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Synthesis of β-O-Glycosides Using Enol Ether and Imidate Derived Leaving Groups. Emphasis on the Use of Nitriles as a Solvent[1)]

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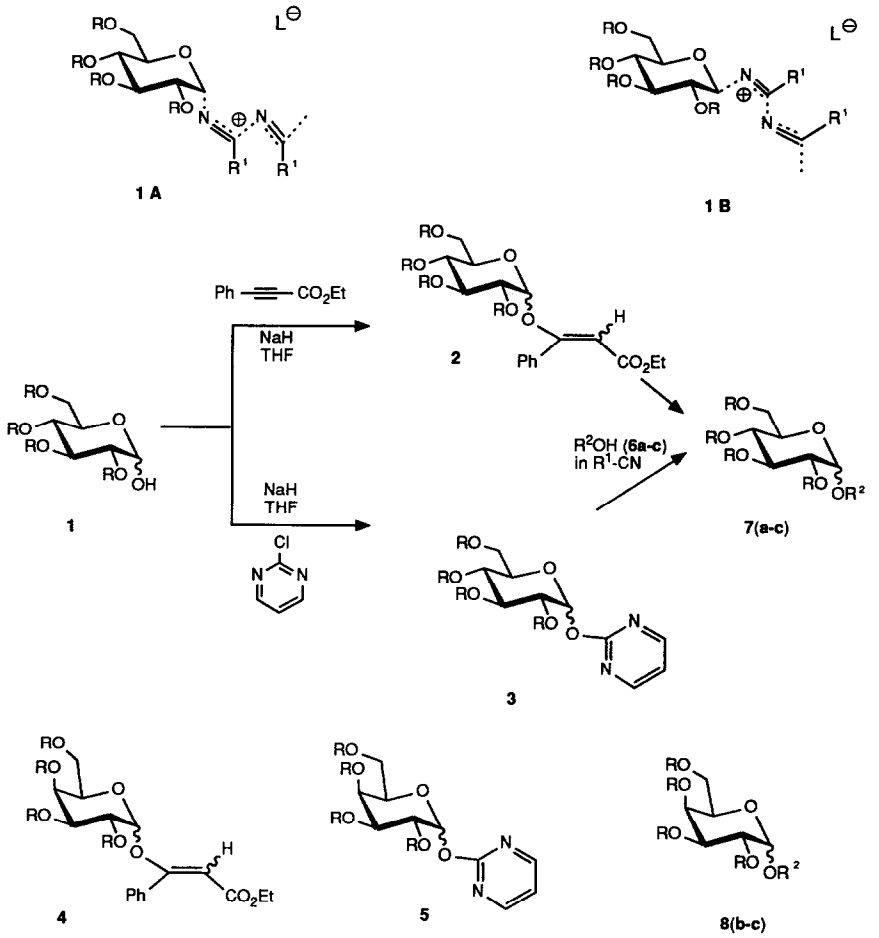
Abstract: *Two new methods of β-glycoside synthesis using donors* ***2*** *and* ***3*** *that contain leaving groups derived from enol ether and imidates have been developed. Effect of nitriles as a solvent in directing mainly β-glycosidations has been compared with various methods reported in the literature. Effectiveness of leaving group at low temperatures and participation of nitriles in the formation of nitrilium-nitrile conjugate has been emphasized.*

Stereochemical outcome in glycosylation reactions due to solvent effects is an important aspect. Developments in this area have led to the synthesis of α- and β-glycosides depending on the nature of leaving groups, the donors, the order of addition of the reactants and the solvent. The effect of diethyl ether as a solvent in influencing the stereochemistry of the product to give mainly α–disaccharides is well known[2]. This is irrespective of what is the nature of the leaving group. Further, glycosylation of halogeno D-glucuronic acid in acetonitrile was reported by us[3] to lead to the formation of α–glycosides. Reaction of $Ag^{+}ClO^{-}_{4}$ with the donor prior to the addition of an acceptor was found to be important for the success of these reactions. On the other hand, reaction of α-trichloroacetimidate donors in acetonitrile was found to give mainly β-glycosides albeit in low yields when $BF_3{\cdot}Et_2O$ was used[4] as activator. However, recently we[5] have reported that α- or β-trichloroacetimidate donors react with acceptors even at -80°C in propionitrile as a solvent if trifluoromethanesulfonate (TMSOTf) is used as a catalyst to give mainly β-glycosides in a short time (cf. ~ 20 min). It was pointed out that high reactivity of nitrilium-nitrile conjugate (**1A** and **1B**, Scheme 1) requires excellent leaving groups at very low temperatures. To this effect trichloroacetimidates proved to be a leaving group of choice. Since our initial observations[3,4] concerning the effect of nitriles as a solvent in glycosylation reactions there have appeared a few more reports in the literature for effecting β-glycosylations reiterating the importance of nitriles[6-11]. In this paper we wish to introduce two new activators for glycosylations and comment on the efficacies of nitriles as a solvent and nature of the leaving group for effecting β-glycosylations in general.

