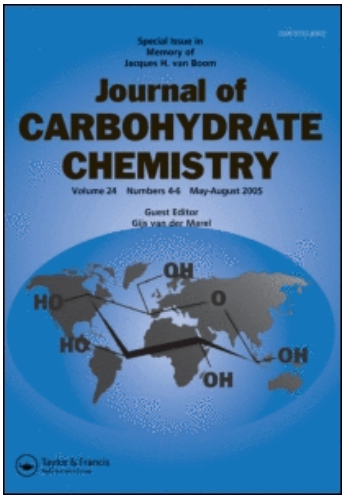

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Silver Trifluoromethanesulfonate(Triflate) Activation of Trichloroacetimidates in Glycosylation Reactions

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COMMUNICATION

SILVER TRIFLUOROMETHANESULFONATE(TRIFLATE) ACTIVATION OF TRICHLOROACETIMIDATES IN GLYCOSYLATION REACTIONS.[1]

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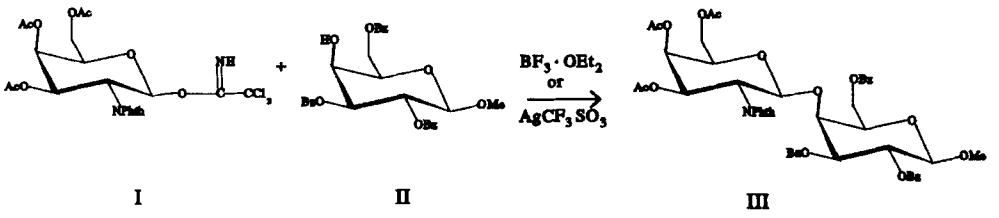
Chemical syntheses of biologically active oligosaccharides, glycolipids and glycopeptides requires efficient stereospecific glycosylation reactions.[2] One of the most effective glycosylation methods involves activation of anomeric imidates, particularly trichloroacetimidates, by Lewis acids such as boron trifluoride etherate ($BF_3 \cdot OEt_2$), trimethylsilyl trifluoromethanesulfonate (TMSOTF)[3] and trifluoromethanesulfonic anhydride.[4] In a recent example from this laboratory, $BF_3 \cdot OEt_2$ has been used to promote the glycosylation of methyl 2,3,6-tri-*O*-benzoyl-ß-D-galactopyranoside (**II**)[5] with 2-deoxy-2-phthalimido-3,4,6-tri-*O*-acetyl-ß-D-galactopyranosyl trichloroacetimidate (**I**),[6] see Scheme 1. The expected ß1-4-linked disaccharide **III** was obtained in 40% yield. The yield was so low since both the α-anomer and a 1-3-linked disaccharide were formed as by-products, the latter in particularly large quantities (cf. Ref. [7]). The 1-3 disaccharide could be formed from a product of acid-catalyzed 3,4-migration of the benzoyl group which is not surprising, considering the *cis* relationship of the 3,4-hydroxyl groups in



