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An approach to the highly stereocontrolled synthesis of α-glycosides. Compatible use of the very acid labile dimethoxytrityl protecting group with $Yb(OTf)_3$-promoted glycosidation☆

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Abstract—The very acid labile dimethoxytrityl group is demonstrated to survive $Yb(OTf)_3$-promoted glycosidations with *N*-phenyl trifluoroacetimidates as the donors. In addition, the installation of this sterically demanding protecting group at the primary position of the donor allows the achievement of a very high selectivity in the synthesis of α-glycosides with a variety of saccharidic acceptors.
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Glycosidation reactions represent the key step for the synthesis oligosaccharides. Despite the impressive progress in glycosylation approaches in the last years,[1] the most employed protocols are still suffering from the use of chemically aggressive acidic promoters whose handling and storage entail serious experimental problems. In addition, use of these promoters limits the choice of protecting groups to those acid stable.[2] Very recently we have reported[3] that the mild and moisture stable Lewis acid $Yb(OTf)_3$ can promote the glycosidation of saccharidic acceptors with armed[4] and disarmed glycosyl trichloro-[5] and *N*-phenyl trifluoroacetimidates.[6] Especially mild conditions could be exploited when acid washed molecular sieves (commercially known as AW MS 300) were used to guarantee anhydrous conditions in the reaction medium. In this paper we wish to report the compatibility of such procedure with the presence of the very acid labile dimethoxytrityl (DMT) protecting group, whose stability in glycosylations promoted by acidic promoters, to the best of our knowledge, was never reported before.[7] Dimethoxytrityl could be a useful transient protecting group in oligosaccharide synthesis due to its easy and fast removal under the mildly acidic conditions currently exploited, for example, in the automated procedures for the synthesis of oligonucleotides.[8] Furthermore, the colorimetric assay of the released dimethoxytrityl cation could be very useful for a fast evaluation of yields in solid phase glycosidations[1b] with dimethoxytritylated donors. In addition to this reactivity concern, the here described investigation was also aimed at establishing a possible improvement in the stereoselective synthesis of α-glycosides.[9]

Actually, in our recent studies[3] we disclosed that good α-selectivity can be achieved with armed *N*-phenyl trifluoroacetimidate donors exploiting solvent mixtures containing diethyl ether and dioxane. However, the synthesis of the α-glycosides proceeded with a disappointing low selectivity with a more reactive primary acceptor (Table 1, entry 1), and in no case exclusive formation of α-glycosides was found (the ratio α:β 4:1 was the higher selectivity obtained).[3] In order to face this issue, the installation of a bulky protecting group on the primary hydroxyl of the donor was anticipated to be beneficial for the improvement of the α-selectivity, as suggested by some reports.[7b,10] Therefore, 6-*O*-dimethoxytritylated model donor **2** was prepared by standard procedures as shown in Scheme 1 and then coupled with model acceptors **4**–**7**, whose reactivity with the perbenzylated trifluoroacetimidate donor **1** (Scheme 1) was previously reported.[3]

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Table 1. Effect of the donor 6-*O*-substituents in the glycosidations of saccahridic acceptors

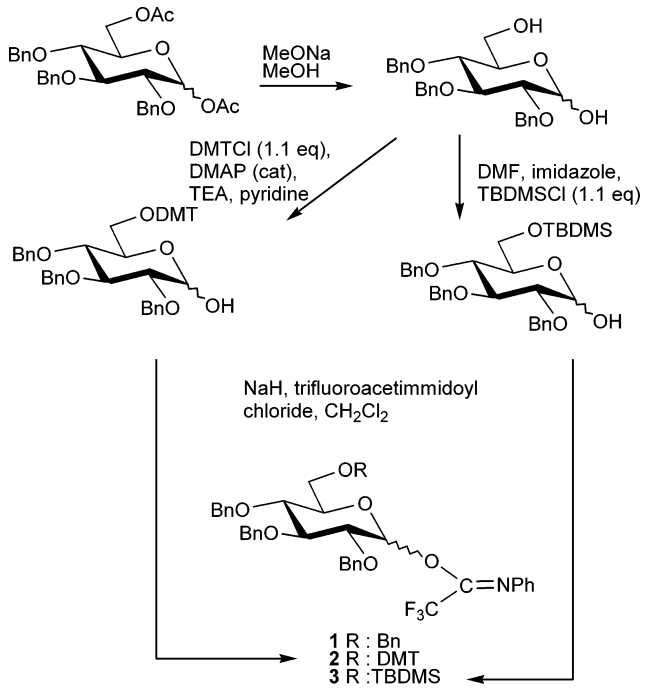
Entry	Acceptor	Donor	Conditions[a]	Product	Yield[b]
1[c]	**4**	**1**	A	**8** R: Bn α:β 1.7:1	86
2	**4**	**2**	B	**9** R: DMT only α	90
3[c]	**4**	**1**	C	**8** R: Bn α:β 1:6	93
4	**4**	**2**	D	**9** R: DMT α:β 1:1.7	83
5	**4**	**3**	B	**10** R: TBDMS α:β 3.5:1	72
6	**5**	**2**	E	**11**	78
7	**6**	**2**	E	**12**	82
8	**7**	**2**	F	**13**	71