Literature survey reveals that a number of activators and catalysts have been used meanwhile for β-glycosylation using nitriles as a solvent. Activators include fluoride (-F)[6,7], methylthio (-SMe)[8], diphenylphosphate [$-OP(O)(OPh)_2$][9], P,P-diphenyl-N-(p-toluenesulfonyl)-phosphin-imidate [$-O-P(=NTs)(Ph)_2$][10], trichloroacet-

imidate [-OC(=NH)CCl_3][4,5], and pent-4–en–1–yloxy [O-$(CH_2)_3$-CH=CH_2][11] as leaving groups at the anomeric carbon and $AgClO_4$, TiF_4, SiF_4, and TMSOTf as catalyst. In order to cover a range of relatively less efficient to excellent leaving groups capability we considered the possibility of a double bond versus nitrogen atom based activators and study their behaviour in nitrile for β-glycosylation. An attempt is also made to compare these activators alongwith the ones already reported from ours as well as from other groups to derive certain general conclusions.

Scheme 1



R = CH_2-Ph, R^1 = CH_3, C_2H_5; R^2OH, see Table 1

In the present study, the two donors chosen were **2** and **3** readily derived from the reaction of tetra-O-benzyl glucose **1** with (i) ethyl phenyl propiolate[12] and (ii) 2-chloropyrimidine, respectively. These donors **2** and **3** which are related to enol ethers and imidates, respectively, were used as a mixture of α and β isomers (cf. Experimental).

Reaction of **2** (1.0 equiv.) was examined with various acceptors (1.1 equiv.) in acetonitrile at -40°C in the presence of TMSOTf (1.0 equiv.) as catalyst and the results are summarized in Table 1. It is clear that the enol ether in **2** at the anomeric carbon is not an effective leaving group. On the other hand, the donor **3** reacted with different acceptors at -80°C in propionitrile and the reaction was completed within a few minutes (cf. ~ 20-30 min) to give β-glycosides as the main product (Table 1). The best conditions of these reactions required 1:1.1:1.1 as the ratios of donor:acceptor:catalyst, when the donor and the acceptor were mixed at -80°C in propionitrile and TMSOTf was added dropwise to it. The β:α selectivity was somewhat reduced at higher temperatures, for example, at -40°C in acetonitrile.

The corresponding donors **4** and **5**, prepared from tetra-O-benzyl-galactose with ethyl phenyl propiolate and 2-chloropyrimidine, were found to exhibit more or less similar reactivity as that shown by **2** and **3** (cf. entries 4,8 and 9, Table 1). These results clearly show that pyrimidinyloxy group is an excellent leaving group under the present reaction conditions and could be useful as a conveniently accessible activator in β-glycoside synthesis. Our earlier hypothesis[5] that, provided a leaving group at C-1 has an excellent tendency to bind with the catalyst and thus getting transformed into a good leaving group, the fast attack of the nitrile (solvent) occurs to form α-nitrilium-nitrile conjugate (**1A**, Scheme 1) resulting ultimately in the β-glycoside bond formation is further confirmed by the present studies. It appears from the comparison of **2** and **4** vs. **3** and **5** that TMSOTf binds with a nitrogen based highly basic activator more efficiently and more readily than with other atom based activators. This is one of the reasons why the trichloroacetimidate is the most efficient leaving group.

In order to compare and then comment on the behaviour of their abilities in β-glycosylations, typical examples of the various activators described in the literature were considered. Table 2 includes comparative data with all those and the presently described new glycosylations. It is clear to judge from these data that as the leaving group has higher tendency to coordinate with an acid, thus making itself more and more labile at low temperatures, the fast formation of the α-nitrilium-nitrile conjugate (**1A**) ultimately results into β-glycosides more selectively. This of course, is irrespective of the configuration at the anomeric centre. The present studies using both the activators were carried out with a mixture of isomers of α and β.

