2)	2	TMSOTf	45
3	(2)	2	AgOTf / $SnCl_2$	65
4	(2)	2	TiF_4	68
5	(2)	2	TfOTf[c]	92

a Solvent in all reactions is diethyl ether.
b Isolated yield of **5**, not optimized.
c 1 equivalent, 4 Å molecular sieves, -20 °C → r.t., 18 h.

A lower excess (cf. entry 1) of glycosyl imidate **2** (1.4 equivalents) resulted in only small amounts of trisaccharide **5**, similar observations were made in a synthesis with a similarly unreactive glycosyl acceptor.[9] It is seen that the use of fluoride **2** (entries 2-4) gives higher yields of **5**. Our attempts to further improve on this glycosylation reaction resulted in the identification of triflic anhydride as a new promoter for fluorides which gives an excellent yield of the desired trisaccharide (entry 5) in the presence of 4 Å molecular sieves as acid scavenger.

The results in Table 1 suggest that a sequence of catalysts with increasing reactivity (TMSOTf < AgOTf / $SnCl_2$ ≤ TiF_4 < TfOTf) for the conversion of glycosyl fluorides can be formulated as it has been done for catalysts in the classical Königs-Knorr reactions.[10] Application of the rules for glycoside syntheses put forward by *Paulsen*[11] would propose that triflic anhydride as very reactive promoter is especially useful for glycosylations with unreactive hydroxyl components and / or unreactive glycosyl fluorides.

Triflic anhydride has been used in the presence of base for the activation of sulfoxides,[13] where it acts presumably by attack of oxygen. In the case presented here, it is assumed that triflic anhydride acts by activating the fluoride with a $CF_3SO_2^{\delta+}$ moiety implicating that $CF_3SO_2^{\delta+}$ has a higher affinity towards F than towards O! This principle may lead to further synthetic applications of triflic anhydride in the future.

References and notes

1) a) For leading references see: R.R. Schmidt, *Angew. Chem. Int. Ed.*, 1986, **25**, 212;

b) G.V. Reddy, V.R. Kulkarni, and H.B. Mereyala, *Tetrahedron Lett.*, 1989, **30**, 4283;

c) B. Fraser-Reid, P. Konradsson, D.R. Mootoo, and U. Udodong, *J. Chem. Soc., Chem. Commun.*, 1988, 823.

2) H.P. Wessel, M. Hosang, T.B. Tschopp, and B.-J. Weimann, *Carbohydr. Res.*, in press.

3) B. Wegmann and R.R. Schmidt, *J. Carbohydr. Chem.*, 1987, **6**, 357.

4) T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, 1981, 431.

5) New compounds synthesised showed satisfactory analytical data. *Selected spectroscopic data*: (**4**): $[\alpha]_D^{20}$ + 95.6 ° (c 0.5, dioxane); ^{1}H n.m.r. ($CDCl_3$) δ 3.46 (dd, 1H, $J_{5',6b'}$ 3.3 Hz, H-6b'), 3.51 (dd, 1H, $J_{5',6a'}$ 3.9 Hz, $J_{6a'6b'}$ 10.5 Hz, H-6a'), 3.596 (dd, 1H, $J_{1',2'}$ 3.6 Hz, $J_{2',3'}$ 9.6 Hz, H-2'), 3.599 (dd, 1H, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.3 Hz, H-2), 3.64, 3.66 (dd ~ t, 2H, $J_{4,5}$ ≠ 10 Hz, H-4, H-6b), 3.68 (ddd ~ dt, 1H, $J_{4',5'}$ ≠ 9.8 Hz, H-4'), 3.87 (dd ~t, 1H, $J_{3',4'}$ ≠ 8.9 Hz, H-3'), 4.11 (dd, 1H, $J_{6a,6b}$ 10.2 Hz, H-6a), 4.12 (2H, dd ~ t, H-3; ddd ~ dt, H-5'), 4.26 (ddd ~ dt, 1H, $J_{5,6a}$ 4.8 Hz, $J_{5,6b}$ ≠ 10 Hz, H-5), 5.17 (d, 1H, H-1), 5.18 (d, 1H, $J_{1',2'}$ ≠ 3.7 Hz, H-1'); (**5**): $[\alpha]_D^{20}$ + 80.8 ° (c 0.5, dioxane); ^{1}H n.m.r. ($CDCl_3$) δ 3.35 (dd, 1H, $J_{5'',6b''}$ 1.5 Hz, $J_{6a'',6b''}$ 10.5 Hz, H-6b''), 3.48 (2H, dd, $J_{2''3''}$ 8.9 Hz, H-2'', dd, H-6b'), 3.49 (dd, 1H, $J_{5'',6a''}$ 3.3 Hz, H-6a''), 3.58 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 3.65 (2H, dd ~ t, $J_{4'',5''}$ 9.7 Hz, H-4''; dd, $J_{5,6b}$ ≠ 9.5 Hz, H-6b), 3.63 (dd ~ t, 1H, H-4), 3.66 (dd, 1H, $J_{2',3'}$ 9.8 Hz, H-2'), 3.70 (dd, 1H, H-6a'), 3.72 (ddd ~ dt, 1H, H-5''), 3.93 (dd, 1H, $J_{3'',4''}$ 9.6 Hz, H-3''), 4.06 (dd ~ t, 1H, H-4'), 4.09 (dd, 1H, $J_{5,6a}$ 4.0 Hz, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.13 (dd ~ t, 1H, $J_{3'4'}$ ≠ 9.5 Hz, H-3'), 4.18 (dd ~ t, 1H, $J_{3,4}$ 9.1 Hz, H-3), 4.23 (ddd ~ dt, 1H, H-5'), 4.26 (ddd ~ dt, 1H, H-5), 5.15 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.19 (d, 1H, $J_{1'2'}$ 3.8 Hz, H-1'), 5.66 (d, 1H, $J_{1'',2''}$ 3.6 Hz, H-1''). Details on n.m.r. spectroscopy will be reported.[6]

6) G. Englert, H.P. Wessel, in preparation.

7) A.F. Hadfield, L. Hough, and A.C. Richardson, *Carbohydr. Res.*, 1978, **63**, 51.

8) S. Hashimoto, M. Hayashi, and R. Noyori, *Tetrahedron Lett.* 1984, **25**, 1379.

9) Y. Takahashi and T. Ogawa, *Carbohydr. Res.* 1987, **164**, 277.

10) M. Kreuzer and J. Thiem, *Carbohydr. Res.*, 1986, **149**, 347.

11) H. Paulsen and Č. Kolář, *Chem. Ber.*, 1981, **114**, 306.

12) H. Paulsen, *Angew. Chem, Int. Ed.*, 1982, **22**, 155.

13) D. Kahne, S. Walker, Y. Cheng, and D. van Engen, *J. Am. Chem. Soc.*, 1989, **111**, 6881.

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