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A GLYCOSYLATION REACTION: CONVERSION OF METHYL GLYCOSIDES TO GLYCOSYL CHLORIDES BY BORON TRICHLORIDE[1]

Guillermo R. Perdomo[a] and Jiri J. Krepinsky[a,b]

[a]Ludwig Institute for Cancer Research, Toronto Branch, 9 Earl Street, Toronto, Ontario, Canada M4Y 1M4, [b]Departments of Medical Biophysics and Medical Genetics, University of Toronto, Toronto, Ontario, Canada, M5S 1A8

Abstract. Methyl glycosides react readily with boron trichloride in dichloromethane solutions at -78 °C to give the corresponding glycosyl chlorides for subsequent use in glycosylation reactions. This reaction is compatible with the presence of glycosyl linkages in the molecule, as well as benzyl and acetyl protecting groups.

The methyl group in methyl glycosides conveniently protects the anomeric center during a variety of transformations in monosaccharide as well as in oligosaccharide chemistry. It withstands a number of conditions commonly used for the removal of other protecting groups (mild acid, alkaline, hydrogenolytic treatment). In the absence of other glycosidic bonds, i.e. in monosaccharide derivatives, the methyl group from a methyl glycoside is most commonly removed either by acid hydrolysis or acetolysis.[2] This approach, however, is of a limited use in the presence glycosidic linkages in oligosaccharides. Therefore, it is of interest to identify specific ways for the removal of the methyl group from methyl glycosides in the presence of other ether or acetal linkages.

One of the possible ways is to convert directly the methoxyl group into a leaving group, eg. a halide, used as such in the glycosylation reaction. Recently, several methods[3] have been reported for the direct conversion of methyl glycosides into the corresponding glycosyl halides. Both trimethylsilyl bromide and iodide have been used for this purpose, but since these reagents require elevated reaction temperatures and are not compatible with the presence of some linkages in the molecule, particularly glycosidic linkages, their use is limited. Dimethylboron bromide converts methyl glycosides into the corresponding bromides and is compatible with a larger number of linkages than trimethylsilyl bromide or iodide. However, this reagent has not been used for this purpose on any oligosaccharide. Dichloromethyl methyl ether - zinc chloride have been used fairly often, but this reagent combination can be used with oligosaccharides containing acyl protecting groups only.

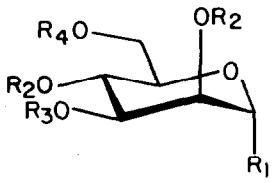
Boron trichloride, since the initial report[4] of dealkylation of various ethers, has been used extensively in organic synthesis.[5] In carbohydrate chemistry it has been used primarily for demethylation of methyl ethers in various ring positions.[6] A possibility that the methyl glycosidic linkage is more reactive in a reaction with BCl_3 than any other ether/acetal functionality in a carbohydrate molecule led us to examine a number of mono- and oligosaccharide substrates.

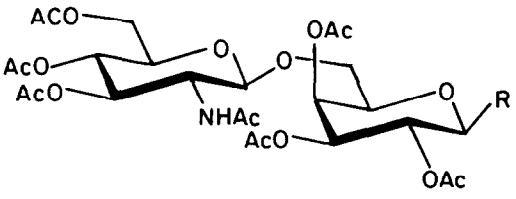
We have found that BCl_3 converts methyl glycosides into the corresponding chlorides in fair to good yields and under mild conditions. For example, treatment of methyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside (1)[7] with 1.0-1.5 equivalents of BCl_3 in CH_2Cl_2, at -78°C, gave 2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl chloride (2) in 45-52% yield. Similarly, treatment of methyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (3)[8] with 1.5-3.0 equivalents of BCl_3 in CH_2Cl_2 at 0 °C gave 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl chloride (4) in 69% yield. The ^1H NMR spectra showed anomeric protons at δ 6.90 ppm (2) and δ5.99 ppm (4), and NOE measurements confirmed their α-configuration.

Although the chlorides 2 and 4 can be isolated, it is more convenient to use the crude products of the de-O-methylation reactions in a glycosylation reaction directly.[9] Thus chloride 2 on treatment with propan-2-ol, using silver triflate as a promoter, gave isopropyl 2,3,4,6-tetra-O-benzyl mannopyranoside (5) in 82% overall yield (α:β 3:7), confirmed by the anomeric proton signals at δ4.96 ppm (-α), and δ4.46 ppm (-β) present in its ^1H NMR spectrum. This "one pot" procedure minimizes side reactions, such as hydrolysis of the chloride during its isolation.