Further work to explore the scope of pyrimidine activation in β-glycoside formation in more complex systems is in progress.

EXPERIMENTAL

General Procedures: ^{1}H n.m.r. spectra were recorded in $CDCl_3$ (Me_4Si, 0.00 ppm) with a Bruker "WM 250 Cryospec". Column chromatography was performed using flash chromatography silica gel ("Baker analyzed" reagent from I.T. Baker B.V. - Deventer - Netherlands) using petroleum-ether-ethyl acetate as solvent system. The glycoside syntheses were performed under a dry nitrogen atmosphere. The solvents used for chromatography were distilled.

General Procedure for the Synthesis of Donors **2- 5**:

To a stirred suspension of NaH (1.1 mole equivalent) in freshly distilled dry THF was added 2,3,4,6-tetra-O-benzylglucose **1** or 2,3,4,6-tetra-O-benzylgalactose (1.0 mol equivalent). After about half an hour a solution of ethyl phenylpropiolate (1.2 mol equivalent, for **2** and **4**) or 2-chloropyrimidine (1.2 mol equivalent for **3** and **5**) in THF was added to it. Stirring was continued for another 3 h at 50°C. The solution was cooled and brine

Table 1

Glycosylation of Acceptors with Donors **2 - 5**

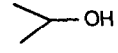
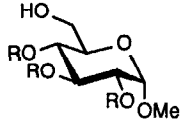
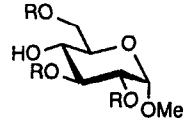
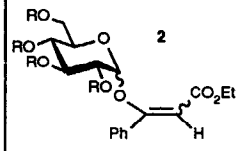
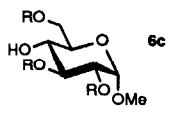
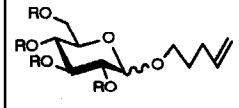
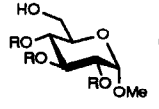
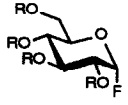
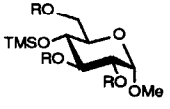
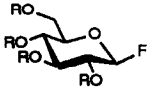
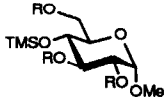
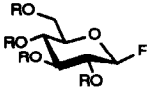
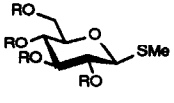
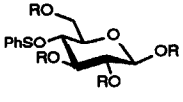
Entry	Donor	Acceptor **6** (R^2OH)		Reaction Conditions: Solvent	Temp. (°C)	Time [min]	Products: Compounds	Yield (%)	β : α
1	**2**		**6a**	CH_3CN	(-40) → (-20)	180	**7a**	90	65 : 35
2	**2**		**6b**	CH_3CN	(-40) → (-20)	180	**7b**	61	85 : 15
3	**2**		**6c**	CH_3CN	(-40) → (-20)	180	**7c**	67	75 : 25
4	**4**	**6c**		CH_3CN	(-40) → (-20)	180	**8c**	71	68 : 32
5	**3**	**6a**		CH_3CN	-40	30	**7a**	78	86 : 14
6	**3**	**6b**		C_2H_5CN	-80	30	**7b**	81	95 : 5
7	**3**	**6c**		C_2H_5CN	-80	30	**7c**	74	88 : 12
8	**5**	**6b**		C_2H_5CN	-80	30	**8b**	79	70 : 30
9	**5**	**6c**		C_2H_5CN	-80	30	**8c**	77	89 : 11

Table 2

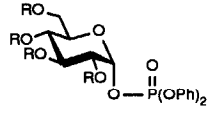
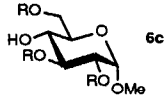
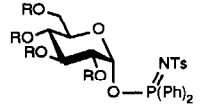
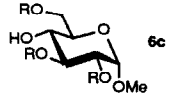
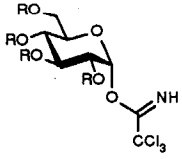
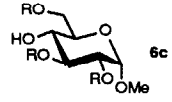
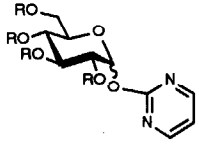
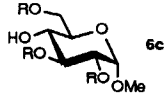
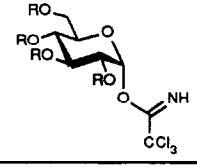
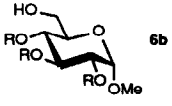
Comparative Data for Glycosylation Using Nitriles as Solvents[a]