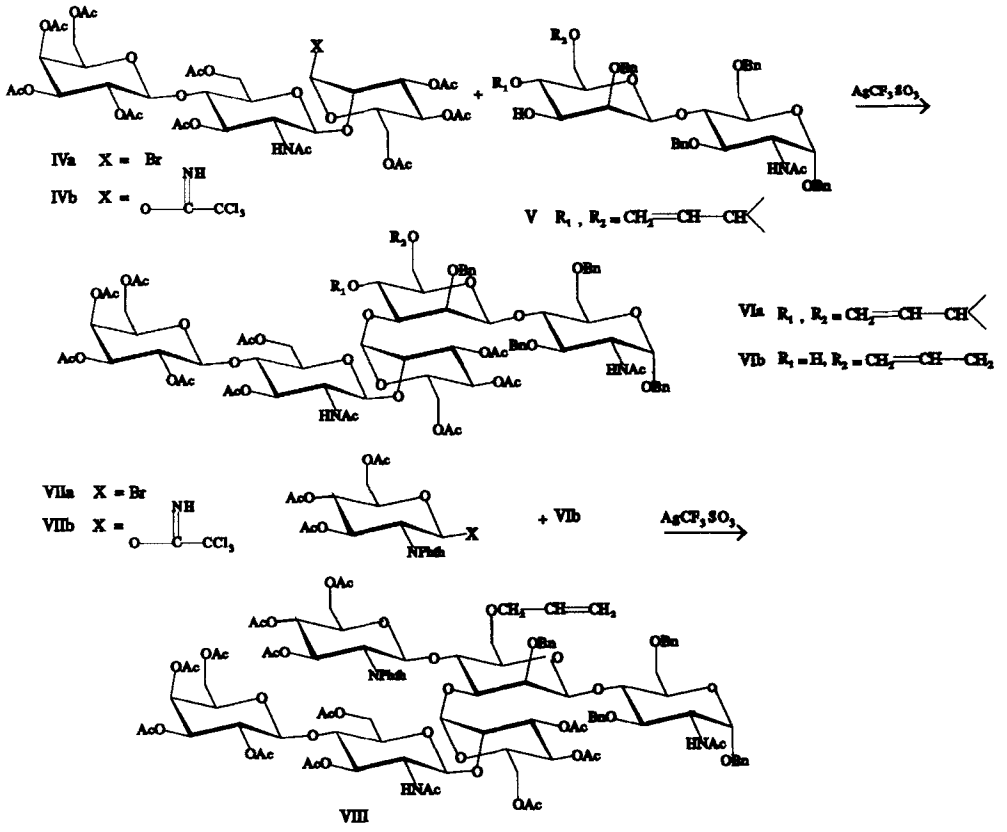
I II III

Scheme 1.

galactose.[8] In fact, when the glycosylation reaction was quenched before all unreacted alcohol was consumed, the chromatographic fraction corresponding to the starting alcohol **II** contained at least three different tribenzoates (as shown by NMR analysis).[9] Other promoters, $ZnBr_2$[10] and TMSOTF, led to lower yields and more complicated mixtures than $BF_3{\cdot}OEt_2$.

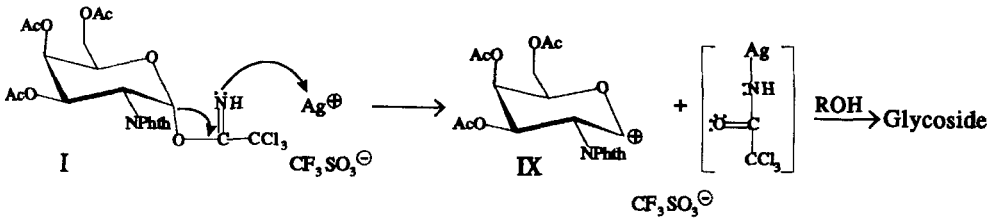
In search for better activation of trichloroacetimidates, we presumed that the process of activation starts with an electrophilic attack by $BF_3{\cdot}OEt_2$ on the imide nitrogen followed by nucleophilic attack by the unprotected hydroxyl oxygen to form the glycosidic bond. Unfortunately, BF_3 also has a high affinity for oxygen and can coordinate carbonyl oxygen atoms. The resulting complexes can lead to acyl migrations. Prevention of such migrations would require a promoter with a much lower affinity for oxygen than for nitrogen. Silver triflate, AgOTF, appears to satisfy this requirement since the silver cation has a higher affinity for nitrogen than for oxygen and triflate is a non-nucleophilic anion.[11] Silver triflate has been used extensively with other glycosyl donors, in particular those with chloride or bromide as the leaving group.[12]

To test the validity of this hypothesis, we have examined the glycosylation of alcohol II with trichloroacetimidate **I** promoted by AgOTF. Indeed the desired ß1-4 disaccharide **III** was isolated in yields of 80-90% accompanied with 2-3% of the α-anomer and, more importantly, no products of benzoyl migration were detected.[13] Next, we have examined glycosylations with more complex synthons, which are oligosaccharide fragments of typical *N*-linked glycoproteins, such as trisaccharide trichloracetimidate **IVb**[14] and disaccharide alcohol **V**, see Scheme 2.[15] Although $BF_3{\cdot}OEt_2$ catalyzed glycosylation of



Scheme 2.

VIb proceeded in higher yield than with Koenigs Knorr chemistry using bromide **IVa**, the expected pentasaccharide **VIa** was isolated in moderate yield, mainly due to extensive decomposition of both the di- and trisaccharide. When AgOTF was used, the pentasaccharide **VIa** was isolated in 70% yield by simple chromatography since no decomposition had occurred during the reaction.[16] Similarly, glycosylation at the usually unreactive O-H of pentasaccharide alcohol **VIb** with trichloroacetimidate **VIIb**[17] promoted by AgOTF gave ß-linked hexasaccharide **VIII**, which was isolated in 50% yield along with unreacted pentasaccharide **VIb**.[18] No α-anomer was detected. All of our previous attempts to glycosylate alcohol **VIb** had lead to extensive if not predominant decomposition of **VIb**, and our best previous condition using bromide **VIIa** and AgOTF



Scheme 3.

in nitromethane gave **VIII** in 30% yield and heavily contaminated with decomposition products.

Among the salts tested with higher affinity for nitrogen, anhydrous $AgClO_4$ and $CoBr_2$ acted as suitable promoters, but less efficiently than AgOTF. As to the mechanism of this reaction, the AgOTF may act as a Lewis acid by coordinating to the imidic nitrogen through Ag^+ leading in turn to the generation of a cation-like species **IX** (cf. Scheme 3). Boron trifluoride and other Lewis acids presumably function in the same way. Time course glycosylation experiments with a trichloroacetimidate and $BF_3{\cdot}OEt_2$ (equimolar) monitored by NMR spectrometry demonstrate that all trichloroacetimidate is consumed within 1 hour at room temperature. The electron-deficient species **IX** is formed more slowly in the presence of AgOTF than in the presence of $BF_3{\cdot}OEt_2$. Thus the concentration of **IX** is more constant and this will minimize decomposition. Moreover, the presence of the non-nucleophilic triflate anion as a counter-ion may slow this decomposition as well.

