GLYCOSYLATION OF SILYL ETHERS: A NOVEL SYNTHESIS OF OLIGOSACCHARIDES AND ARYL GLYCOSIDES[1]

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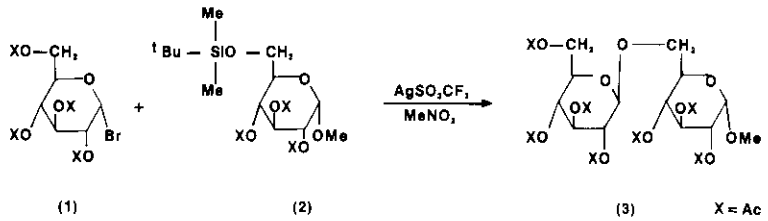
Abstract —— A novel procedure for the synthesis of oligosaccharides and aryl glycosides involving the glycosylation of silyl ethers is described.

The conventional methodology for the synthesis of oligosaccharides consists of the Königs-Knorr reaction[2,3] and its modifications[4]. Although the problems associated with this reaction are well documented, no major development in this field occurred until the introduction of the orthoester glycosylation by Kochetkov[5]. Another significant improvement has been the use of imidates in glycosylation by Sinaÿ[6]. A number of other innovative procedures have been introduced in recent years, particularly noteworthy being those developed by Mukaiyama[7] and Nicolau[8]. In our search for simple, efficient and economical procedures for the synthesis of oligosaccharides, we have studied the glycosylation of trityl ethers introduced by Bredereck[9] and have established it as a viable and rapid procedure for the synthesis of 1,6-linked oligosaccharides[10].

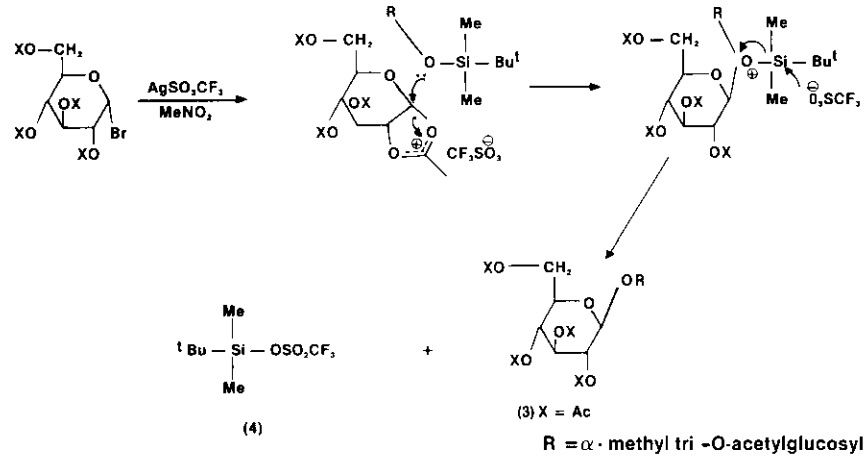
Subsequently, we were intrigued by the possibility of using silyl ethers as nucleophiles in glycosylation.[11] To test the usefulness of this approach, tetra-O-acetyl glucopyranosyl bromide (1) was reacted with methyl-2,3,4-tri-O-acetyl-6-O-t-butyldimethylsilylgluco-pyranoside (2) as described in the following procedure (Scheme 1): silver triflate (3.21 g, 0.0125 mole) and Drierite® (10 g) were taken in nitromethane (70 ml) and the mixture stirred in an ice bath for 5 min. A solution of 2, (4.34 g, 0.01 mole) in dichloromethane (10 ml) was added to it and this was followed by the rapid addition of 1, (5.13 g, 0.0125 mole). The reaction mixture was stirred for 20 min. It was then diluted with dichloromethane (150 ml) and filtered. The filtrate was washed with sodium bicarbonate solution and then dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by routine acetylation and work-up afforded the product, methylgentiobioside heptaacetate (3), as colorless crystals from chloroform/heptane (5.2 g, 89%), mp 173-174°C (undepressed when mixed with an authentic

sample), $[\alpha]_D$ + 34.9° (chloroform); ^1H NMR ($CDCl_3$) δ 3.4 (3H, s, OCH_3), 4.5 (1H, d, 7Hz, C_1 axial H), 5.38 (1H, d, 4Hz, C_1' equatorial H); ^{13}C NMR($CDlC_3$) δ 21(OCH_3),97(C_1, α anomeric), 102 (C_1', β-anomeric); MS(FAB): 651 (M + H) Anal. Calc. for $C_{27}H_{38}O_{18}$: C, 49.89; H, 5.84. Found: C, 49.61; H, 5.73



Scheme 1

Similar high yield glycosylations were observed with other silylated mono and disaccharides and the reaction appears to be general in its scope for the synthesis of oligosaccharides. Mechanistically, the reaction is quite interesting and can be rationalized as shown in Scheme 2.

