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Minireview

Common side reactions of the glycosyl donor in chemical glycosylation

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ABSTRACT

Chemical glycosylation is central to carbohydrate chemistry and is generally recognised as a challenging reaction. This review describes the most reoccurring side reactions of glycosyl donors in glycosylation and how scientists have attempted to explain their observations and in some cases succeeded in solving a particular encountered problem. The topics covered are donor hydrolysis, elimination to form glycals, intermolecular aglycon transfer of thioglycosides and glycosyl imidate rearrangement.

1. Introduction

At first sight a glycosylation reaction doesn't look too complex. A glycosyl donor is reacted with a glycosyl acceptor in the presence of a promoter. However, everyone with experience in carbohydrate chemistry and oligosaccharide synthesis knows that each glycosylation is a unique reaction that has to be optimized individually and often the first attempt leaves the experimentalist with a bar code of spots on the TLC plate. As for all chemical reactions, the type of reagents, their concentration as well as order and way of addition, solvent, temperature, etc. will affect the outcome. For glycosylations, also the abundant and variant nature of protecting groups on both glycosyl donor and acceptor will play a major role, making it even harder to predict the result. Usually (as would be expected) the focus is on the target glycosides both considering yield and stereochemical outcome and a large number of reviews summing up the features of glycosyl donors and their effective activation by variant promoters to give glycosides exist. However, there are hardly any reviews on by-products found in glycosylation reactions although, as mentioned, they are frequently formed. This information can be difficult to find since only the successful experiments are reported and, especially in multistep synthesis, there is no time to take a closer look at the by-products.

We have for a longer time been interested in trying to compile reports of by-products in glycosylation reactions into a review, considering that the knowledge of the nature of by-products and the conditions and mechanism of their formation as well as prevention would be most important information for optimisation of glycosylation reactions. In this review we have focused on major by-products, frequently referenced to in the literature, including both general ones found for all types of glycosyl donors, i.e. hydrolysis and elimination, and also by-products specific for certain types of donors: by-products resulting from aglycon transfer reactions when using thioglycoside acceptors in orthogonal glycosylations and rearranged thichloroacetimidate donors. This review

Abbreviations: 5AcNeu, 5-acetylneuraminic acid; Boc, *tert*-butoxycarbonyl; Cbz, benzyloxycarbonyl; Cp, cyclopentadienyl; DIPEA, diisopropylethyl amine; ClBn, 4-chlorobenzyl; DMDO, dimethyldioxirane; DMP, 2,6-dimethylphenyl; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; Fmoc, 9-fluorenylmethoxycarbonyl; LG, leaving group; MP, 4-methoxyphenyl; MS, molecular sieves; MSB, methyl sulfenyl bromide; NAP, 2-naphthylmethyl; NIS, N-iodosuccinimide; NMM, N-methylmorpholine; Tol, *ortho*-tolyl; PG, protecting group; PMB, *para*-methoxybenzyl; ROMP, ring opening metathesis polymerisation; TBAB, tetrabutylammonium bromide; TBAI, tetrabutylammonium iodide; TBDPS, *tert*-butyldimethylsilyl; $TBPA^{+}$, tris(4-bromophenyl) ammonium hexachloroantimonate; TBS, *tert*-butyldimethylsilyl; TCA, trichloroacetyl; Tf, triflyl; TFA, trifluoroacetyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSE, 2-(trimethyl-silyl)ethyl; TMU, tetramethylurea; Troc, trichloroethoxycarbonyl.

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does not cover all thinkable and known glycosylation side reactions and major topics like 1,6-anhydro formation, acyl transfer, orthoester formation for donors with a 2-O-participating group and more infrequently reported by-products that require a certain promoter, solvent or protecting group scheme will be covered in a later review. Our hope is that this compilation of published results on glycosylation side reactions will be an easily accessible source of information to identify obtained by-products and finding ways on how to avoid them.

2. Donor hydrolysis

An extremely common side reaction observed in glycosylation reactions is hydrolysis of the donor to the corresponding hemiacetal (for selected examples see ref. [1–25]). Given the large number of reported cases of this common by-product, it falls outside the scope of this review to comprehensively cover all literature examples. Moreover, this lactol by-product is observed so frequently during glycosylations that it is reasonable to assume that chemists not always isolate, characterise, quantify and report this. Additionally, it might be problematic to properly monitor this by-product due to possible donor hydrolysis on the TLC-plates during elution.[18]

During glycosylation, the hydrolysis is a result of the reaction between the activated donor and water present in the reaction mixture, either from moisture present in the solvent or atmosphere or from water generated during the glycosylation reaction, e.g. when employing Koenigs-Knorr[26] conditions with Ag_2O or Ag_2CO_3 promoters. The unfavourable hydrolysis of the donor can in most cases be diminished significantly by carefully performing the glycosylation reaction under anhydrous conditions. Commonly, chemists rigorously flame dry the reaction vessel and use solvents dried either by distillation from a solution containing a water scavenging reagent,[27,28] or from a solvent purification system, where the solvent has been dried by passing through a column of alumina. Furthermore, chemists often also dry out the donor/acceptor mixture prior to activation by removing traces of water through several azeotropic evaporations with toluene. Lastly, the addition of desiccants to the reaction mixture is part of many carbohydrate chemists' standard protocol.

