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Effect of dimethoxyethane in $Yb(OTf)_3$-promoted glycosidations ☆

Matteo Adinolfi, Alfonso Iadonisi,* Alessandra Ravidà and Marialuisa Schiattarella

Dipartimento di Chimica Organica e Biochimica, Università degli Studi di Napoli Federico II, Via Cynthia 4, I-80126 Napoli, Italy

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Abstract—1,2-Dimethoxyethane (DME) is shown to be a suitable co-solvent for sensibly improving the α-selectivity of glycosidations performed with trihaloacetimidate donors. This solvent works equally well by using either moisture stable $Yb(OTf)_3$ or standard TMSOTf as the promoters.

Oligosaccharide synthesis has received an increasing interest over the last years due to the decisive role of these molecules in biochemistry and biomedicine, and to the difficult isolation of oligosaccharidic samples in a homogeneous form from natural sources.[1] One of the most relevant problems is the stereochemical control of glycosidations. Actually, while 1,2-*trans* glycosides can be prepared with high selectivity by using 2-*O*-acylated glycosyl donors,[2] the more difficult 1,2-*cis* glycoside synthesis can be faced only by resorting to specific tactics.[3] For example, a long range participating effect of 4-*O*- and 3-*O*-acyl groups can be exploited for improving the stereocontrol in the synthesis of α-galactosides and α-glucosides, respectively.[4] Alternatively, the installation of sterically demanding groups at the 6-OH position can provide the same result.[5] Both these approaches require a differentiation in the protecting group pattern of the donors, and therefore an increased number of synthetic steps for their preparation.

In a quite different approach, ether solvents can be purposely used to conduct α-selective glycosylations with perbenzylated donors. Such a selectivity is commonly ascribed to the conversion of the activated donor into a glycosyl cation, the initial attack of an ether solvent molecule occurring at the α-side, and the fast conversion of this kinetic α-adduct into the thermodynamically more stable (due to the inverse anomeric effect) β-adduct.[6] Finally, nucleophilic attack of the alcoholic acceptor on this latter intermediate can account for the α-selectivity, especially with less reactive secondary acceptors (Fig. 1).

Very recently, our interest was attracted by the development of glycosylation promoters featuring convenient advantages such as chemical mildness and moisture stability in contrast to the acidic agents employed in standard procedures. Among others, ytterbium(III) triflate proved[7] to be an interesting promoter for glycosylations performed with glycosyl trichloro-[8] and *N*-phenyl trifluoroacetimidates.[9] In the course of this research, use of solvent mixtures containing diethyl ether and dioxane was found to give good α-selectivity in the glucosylation of secondary acceptors with a perbenzylated glucosyl imidate (α/β ratios 3/4).[7] Unfortunately, poor selectivity was achieved by coupling a more reactive primary acceptor with a perbenzylated glucosyl trifluoroacetimidate (α/β 1.7, Table 1, entry 1), while no selectivity was registered with the corresponding glucosyl trichloroacetimidate (Table 1, entry 3).

Further investigations were dedicated to the directing solvent effect to improve these disappointing results. On the bases of the previously conjectured mechanism, we hypothesized that improved α-selectivity might be achieved by favouring the conversion of the kinetic α-linked solvent-glycosyl cation adduct (affording the undesired β-glycosides) into the corresponding β-adduct (providing the desired α-glycoside). On this regard, use of a bidentate ether as the solvent could appear beneficial, as the anomerization would be kinetically favoured

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* Corresponding author. Tel.: +39-081-674153; fax: +39-081-674393; e-mail: iadonisi@unina.it

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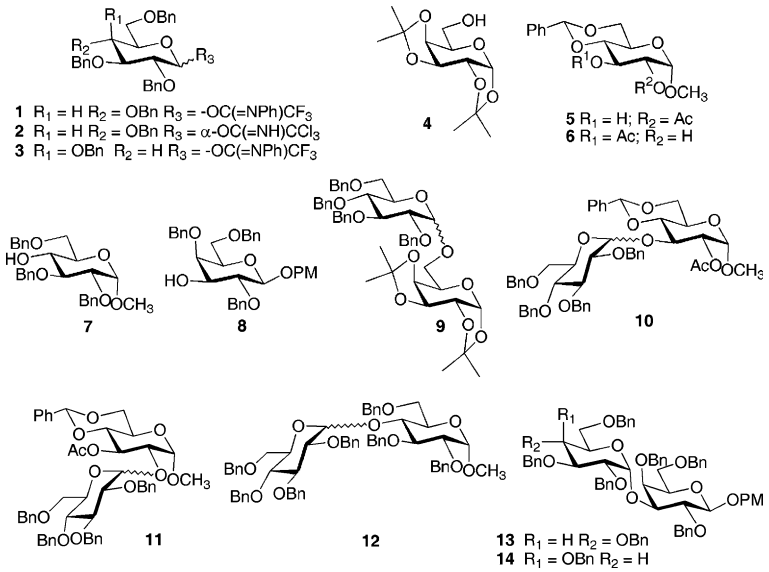
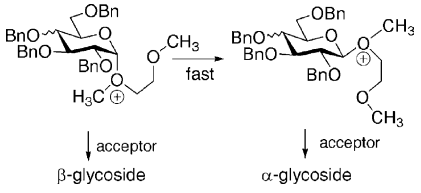


