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Highly stereoselective synthesis of peracylated α-aldopyranosyl chlorides from aldopyranose peracetates and thionyl chloride catalyzed by $BiCl_3$ generated in situ from the procatalyst BiOCl

Rina Ghosh,* Arijit Chakraborty and Swarupananda Maiti

Department of Chemistry, Jadavpur University, Kolkata 700 032, India

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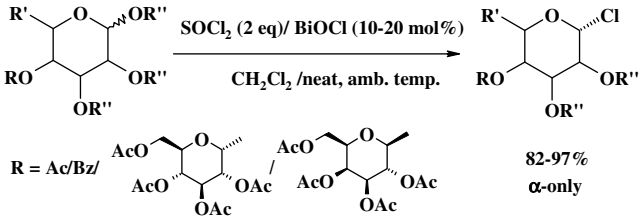
Abstract—Aldopyranose peracetates react with thionyl chloride and $BiCl_3$, generated in situ from a substoichiometric amount of the procatalyst BiOCl, producing the corresponding peracylated aldopyranosyl chlorides in very good to excellent yields (82–97%) with exclusive α-anomeric selectivity.

Acylated glycosyl chlorides are important synthetic intermediates for stereoselective glycosylation.[1a] They have been widely employed for the generation of anomeric carbocations,[1b] radicals[1c] or carbanions.[1d] Several procedures have been developed for the synthesis of β-glycosyl chlorides[2] but only a few literature reports are available for the preparation of the corresponding α-anomers.[3] Among these, methods utilizing $ZnCl_2$–thionyl chloride[3b,c] and $BiCl_3$–trimethylsilyl chloride[3d] are worth mentioning. Some of the reported methods have limitations in terms of yield and selectivity of the products or in respect of the stability, load and cost of the catalyst. Thus, the search for new methodologies for their preparation continues.

In recent years, Bi(III) salts have been widely used in organic synthesis.[4] BiOCl, although a very mild Lewis acid[5] can generate $BiCl_3$ in reaction with chlorinating agents.[6] Dubac and co-workers first utilized BiOCl as a procatalyst for Friedel–Crafts acylation reactions.[6] BiOCl is a moisture stable oxysalt of Bi(III) having very low toxicity (LD_{50} rat_{oral}: 22 g/kg).[4b] In continuation of our investigations on organic reactions based on $BiCl_3$ generated in situ from the inexpensive procatalyst BiOCl,[7] we report herein an efficient and stereoselective synthesis of peracylated α-aldopyranosyl chlorides from aldopyranosyl peracetates and thionyl chloride based on $BiCl_3$ generated in situ from a substoichiometric amount of the procatalyst BiOCl (Schemes 1, 2, and Table 1). The reported methods show that whereas a protic acid such as acetic acid or HCl along with thionyl chloride furnishes the β-chloride,[2i,l,m] Lewis acid analogues provide exactly the opposite result, producing the α-anomer.[3b,c]

To establish the minimum procatalyst load and the optimal conditions several experiments were performed. Under optimized conditions, 1,2,3,4,6-penta-*O*-acetyl-D-glucopyranose (1 equiv) reacted with thionyl chloride (2 equiv) in the presence of BiOCl (10 mol%) in dry dichloromethane at ambient temperature furnishing



R'= H/Me/CH_2OAc/CH_2OBz

R''= Ac/Bz

Scheme 1.

Keywords: Stereoselective; Aldopyranosyl chloride; $BiCl_3$; BiOCl; Procatalyst; Thionyl chloride.
* Corresponding author. E-mail: ghoshrina@yahoo.com