Recently we have found that intra-molecular hydrogen bonding of the nucleophilic hydroxyl in glycosylation reactions can greatly diminish the reactivity of the hydroxyl by adding an additional energy barrier to reaction.[19] The *cis*-hydroxyls in alcohols **II** and **V** can readily hydrogen bond to their vicinal oxygens and the O-4 hydroxyl in **VIb** likely interacts with a protecting group, for instance the O-6 allyl ether. Lewis acids, including AgOTF, can break up this hydrogen bonding thus lowering the energy barrier. However, AgOTF in contrast to other Lewis acids is more specific for activation of the imidate group. Thus glycosylations with AgOTF can be performed at room temperature, eliminating the need for work at low temperatures (-20 to -40 °C), customary for BF_3 promoted glycosylations.

In summary, AgOTF is recommended as promoter for glycosylation using glycosyl trichloroacetimidates as glycosylating agents.

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9. It has been repeatedly observed that the intensity of the spot on a TLC plate corresponding to the starting acceptor diminishes only to a certain point as the glycosylation reaction progresses. Beyond this point, addition of more glycosylation agent, or prolonged reaction time, does not diminish the intensity of this spot any further. The reason for this apparently mysterious behaviour is that the original acceptor has undergone a reaction, products of which by chance have the same R_f as the starting material. The cited benzoyl migration is an example of such misleading TLC behaviour.
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13. Typical conditions: The alcohol (2 mMol), the imidate (2.6 Mmol) and AgOTF (2.6 mMol) were dried in the dark in a RB flask at high vacuum. Note that the best yields are obtained without molecular sieves or added base. The flask was opened to argon and dichloromethane (10 mL) was added and the reaction left to stir at room temperature in the dark. When TLC of the reaction mixture indicated that the reaction was complete (24-48 h) the mixture was added directly to a flash silica gel column and eluted with the appropriate solvent mixture. Values of $[\alpha]_D$, δ_H and δ_C were measured in $CHCl_3$ or $CDCl_3$ at 22 °C, III:$[\alpha]_D$ +32.7 (c 0.83); ^1H (500 MHz) 5.459 d J_{12} 8.1 H1 GalNAc; 4.571 d J_{12} 7.7 H1 Gal; 3.379 s OCH_3; 2.164, 1.970, 1.814 3xs $COCH_3$; ^{13}C 101.4 C1 GalNAc; 97.8 C1 Gal; FAB-MS Obs. MH^+ 946.2516 Calcd. for $C_{48}H_{45}O_{18}N$·Na 946.2534.

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16. Values of $[\alpha]_D$, δ_H and δ_C were measured in $CHCl_3$ or $CDCl_3$ at 22 °C, VIa:$[\alpha]_D$ +24.8° (c 0.7); ^1H (500 MHz) 4.546 d J_{12} 1.0 H1 ß-Man; 4.961 d J_{12} 3.8 H1 α-GlcNAc; 4.467 d J_{12} 7.8 H1 ß-Gal; 4.253 d J_{12} 7.8 ß-GlcNAc; 5.082 d J_{12} 2.0 H-1 α-Man; ^{13}C 101.21 C1 ß-Man; 97.10 C1 α-GlcNAc; 101.16 C1 ß-Gal; 100.63 C1 ß-GlcNAc; 98.59 α-Man; FAB-MS Obs. $[M\text{-}HOCH_2Ph]^+$ 1579.5739 Calcd. for. $C_{76}H_{95}O_{34}N_2$ 1579.5765.

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18. Values of $[\alpha]_D$ and δ_H were measured in $CHCl_3$ or $CDCl_3$ at 22 °C, VIII:$[\alpha]_D$ +28.5 (c 0.27); ^1H (500 MHz) 4.238 brs J_{12} <0.5 H1 ß-Man; 2.607 ddd J_{45} 10.0, J_{56} 3.2, $J_{56'}$ <1 H5 ß-Man; 4.916 d J_{12} 3.8 H1 α-GlcNAc; 4.509 d J_{12} 8.5 H1 ß-Gal; 5.065 d J_{12} 7.5 ß1,2-GlcNAc; 4.666 brs J_{12} <0.5 H-1 α-Man; 5.298 d J_{12} 8.5 H1 ß1,4-GlcNPhth; 5.793 dd J_{23} 10.8, J_{34} 8.7 H3 GlcNPhth; FAB-MS Obs. MH^+ 2106.7600 Calcd. for. $C_{103}H_{124}O_{44}N_3$ 2106.7557.

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