Of the desiccants used for in situ drying are $CaSO_4$,[29] drierite[30] and zeolite molecular sieves (MS).[31] Regarding the latter, both powdered and non-powdered MS and both 3 Å and 4 Å are commonly used.[28]

The book 'Handbook of chemical glycosylation' edited by Demchenko,[32] gives typical experimental procedures for glycosylation conditions using specific glycosyl donor types (Table 1). It can be observed that glycosylation reactions in general are carried out both with or without the addition of MS, and no consistent trend is obvious. In some cases the donor or both the donor and the acceptor are pre-stirred with MS prior to activation. Additionally, we assume most procedures in Table 1 not mentioning the addition of MS still might function in their presence, and furthermore we assume that procedures utilizing MS also might function without their presence if anhydrous conditions are employed. To the best of our knowledge the kinetics of water scavenging by MS has not been rigorously investigated, and we speculate whether it is possible for the MS to make a difference in the cases, where the glycosylation reaction is very fast. Recently, Williams and Lawton[33] have investigated the drying of several organic solvents with different drying agents using colorimetric Karl Fischer titrations in order to obtain 'super dry solvents' with residual moisture in the sub-10 ppm range, but ordinarily carbohydrate synthetic chemists tend not to go to this length or even use a glovebox for the reaction setup. Nonetheless, there are several cases where beneficial effects of the use of MS have been reported.[13,16,34,35]

Table 1
Typical experimental procedures given for glycosylation reactions as listed in 'Handbook of chemical glycosylation'[32]

Entry	Donor-type	Promoter	MS	Author
1	Fluorides	$SnCl_2$–$AgClO_4$	4 Å MS	Shoda[36]
2		$SnCl_2$-$TrClO_4$	4 Å MS	
3		Cp_2ZrCl_2–$AgClO_4$	4 Å MS (pdw)	
4		SiF_4	—	
5		TfOH	5 Å MS	
6	Iodides	TBAI/DIPEA	4 Å MS	Kulkarni and Gervay-Hague[36]
7	Acetates	$SnCl_4$	—	Ryan and Gin[37]
8		TMSI/Ph_3PO	5 Å MS[a]	
9	Trichloroacetimidates	TMS-OTf	—	Zhu and Schmidt[38]
10	N-Phenyl trifluoroacetimidates	TMS-OTf	4 Å MS	Zhu and Schmidt[38]
11	Vinyl	TMS-OTf	4 Å MS[a]	Kim and Jeon[37]
12	*n*-Pentenyl	NIS/TESOTf	—	Kim and Jeon[37]
13		IDCP	4 Å MS	
14	2′-Carboxybenzyl	Tf_2O/DTBMP	4 Å MS[a]	Kim and Jeon[37]
15	Thioglycosides	Ph_2SO/Tf_2O	—	Zhong and Boons[39]
16		BSP/TTBP/Tf_2O	3 Å MS (pdw)	
17	Sialyl thioglycosides	NIS/TfOH	3 Å MS (pdw)	Zhong and Boons[39]
18	Sulfoxides	Tf_2O/TTBP	4 Å MS (pdw)	Crich and Bowers[40]
19	Xanthates	DMTST	4 Å MS (pdw)[a]	Szeja and Grynkiewicz[41]
20		$Cu(OTf)_2$	4 Å MS (pdw)[a]	
21		AgOTf/DTBP	4 Å MS (pdw)[a]	

pdw: powdered MS.
[a] Donor or both donor and acceptor are prestirred/premixed with MS 15–90 min prior to addition of promoter.

A side effect of the use of zeolite sieves can be their alkaline nature[42,43] requiring the addition of higher amounts of Brønsted/Lewis acid promoter to achieve full donor activation. Noteworthy is the study reported by Yamada and co-workers,[44] in which a successful activation of a glycosyl fluoride donor with $SnCl_2$–$AgB(C_6F_5)_4$ could only be obtained in absence of MS or in the presence of acidic 5 Å MS,[45] affording approximately 80% yield of the glycoside product. Interestingly, no reaction occurred in the presence of basic 3 Å and 4 Å MS. Another study by Shen and co-workers[46] reports that the addition of 3 Å MS completely inhibited the glycosylation employing 1-OH donors under Tf_2O mediated direct dehydrative conditions.

The hydrolysed donor might give rise to other types of by-products as the 1-OH can function as acceptor for another donor, which subsequently will lead to a trehalose type 1,1′-linked derivative (e.g., Refs. 5,8,16–19,22,23,47,48). As an example, Bundle and co-workers[16] reported in 1981 the synthesis of the disaccharide **1** from the glycosyl bromide **2**β and rhamnoside acceptor **3**. A yield of 90% was obtained when the reaction was conducted at room temperature in the presence of 4 Å MS (Scheme 1A). In the absence of MS, the yield of **1** was reduced to 60% and the purification was complicated due to the formation of a by-product, thought to be the 1,1′-dimer **4** (Scheme 1B) originating from hydrolysis of the glycosyl bromide donor **2**β, which then further reacted with **2**β to afford the trehalose type disaccharide **4**.

Another possible side reaction originating from donor hydrolysis is intermolecular transacetylation, which has been reported by Jeanloz and co-workers during the glycosylation between donor **5** and acceptor **6** to afford disaccharide **7** (Scheme 2).[15] It was speculated that the 1-O-acetyl compound **8** originated from hydrolysis of donor **5** followed by acetyl transfer. By analogy, transacylation to the free hydroxyl function on the glycosyl acceptor is a common side-reaction, which will be covered in a later review.