All benzyl groups were stable under the conditions described above. However, when quantitites greater than 2 equivalents of BCl_3 were used in the reaction with 1, the 6-O-benzyl group was cleaved, in addition to de-O-methylation. Thus treatment of 1 with 2.5 equivalents of BCl_3, followed by reaction with propan-2-ol, as above, resulted in the formation of isopropyl 2,3,4-tri-O-benzyl mannopyranoside [6: 75%; α:β 1:1; ^1H NMR: δ4.87 ppm (α); 4.49 ppm (β)]. When potassium thiocyanate in acetonitrile, at 70 °C, was used in the follow-up reaction instead of propan-2-ol, the corresponding isothiocyanate was the product (7, 24%; IR: 2480, 2030 cm^{-1}; ^1H NMR: δ5.38 ppm; H-1).

The stability of glycosidic linkages toward BCl_3 under de-O-methylation conditions is crucial to its use in the synthesis of complex oligosaccharides. The methyl glycosides of two oligosaccharides were thus investigated. Methyl 2,4-di-O-benzyl-3,6-di-O-(2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl)-α-D-mannopyranoside (8) when treated with less than one equivalent of BCl_3, at -78 °C, followed by glycosylation with propan-2-ol, using silver triflate gave the isopropyl glycoside 9 (25%; ^{1}H NMR: δ 4.62, 5.08, and 5.26 ppm; H-1', H-1", H-1"').





1) R_1 = OMe; R_2 = R_3 = R_4 = Bn
2) R_1 = Cl; R_2 = R_3 = R_4 = Bn
3) R_1 = OMe; R_2 = R_3 = R_4 = Ac
4) R_1 = Cl; R_2 = R_3 = R_4 = Ac
5) R_1 = OC_3H_7; R_2 = R_3 = R_4 = Bn
6) R_1 = OC_3H_7; R_2 = R_3 = Bn; R_4 = H
7) R_1 = NCS; R_2 = R_3 = R_4 = Bn
8) R_1 = OMe; R_2 = Bn; R_3 = R_4 = 2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl
9) R_1 = OC_3H_7; R_2 = Bn; R_3 = R_4 = 2,3,4,6-tetra-O-benzyl-α-D-mannopyranosyl

10) R = OCD_3
11) R = Cl

The methyl 2,3,4-tri-O-acetyl-6-O-(2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranosyl)-β-D-galactopyranoside[10] (10) showed increased stability towards BCl_3. This disaccharide required 13 equivalents of BCl_3 for its complete conversion to the corresponding stable chloride 11 which was isolated in 55% yield (^{1}H NMR: δ 6.40, 4.87 ppm; H-1' and H-1").

The above examples show that methyl glycosides can be successfully converted to the corresponding chlorides which can be used without purification for glycosylation reactions. As an example of experimental procedure employed, the conversion of 1 to 5 is described in detail. To a solution of 1 (321 mg; 0.42 mmol) in CH_2Cl_2 (2 mL) containing 2,6-di-tert.butyl-4-methylpyridine[11] (DTBMP; 228 mg; 1.1 mmol) was added freshly activated molecular sieve[12] (3A, 2.68 g), followed by the slow addition of 1.0M solution of BCl_3 in CH_2Cl_2 (400 μL), at -78 °C. After stirring for 30 minutes,[13] the reaction mixture was brought to dryness in vacuo, while warming it to room temperature. Then the reaction flask was cooled to -78 °C, and a solution of DTBMP (1.0 g; 4.87 mmol) and propan-2-ol(600 μL, 7.8 mmol) in

CH_2Cl_2(2.0 mL) was added, followed by the addition, in one portion, of silver triflate (764 mg; 2.97 mmol). The reaction mixture was then warmed to room temperature and stirred for 13 hours. After filtration through a Celite bed, which was subsequently washed with ethyl acetate, the combined filtrates were concentrated in vacuo, and the resulting oily residue was purified by chromatography on a silica gel column. Hexane-ethyl acetate (4:1) elute 5 (164.5 mg; 51%) and recovered 1 (43.9 mg; 14%).

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9. In some cases, e.g. acylated carbohydrates, the isolated chlorides give better yields in the glycosylation reaction.

10. Trideuteriomethyl glycosides are often used in our NMR conformational studies; 10 was prepared in larger quantity and later it was needed to transform it into a glycosylating agent.

11. The base is used to minimize side reactions caused by acids formed if any moisture is present in the reaction mixture. The reaction can be successfully performed in its absence; however, 0.5 eq. is routinely used for chloride formation, and up to 4.5 eq. if chloride formation and glycosylation is done in one pot.

12. The reaction can be successfully done without molecular sieves; in fact, in the case of acylated starting materials they should be avoided as they lead to by-products.

13. Acylated compounds may require longer reaction times.

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