Figure 1.

Table 1. α-Selective glycosidation of acceptor **4** with glucosyl imidate donors **1** and **2** promoted by $Yb(OTf)_3$ (0.1 equiv)

Entry	Donor	Solvent	Temp (°C)	Time (h)	Yield[a] of **9** (α/β)[b]
1	**1**	Et_2O/dioxane 4:1	−10	4	86 (1.7)
2	**1**	DME	rt	4	80 (3.5)
3[c]	**2**	Et_2O/dioxane 4:1	−10	2	81 (1.0)
4	**2**	DME	−15	2	90 (1.7)
5	**1**	Dioxane/DME 1:4	rt	6	76 (3.1)
6	**1**	Dioxane/DME 1:1	0 to rt	6	79 (4.0)
7	**1**	Dioxane/DME 4:1	0 to rt	4	84 (3.9)
8	**1**	Toluene/DME 4:1	0 to rt	6	73 (3.0)
9	**1**	Dioxane/DME/toluene 4:1:1	0 to rt	8	79 (4.3)

[a] Isolated yield.
[b] Measured by ^1H NMR.
[c] With 0.03 equiv of $Yb(OTf)_3$.



Scheme 1. Hypothesized intramolecular mechanism of anomerization of the glycosyl cation-solvent adduct with DME.

by entropic factors as depicted in Scheme 1. 1,2-Dimethoxyethane (DME) appeared to be an especially interesting option, because it is sufficiently cheap and volatile (bp 85 °C) to be practically used as the solvent.

In a first experiment, donor **1** and acceptor **4** were coupled under the activation of ytterbium(III) triflate in DME (Table 1, entry 2). Both good yield and selectivity were obtained (80%, α/β 3.5), but the reaction rate was sensibly lower than in a dioxane/diethyl ether mixture (Table 1, entry 1). This difference could be ascribed to the ability of DME to depress the activity of the promoter by chelation at the lanthanide site. In an attempt to improve both selectivity and rate, several co-solvents were tested (entries 5–9), and even improved stereoselectivities were registered by using dioxane/DME mixtures. The best result in terms of stereocontrol was registered with the ternary mixture dioxane/DME/toluene 4:1:1 (α/β 4.3, entry 9). Interestingly, very sluggish reactions were observed when diethyl ether was used as the cosolvent, despite its usual adoption in TMSOTf promoted glycosidations with trichloroacetimidate donors.[8]

These results led us to reconsider the α-selective glycosylation of a range of secondary glycosyl acceptors. In these cases, use of DME as the sole solvent often resulted in too lengthy reactions. In contrast, use of binary and ternary solvent mixtures containing dioxane and toluene provided appreciable glycosidation yields within a few hours and even higher stereoselectivities than in the previously[7] reported conditions (Table 2). In two cases (entries 10 and 11), exclusive formation of α-linked disaccharides was observed, the latter example constituting the preparation of protected disaccharide fragment **14**, an extensively studied epitope involved in the antibody-mediated hyperacute rejection in xenotransplantations.[10]

Table 2. α-Selective glycosidation of secondary acceptors promoted by $Yb(OTf)_3$ (0.1 equiv)

