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Orthogonal protecting group strategies in carbohydrate chemistry

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ABSTRACT

A large number of different sets of orthogonal protecting groups have been developed and used in carbohydrate chemistry over the last decade. These orthogonal sets are collected and summarized in this report. The 'artificial' classification of this review is based on the number of the protecting groups involved in the examined set.

Contents

1. Introduction

The extensive use of protecting groups in carbohydrate chemistry is routine today. Whilst simple modifications of monosaccharides can be performed without the use of any protecting groups, the chemical synthesis of oligosaccharides is currently not feasible without their aid. Generally, a successful chemical oligosaccharide synthesis depends crucially on the well-designed use of so-called persistent and temporary protecting groups. In most cases, the persistent protecting groups used are benzyl ether and acetyl and benzoyl ester groups. Temporary protecting groups are however, of a large variety depending on the nature of the persistent protecting group(s) and the structure of the target molecule. The greater the complexity of the target compound, increases the number of the temporary protecting groups used during the respective synthesis. Consequently, if there is a requirement for the parallel use of more than one temporary protecting group

Abbreviations: ADMB, 4-Acetoxy-2,2-dimethylbutanoyl; AMPA, 2-(Azidomethyl)phenylacetyl; APAC, 2-(Allyloxy)phenylacetyl; AZDMB, 4-Azido-2,2-dimethylbutanoyl; BOM, Benzyloxymethyl; Car, *N*-Phenylcarbamoyl; DMM, Dimethylmaleimido; DMPBn, Dimethoxyphenylbenzyl; DOX, Dioxyxylene; FPsc, Fluorous propylsulfonylethoxycarbonyl; IPMB, 3-Iodo-4-methoxybenzyl; MCPM, 1-Methyl-1′-cyclopropylmethyl; MMTr, (4-Methoxy)trityl; MPDMB, 4-(4-Methoxyphenoxy)-2,2-dimethylbutanoyl; MPEG, Polyethylene glycol monomethyl ether; Msc, Methylsulfonylethoxycarbonyl; 2NAP, 2-Naphthylmethyl; NAPBz, 2-((2-Naphthylmethyloxy)methyl)benzoyl; NPAc, (2-Nitrophenyl)acetyl; Npes, 2-(*p*-Nitrobenzyl)ethylsulfonyl; PA, Phenoxyacetyl; PBB, *p*-Bromobenzyl; PCB, *p*-Chlorobenzyl; PG1, Protecting group 1; Poc, Propargyloxycarbonyl; POMB, 2-(Prenyloxymethyl) benzoyl; PMB, 4-Methoxybenzyl; PMBBz, 2-((4-Methoxybenzyloxy)methyl)benzoyl; SEM, 2-Trimethylsilylethoxymethyl; TBDPS-FBn, 4-(*tert*-Butyldiphenylsiloxy)-3-fluorobenzyl; TOM, Triisopropylsilyloxymethyl; Z, Benzyloxycarbonyl (Cbz).

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during a synthesis, it is highly advantageous if the used temporary protecting groups are 'orthogonal' to each other. The term 'orthogonal' in the context of protecting groups was introduced by Merrifield as early as 1977 for amino protecting groups in peptide synthesis.[1] This concept of orthogonal protection[2] has proven particularly useful in the field of carbohydrate chemistry due to their intrinsically high number of hydroxyl functions. Since these hydroxyl functions display similar chemical reactivity, the preparation of oligosaccharides requires their selective protection. This is particularly important for the synthesis of branched oligosaccharides, where typically more than one temporary protecting group is required. The orthogonality of temporary protecting groups thus renders such syntheses more flexible and increases their likelihood of being successful.

The other advantage of an orthogonal protection strategy comes to light when the target of the synthesis is not one single compound, but multiple compounds with different functional groups installed on different, but well defined positions. Representative examples of such projects like this would be target saccharides with varied sulfation patterns, such as the synthesis of glycosaminoglycans. The synthesis of such a library of glycosaminoglycans without the use of an orthogonal protecting group strategy is much more time-consuming since every single final (target) compound would have to be made from a different precursor. In contrast, a well-designed orthogonal protecting group strategy allows for the preparation of a medium size library in an effective manner.

Over the last 15 years, many excellent review articles have been published that summarize the development of new protecting groups;[3] however to the best of our knowledge, hardly any reviews have focused on orthogonal protecting group strategies. In stark contrast to this finding, many different sets of orthogonal protecting groups have been developed and used in carbohydrate chemistry over the last decade. These orthogonal sets are collected and summarized herein.

Our focus will mainly be on the use of hydroxyl protecting groups, but if amino protecting groups are present or even involved as part of the orthogonal set, they are listed in the tables and highlighted with different colors in the Schemes.