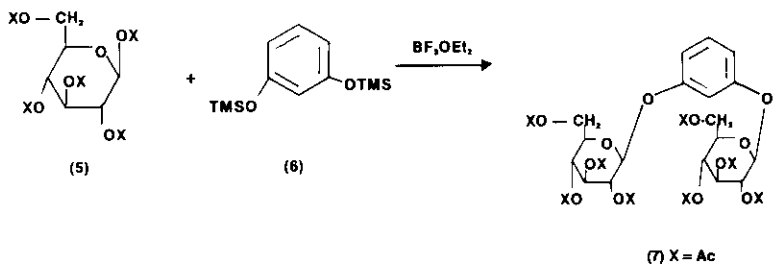


Scheme 2

Positive evidence for such a course of reaction was obtained by observing t-butyldimethylsilyl triflate (4) as the only silyl species remaining at the end of the reaction by ^{29}Si NMR determination[13].

While the above procedure was applicable to the synthesis of aryl glycosides also, the yields were not as impressive as in the case of oligosaccharides. However, a variation of the above procedure was found to be applicable to the efficient synthesis of such compounds. The latter procedure utilizes β-glycosyl acetates instead of glycosyl bromides and boron trifluoride etherate is used to generate the glycosyl cation which then reacts with the silyl ether of the

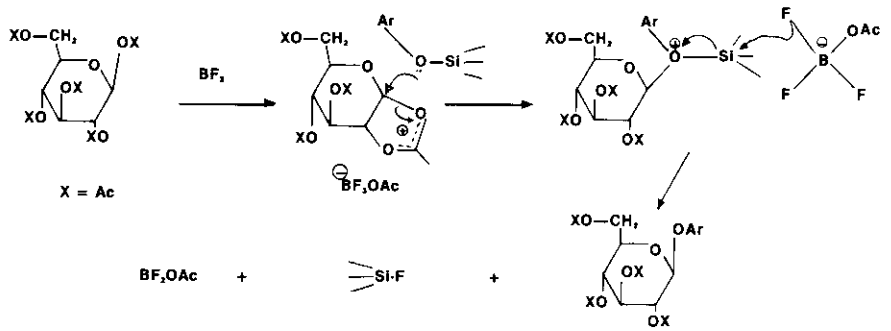
phenolic compound. The synthesis of resorcinol diglucoside octaacetate (Scheme 3) provides an illustration of the procedure.



Scheme 3

Experimental details for the synthesis of (7) are as follows: resorcinol bistrimethylsilyl ether 6, (1.27 g, 0.005 mole) was dissolved in dichloromethane (20 ml), and a solution of β-D-glucose pentaacetate 5,(4.3 g, 0.0055 mol) in the same solvent (50 ml) and BF_3 etherate (10 ml) were added to it and the mixture stirred at r.t. for 16 h. The reaction mixture on processing afforded a crystalline product, 4.0 g. Recrystallization from methanol afforded pure (7) as colorless needles (3.28 g, 85%), mp 193-195°C, ^1H NMR($CDCl_3$) δ 5.92 (2H, d, 7.4 Hz, C-1H(α) of the glucosyl moieties); ^{13}C NMR ($CDCl_3$) δ 157 (C_1 of β glucoside); MS(FAB): 771 (M+H); $[\alpha]_D^{26°}$ -29°($CHCl_3$). Anal Calc. for $C_{34}H_{42}O_{20}$: C, 52.94; H, 5.49. Found: C, 52.54; H, 5.36.

Mechanistically, the reaction can be considered to involve a variation of the pathway suggested for the oligosaccharide synthesis (Scheme 2) as shown below:



Scheme 4

Since the ate complex $^{-}BF_3OAc$ cannot directly function as a nucleophile, we are suggesting that it sheds a fluoride ion which then displaces on the silicon to complete the reaction. A similar observation where $^{-}BF_4$ acts as a source of F^{-} has been reported[14]. Validity for such a course reaction was established by the detection TMSF in the reaction mixture by ^{29}Si NMR determination[13]. As in the case of oligosaccharides, this reaction is generally applicable to the synthesis of aryl glycosides even in cases where these are not accessible by Königs-Knorr and other conventional procedures.

Since our initial report[11], other approaches [15-17] to glycosylation of silyl ethers have been introduced. Unlike in these cases, our procedure utilizes readily-often commercially-available glycosylating agents (glycosyl bromides and acetates). The experimental procedure is simpler and chromatography is seldom required for the isolation of the product. Complete stereoselection resulting the exclusive formation of the β-anomer is also noteworthy.

In conclusion, we have developed a general procedure for the synthesis of oligosaccharides and glycosides using a novel glycosylation of silyl ethers[14]. The procedure is facile, practical and mechanistically interesting.

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