Entry	Donor	Acceptor	Product	Solvent	Yield[a] (α/β)[b]
1	**1**	**5**	**10**	Dioxane/DME 4:1	73 (7.4)
2	**1**	**5**	**10**	Dioxane/DME 1:1	77 (7.2)
3	**1**	**5**	**10**	Dioxane/DME/toluene 4:1:1	70 (8.2)
4	**1**	**6**	**11**	Dioxane/DME 4:1	82 (8.0)
5	**1**	**6**	**11**	Dioxane/DME 1:1	51 (7.5)
6	**1**	**6**	**11**	Dioxane/DME/toluene 4:1:1	80 (7.6)
7	**2**	**7**	**12**	Dioxane/DME 4:1	63 (6.3)
8	**1**	**7**	**12**	Dioxane/DME 4:1	55 (6.0)
9	**1**	**7**	**12**	Dioxane/DME/toluene 4:1:1	51 (5.8)
10	**1**	**8**	**13**	Dioxane/DME/toluene 4:1:1	65 (only α)
11	**3**	**8**	**14**	Dioxane/DME/toluene 4:1:1	81 (only α)

[a] Isolated yield. All products were identified by ^1H and ^{13}C NMR spectroscopy (see Supplementary material).
[b] Measured by ^1H NMR.

Table 3. TMSOTf (0.05 equiv) promoted glycosylation of acceptor **5** with donor **1** (1.4 equiv) at 0 °C

Entry	Solvent	Yield[a] of product **10** (α/β)[b]
1	DCM	76 (1.8)
2	Diethyl ether	53 (8.8)
3	DME	83 (6.5)
4	Dioxane/DME/toluene 4:1:1	84 (7.2)

[a] Isolated yield.
[b] Measured by ^1H NMR.

Encouraged by these results, the stereodirecting ability of DME was also examined in combination with the usual TMSOTf promoter. On the other hand, the stereocontrolled synthesis of α-glucosides and -galactosides with the recently introduced *N*-phenyl trifluoroacetimidate donors has not yet been explored as extensively as with standard trichloroacetimidate donors. Therefore, the model coupling between donor **1** (1.4 equiv) and acceptor **5** was examined under the activation of TMSOTf (0.05 equiv) at 0 °C in four different solvents (Table 3).

Under Yu's conditions (dichloromethane as the solvent)[9] the reaction proceeded with high yield but poor selectivity (Table 3, entry 1). In diethyl ether, commonly used to induce α-selectivity with glucosyl and galactosyl trichloroacetimidate donors,[8] the coupling proceeded with high stereocontrol but moderate yield (entry 2). In DME (entry 3) the disaccharide was obtained with both high yield and selectivity, although a slightly lower α/β ratio than in diethyl ether was obtained. Comparable yield and an improved α-selectivity were registered with the ternary mixture dioxane/toluene/DME 4:1:1 (entry 4), consistently with the trend observed with $Yb(OTf)_3$.

In conclusion, DME has been shown to be a suitable co-solvent for achieving high selectivity in α-glycosidations catalytically promoted by ytterbium(III) triflate.[11] Under these conditions good results can be obtained even with reactive primary acceptors. These results expand the potential of this moisture stable promoter in oligosaccharide synthesis. In addition, DME could be an interesting alternative to conventional ether solvents, even in the glycosidations performed with the standard TMSOTf activation of trifluoroacetimidates.

Supplementary material: Spectral data (^1H and ^{13}C NMR) of compounds **9**–**14** are available.

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11. General procedure of glycosidation with $Yb(OTf)_3$: A mixture of acceptor (0.10 mmol) and donor (0.13–0.15 mmol) were coevaporated three times in anhydrous toluene. After adding freshly activated 4 Å acid washed molecular sieves (AW 300 MS) in pellets, the mixture was dissolved at 0 °C under argon in 1:4 toluene/dioxane (1.5 mL). After stirring for 20 min, a DME solution of $Yb(OTf)_3$ (0.05 M, 200 μL, 0.01 mmol) was added dropwise. The temperature was then allowed to raise to rt. After completion of the reaction (TLC analysis), a few drops of pyridine were added, the mixture filtered through a short pad of silica gel and then evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate mixtures).
Glycosidations with TMSOTf: A mixture of acceptor **5** (11 mg, 35 μmol) and donor **1** (32 mg, 45 μmol) were coevaporated three times in anhydrous toluene. After adding freshly activated 4 Å molecular sieves in pellets, the mixture was dissolved in dichloromethane, or diethyl ether, or dimethoxyethane, or 4:1 dioxane/toluene (0.8 mL). After stirring for 20 min, a solution of TMSOTf in the reaction solvent (for entries 1–3 of Table 3) or dimethoxyethane (for entry 4) (160 μL, 1.7 μmol) was added dropwise to the mixture at 0 °C. After completion of the reaction (1–3 h, TLC analysis), a few drops of pyridine were added and the mixture concentrated. The disaccharide **10** was purified by PLC (petroleum ether/ethyl acetate, 7:3).