[a] Condition A: donor (1.3 equiv.), $Yb(OTf)_3$ (0.1 equiv.), Et_2O:dioxane 4:1, −10°C, 2 h; B: donor (1.3 equiv.), $Yb(OTf)_3$ (0.1 equiv.), Et_2O:dioxane 4:1, 0°C to rt, 12 h; C: donor (1.3 equiv.), $Yb(OTf)_3$ (0.1 equiv.), CH_3CN:EtCN 4:1, −10°C, 2 h; D: donor (1.3 equiv.), $Yb(OTf)_3$ (0.1 equiv.), CH_3CN:EtCN 4:1, 0°C to rt, 24 h; E: donor (1.4 equiv.), $Yb(OTf)_3$ (0.1 equiv.), toluene: Et_2O:dioxane 4:1:1, 0°C to rt, 24 h; E: donor (2.1 equiv.), $Yb(OTf)_3$ (0.15 equiv.), toluene: Et_2O:dioxane 4:1:1, 0°C to rt, 24 h.

[b] Isolated yield. All products were characterized by ^1H and ^{13}C NMR (see supporting information).

[c] Ref. 3.

Interestingly, donor **2** turned out to be much less reactive than its 6-*O*-benzylated counterpart **1** (Scheme 1), so that its activation with catalytic $Yb(OTf)_3$ could be achieved at room temperature rather than at −10°C and longer reaction times were required for the glycosidations to occur. However, use of this donor in diethyl ether/dioxane mixtures was quite rewarding in terms of yield and α-selectivity.



Scheme 1. Synthesis of donors **2** and **3**.

Indeed, glycosidations with donor **2** in ether mixtures (entries 2, 6, 7 and 8) proceeded in all cases in high yields. In addition, exclusive formation of the α-anomers could be detected in all cases in the limits of the NMR analysis. Interestingly, no appreciable detritylation process was observed despite the prolonged reaction times, consistently with the extreme mildness of the activation conditions. In order to confirm the sterical effect of the bulky dimethoxy trityl group of the donor, the coupling between donor **2** and the primary acceptor **4** was next examined in the nitrile solvent mixture acetonitrile/propionitrile 4:1 which was previously shown[3] to address the selectivity of glycosidations with armed imidates toward β-selectivity,[11] especially with a more reactive primary acceptor (see entry 3). As expected, in this case (entry 4) an equally high yield was achieved, and the β-selectivity was sensibly decreased (β:α 1.7:1) by the 6-*O*-protecting group of the donor which renders much more difficult the access of the nucleophilic acceptor from the β-side. It should be outlined that also with this alternative solvent mixture no appreciable detritylation process was detected.

The compatibility of the approach for the synthesis of α-glycosides was also investigated with the donor **3** equipped with another acid labile and sterically demanding group such as the TBDMS. In this case (entry 5), a good yield and selectivity were again attained, but appreciable amounts of the β-linked disaccharide were obtained (α:β 3.5:1). This result confirms the importance of the sterical bulk of the 6-*O*-protecting group of the donor in determining the level α-selectivity of the reaction.

It should be noted that several reports are concerned with the lanthanide triflates mediated removal of acid labile protecting groups such as trityl,[12] TBDMS,[13] primary acetonides.[14] In all cases these deprotections are conducted in wet solvents, and therefore anhydrous conditions required in the present glycosidation procedure should be important for the preservation of the acid labile functionalities.

In conclusion, in this paper we report the feasible use of the very acid labile dimethoxytrityl group in glycosidation reactions. In addition, the installation of this sterically demanding protecting group at the primary position of the donor in combination with the use of a suitable solvent allows the achievement of very high selectivity in the synthesis of α-glycosides with a variety of acceptors.

Supplementary material. Experimental procedures for preparation of donors **2** and **3**, glycosidations, and spectral (^{1}H and ^{13}C NMR) data of disaccharides **8–13** are available.

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