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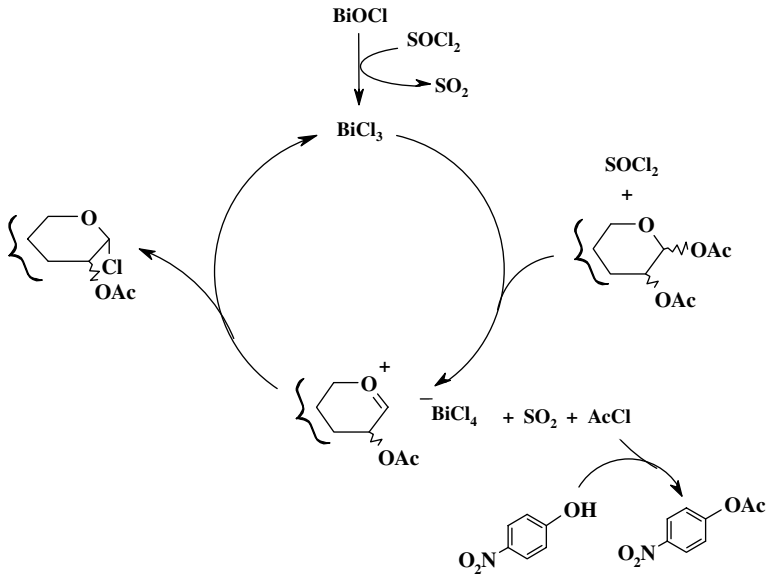

Scheme 2. Probable mechanistic pathway and catalytic cycle involving the in situ generated $BiCl_3$.

Table 1. Synthesis of peracylated α-aldopyranosyl chlorides

Entry	Products	Time	% Yield[a]
1	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	Overnight	91
2	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	Overnight	91[b]
3	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	Overnight	94[c]
4	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	Overnight	88[d]
5	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	4.5 h	97[e]
6	2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride	Overnight	95[f]
7	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	Overnight	94
8	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	24 h	94[d]
9	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	2 h	96[e]
10	2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl chloride	Overnight	96[g]
11	2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl chloride	Overnight	93
12	2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl chloride	1.5 h	93
13	2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl chloride	Overnight	82
14	2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl chloride	Overnight	92
15	2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl chloride	Overnight	85
16	Hepta-*O*-acetyl-α-lactosyl chloride	Overnight	83[h]
17	Hepta-*O*-acetyl-α-maltosyl chloride	Overnight	89[h]

[a] Isolated pure yield; all products were characterized by IR, NMR and also by comparing the physical data with those of known compounds.[3]
[b] Scale-up (~20-fold).
[c] With recovered BiOCl.
[d] Without BiOCl.
[e] In solvent-free conditions.
[f] From 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose.
[g] From 2,3,4,6-tetra-*O*-acetyl-D-galactopyranose.
[h] Using 20 mol% BiOCl.

exclusively, tetra-*O*-acetyl-α-D-glucopyranosyl chloride in 91% yield (entry 1, Table 1).[8,9] Similarly, D-galactopyranose pentaacetate (entry 7), D-mannopyranose pentaacetate (entry 11) and L-rhamnopyranose tetraacetate (entry 12) were converted into the corresponding α-chloro derivatives overnight in almost quantitative yield. Pentose sugars such as tetra-*O*-acetyl-D-arabinopyranose (entry 13) and tetra-*O*-acetyl-D-xylo- pyranose (entry 14) also reacted efficiently with thionyl chloride in the presence of BiOCl (10 mol%) resulting in the corresponding α-chlorides in very good to excellent yields. Reactions of octa-*O*-acetyllactopyranose (entry 16) and octa-*O*-acetylmaltopyranose (entry 17) proceeded smoothly in the presence of BiOCl (20 mol%) leading to the exclusive generation of the desired α-chlorides in very good yields without any cleavage of the glycosidic bond, which indicates the mildness of the present procedure compared to some existing methods.[2i,10]

The reaction was similarly applied to 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (entry 6) and its D-galactose

analogue (entry 10). Both of these substrates resulted in the generation of the corresponding α-glycopyranosyl chlorides in almost quantitative yields.

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl chloride was also easily prepared from penta-*O*-benzoyl-D-glucopyranose in excellent yield and exclusive anomeric selectivity (entry 15, Table 1), thus establishing the superiority of this procedure compared to that based on $ZnCl_2$-thionyl chloride.[3b] Attempted chlorination of glucopyranose pentaacetate with another chlorinating agent, acetyl chloride and $BiCl_3$ generated in situ from 30 mol% of BiOCl, however, did not proceed well.