Entry	Donor	Acceptor	Catalyst	Temp. (°C)	Solvent	Time	Pro-duct	β : α - Ratio (Yield %)	Range of β:α-Ratios in the Examples Studied
1	 2	 6c	TMSOTf	- 40	CH_3CN	3 h	**7c**	3:1 (67)	1.9:1 to 5.6:1 (present paper)
2		 6b	NBS	RT	CH_3CN	3 h	**7b**	4:1 (56)	1:2 to 4:1 (ref. 11)
3			SiF_4	0	CH_3CN	3 h		3.5:1 (84)	
			SiF_4	0	CH_3CN	2 h		3.3:1 (87)	1.94:1 to 10:1 (ref. 6)
4			TiF_4	22	CH_3CN	3 h		8:1 (64)	
			SnF_4	22	CH_3CN	3 h		6.7:1 (93)	2:1 to 8:1 (ref. 7)
			TMSOTf	22	CH_3CN	3 h		2.1:1 (42)	
5			TMSOTf	-35	CH_3CN	30 min		3.7:1 (68)	3.5:1 to 19:1 (ref. 8)

continued.....

Table 2 (continued)

Comparative Data for Glycosylation Using Nitriles as Solvents

Entry	Donor	Acceptor	Catalyst	Temp. (°C)	Solvent	Time	Product	β : α - Ratio (Yield %)	Range of β:α-Ratios in the Examples Studied
6		 **6c**	TMSOTf	-78	C_2H_5CN	~ 10 min	**7c**	13:1(85)	6:1 to 32:1 (ref. 9)
7		 **6c**	TMSOTf	-70	C_2H_5CN	50 min	**7c**	7.3:1 (84)	6.7:1 to 13:1 (ref. 10)
8		 **6c**	TMSOTf	-80	C_2H_5CN	10 min	**7c**	19:1 (81)	9:1 to 24:1 (ref. 5)
9		 **6c**	TMSOTf	-80	C_2H_5CN	30 min	**7c**	7.3:1 (74)	3:1 to 19:1 (present paper)
10		 **6b**	CCl_3CHO	-40	CH_3CN	18 h	**7b**	100:0 (79)	3:1 to β only (ref. 13)

[a] R = $-CH_2-Ph$

was added to it. Extraction with ether followed by evaporation of the solvent gave a crude product. In case of **2** and **4** flash chromatography was performed using 3:7, ethyl acetate, petroleum ether solvent system whereas for **3** and **5** the ratio of ethyl acetate: petroleum-ether was 4:6.

Compound **2**: ^{1}H n.m.r. ($CDCl_3$): δ 1.08-1.29 (m, 3 H), 3.43-5.11 (m, 16 H), 5.40-5.93 (m, 2 H), 7.09-7.71 (m, 25 H). (Found: C, 75.77; H, 6.59. Calc. for $C_{45}H_{46}O_8$ (714.863): C, 75.61; H, 6.49.)

Compound **3**: ^{1}H n.m.r. ($CDCl_3$): δ 3.56-5.02 (m, 14 H), 6.02-6.05 (d, 1 Hα, $J_{1,2}$ = 7.5 Hz), 6.68-6.70 (d, 1 Hβ, $J_{1,2}$ = 3.5 Hz), 6.89-6.96 (m, 1 H), 7.14-7.3 (m, 20 H), 8.47-8.51 (t, 2 H, J = 4.7 Hz), (β:α = 60:40). (Found: C, 73.38; H, 6.15; N, 5.00. Calc. for $C_{38}H_{38}N_2O_6$ (618.74): C, 73.77; H, 6.19; N, 4.53.)

Compound **4**: ^{1}H n.m.r. ($CDCl_3$): δ 1.05-1.24 (m, 3 H), 3.53-5.04 (m, 16 H), 5.42-5.69 (m, 2 H), 7.14-7.53 (m, 25 H). (Found: C, 75.46; H, 6.62. Calc. for $C_{45}H_{46}O_8$ (714.863): C, 75.61; H, 6.49.)