We limit this summary to results generated over the past 15 years. For basic principles of organic chemistry, such as the different reactivities of esters, ethers and acetals the reader is referred to earlier reviews,[4] since those are not discussed in this summary. Syntheses of carbohydrate based scaffolds,[5] although their preparation requires very similar know-how, are not discussed in this review unless they are using orthogonal protecting groups.

The artificial classification of this summary is based on the number of protecting groups involved in the examined set. In most studies, there are no more than two temporary protecting groups involved and these studies are further classified according to their respective purpose. A significant number of the published studies contain the development of synthetic methodologies, e.g. the introduction of new protecting groups and/or the investigation of their chemoselective cleavage (Table 1). We have included such studies in the Tables, although in many cases the orthogonality of the protecting groups used was not demonstrated.

In the second group of cases, two orthogonal protecting groups, which were already established and their orthogonality proven in previous studies, were used to synthesize the target compounds. These results including the target of the study are listed in Table 2. There are rare cases when next to the use of two orthogonal protecting groups for hydroxyl functions, one or two amino protecting groups were used. These studies are shown in Table 3.

Studies applying more than two orthogonal hydroxyl protecting groups are listed in Table 4. In most cases, three or four temporary protecting groups were used; in one example, five orthogonal protecting groups could be found but no examples for more than that. It is hard to imagine a realistic synthetic target where more than five orthogonal (or even 'only' temporary) protecting groups would be required to complete the synthesis.

2. Two orthogonal protecting groups

2.1 At least one of them is either newly developed or has not been used before in carbohydrate chemistry

Most of these studies focus on the development of a new protecting group or applying one that has not been used in carbohydrate chemistry before. In some cases, the orthogonality of the protecting groups is not demonstrated, just the chemoselective removal of the newly introduced one. We have added comments highlighting this fact, although in most of the cases the orthogonality of the protecting groups is obvious for a person skilled in the art or independently demonstrated elsewhere. The collection of the studies discussed in this part is summarized in Table 1.

p-Chloro and *p*-bromobenzyl ethers as temporary protecting groups were introduced in 2000.[6] Selective deprotection of these ether groups in the presence of silyl ethers, and acetyl, benzoyl and pivaloyl esters was demonstrated. The halobenzyl ethers are cleaved in an iterative fashion first by Pd-catalyzed amination followed by treatment with a Lewis or protic acid (Scheme 1).[6]

The 2-(allyloxy)phenylacetylester (APAC) was developed as a temporary protecting group in 2001.[7] It is removed by relay deprotection whereby the phenolic allyl ether is cleaved by treatment with a palladium catalyst followed by intramolecular lactone formation with the liberated hydroxyl group (Scheme 2). The conditions used for the deprotection of the APAC ester are tolerated by acetate and levulinate esters. Based on this principle (remote deprotection plus assisted cleavage) a number of other protecting groups were developed.

2.1.1 Remote deprotection (assisted cleavage)

The principle of remote deprotection is depicted below with these protecting groups being always ester-type groups. A masked or protected nucleophile is placed in a distance of 3 or 4 carbon atoms from the carbonyl group of the ester linkage (Fig. 1). The nucleophile is then unmasked and the resulting 'free' nucleophile attacks the carbonyl of the ester function. The driving force of the deprotection is the favored five- or six-membered ring formation resulting in a lactam or lactone depending on the nucleophile.

(4-Azidomethyl)benzoyl (AZMB),[8] (4-azidomethyl)phenylacetyl (AMPA)[9] and 2-nitrophenylacetyl (NPAc)[10] as new, reductively cleavable protecting groups were also developed for the protection of hydroxyl groups in carbohydrate chemistry (Scheme 3). The AZMB protecting group was cleaved under Staudinger conditions and the compatibility of the method was tested with traditional temporary protecting groups. Thus, AZMB was found to be orthogonal to the Lev-, All-, PMB- and TIPS-groups. With AZMB, a linear H-type II pentasaccharide was synthesized using a linear glycosylation strategy. The AMPA group is cleaved after reduction of the azido function in the presence of acetal protecting groups. The Lindlar catalyst was used for the reduction, resulting in mild conditions under which no cleavage of benzyl-, acyl-, acetal- and ketal-type protecting groups was observed. Although the orthogonality of AMPA with commonly used protecting groups was not demonstrated, it seems obvious that these groups are most likely orthogonal with AMPA. The NPAc protecting group was introduced in 2010 and cleaved after reduction of the nitro function. The NPAc group was found to be orthogonal with benzoate, chloroacetate and levulinate esters, Fmoc carbonates, TBDMS and NAP ethers. During the deprotection the Zn(II) complex, of the corresponding (2-aminophenyl)acetic acid is most likely formed, not the cyclic lactam.