The scope and limitation of this method was further evaluated by the reaction of penta-*O*-acetyl-D-glucofuranose[11] and 2,3:5,6-diisopropylidene mannose acetate[12] with thionyl chloride in the presence of BiOCl (10 mol%), which proceeded at a very slow rate with decomposition and generation of side products.[3b] 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride was prepared both from the corresponding hemiacetal and its 1-*O*-acetyl derivative at ~10 °C, but being unstable, it could only be isolated in poor yields (30 and 32%).

To examine further the efficacy of the present procedure a scale-up experiment (~20-fold) was performed with penta-*O*-acetyl-D-glucopyranose, which proceeded efficiently furnishing the desired product in excellent yield and with α-selectivity as in the case of entry 1 (entry 2, Table 1). BiOCl was recovered[6,7] and reused in a second experiment without any loss of activity in terms of yield and selectivity (entry 3, Table 1). To establish eco-friendly conditions for these reactions, solventless examples with gluco and galactopyranose pentaacetates were performed which proceeded faster than those in solvents generating the corresponding α-chlorides in almost quantitative yields (entries 5 and 9, Table 1).

Unlike some of the reported methods all the peracetylated monosaccharides and disaccharides furnished the corresponding α-chlorides irrespective of the anomeric purity or the stereochemistry of the anomeric carbon and carbon-2 of the starting materials, thus apparently indicating that C-2 acetoxy group participation is not involved in the generation of α-products exclusively. The reaction probably proceeds initially via anomeric participation in the removal of the C-l acetoxy group with synchronous pull by thionyl chloride and $BiCl_3$, followed by nucleophilic attack by the chloride ion at C-l with concomitant regeneration of $BiCl_3$, as depicted in Scheme 2 and Figure 1. That acetyl chloride was formed as a by-product in this process was also supported by trapping the same with *p*-nitrophenol as *p*-nitrophenyl acetate (Scheme 2).

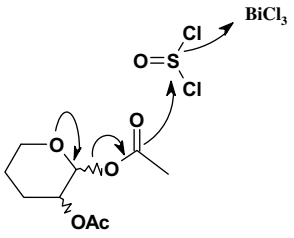

Figure 1.

It should be mentioned here that while thionyl chloride alone was found to be capable of transforming penta-*O*-acetylgluco- and galactopyranose to the corresponding tetra-*O*-acetyl-α-chlorides in excellent yields (entries 4 and 8, Table 1), with other peracetylglycopyranoses of D-xylose, maltose and lactose, reactions were either sluggish or reluctant to proceed.

In summary, we have demonstrated a new, highly efficient stereoselective synthesis of peracylated-α-aldopyranosyl chlorides from aldopyranose peracetates based on thionyl chloride and the moisture compatible procatalyst BiOCl in solvent and solvent-free conditions. The advantages of the present procedure are: the method is simple, highly productive and proceeds with exclusive α-selectivity. BiOCl is an easily available reagent of very low toxicity and can be used to generate $BiCl_3$ in situ in reaction with thionyl chloride; thus direct handling of moisture sensitive $BiCl_3$ can be avoided. Moreover, the efficient applicability of this methodology in solventless and in scale-up conditions makes it eco-friendly and it can thus also be considered for industrial application.

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8. *General experimental procedure:* (a) In CH_2Cl_2—to a solution of aldopyranose peracetate (1 mmol) in dichloromethane (3 mL), BiOCl (10 mol%) and thionyl chloride (2 mmol) were added. The mixture was stirred at ambient temperature (26–32 °C) until completion (checked by TLC, EtOAc–pet. ether, b.p. 60–80 °C). The reaction mixture was then poured onto cold saturated $NaHCO_3$ solution and the product was extracted with dichloromethane (3×10 mL). The combined organic layer was washed with water (2×15 mL) and then dried over anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the crude residue was purified by column filtration, where necessary. (b) In solvent-free conditions—to an ice-cold mixture of aldopyranosyl peracetate (1 equiv) and BiOCl (10 mol%) was added thionyl chloride (3 equiv) and the reaction was stirred at ambient temperature. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (5 mL) and then was worked up as described in method (a).
9. All products were characterized by NMR, IR and by comparing the physical data with those in the literature.[3]
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