Compound **5**: ^{1}H n.m.r. ($CDCl_3$): δ 3.52-5.04 (m, 14 H), 5.98-6.01 (d, 1 Hα, $J_{1,2}$ = 8 Hz), 6.73-6.74 (d, 1 Hβ, $J_{1,2}$ = 2.5 Hz), 6.83-6.89 (m, 1 H), 6.97-7.39 (m, 20 H), 8.42-8.47 (m, 1 H) (β:α = 75:25). (Found: C, 72.97; H, 6.16; N, 4.41. Calc. for $C_{38}H_{38}N_2O_6$ (618.736): C, 73.77; H, 6.19; N, 4.53.)

General Procedure for Glycosylations:

To a solution of appropriate donors (**2-5**; 1.0 mol equivalent) and acceptors (**6a-c**; 1.1 mol equivalent) in acetonitrile (for **2** and **4**) [or in propionitrile (for **3** and **5**)] at -40°C [or at -80°C] (cf. see Table 1) was added TMSOTf (1.1 mol equivalent) dropwise. After the reaction was over (see Table for time), the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with diethyl ether. The organic layer was further washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a crude product whose purification by flash chromatography using petroleum-ether-ethyl acetate as eluents. Corresponding to the entries **1-4** the eluents used were 20:80: ethyl acetate:petroleum ether, whereas for entries **5-9** it was 30:70:: ethyl acetate:petroleum ether. Products were characterised by their ^{1}H n.m.r. spectra and comparison with the literature data for them. Except compound **8c** all the other disaccharides viz. **7a-7c** and **8b** are known in the literature.

Methyl 6-O(2,3,4,6-Tetra-O-benzyl-α and β-D-galactopyranosyl)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**8c**) α,β: ^{1}H n.m.r.: δ 3.29-3.92 (2 s, 3 H, OCH_3) 3.37-4.16 (m, 12 H), 4.29-4.98 (m, 16 H containing a doublet at δ 4.3, $J_{1,2}$ = 7.6 Hz, 1'-H), 7.14-7.37 (m, 35 H). Found: C, 75.28; H, 6.71. Calc.for: $C_{62}H_{66}H_{11}$: C, 75.43; H, 6.74.

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REFERENCES AND NOTES

1. Glycosylimidates, Part 51. For Part 50, see Schmidt, R.R.; Toepfer, A. *Tetrahedron Lett.* **32** (1991) 3353.
2. Wulff, G.; Röhle, G. *Angew. Chem.* **86** (1974) 173; *Angew. Chem., Int.Ed.Engl.* **13** (1974) 157; Wulff, G.; Schmidt, W. *Carbohydr. Res.* **53** (1977) 33; Wulff, G.; Schröder, U.; Wichelhaus, J. *ibid.*, **72**, (1979) 280; Wegmann, B.; Schmidt, R.R. *J. Carbohydr. Chem.*, **6** (1987) 357.
3. Schmidt, R.R.; Rücker, E. *Tetrahedron Lett.* **21** (1980) 1421.
4. Schmidt, R.R.; J. Michel, J. *J. Carbohydr. Chem.* **4** (1985) 141.
5. Schmidt, R.R.; Behrendt, M.; Toepfer, A. *Synlett* (**1990**) 694.
6. Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **25** (1984) 1379.

7. Kreuzer, M.; Thiem, J. *Carbohydr. Res.* **149** (1986) 347.
8. Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **28** (1987) 4701.
9. Hashimoto, S.; Honda, T.; Ikegami, S. *J.C.S. Chem. Commun.* (1989) 685.
10. Hashimoto, S.; Honda, T.; Ikegami, S. *Chem. Pharm. Bull* **38** (1990) 2323.
11. Fraser-Reid, B.; Konradsson, P.; Mootoo, D.R.; Udodong, U. *J.C.S. Chem. Commun.* (1988) 823.
12. (i) Preliminary studies using this and similar systems was carried out by J. Michel, Dissertation, Universität Konstanz, 1983.
(ii) For studies related to anomeric enol ethers in glycosylations, see P. Sinaÿ, *Pure and Appl. Chem.* **63** (1991) 519.
13. Schmidt, R.R; Gaden, H.; Jatzke, H. *Tetrahedron Lett.* **31** (1990) 327.