Carbohydrate Research 413 (2015) 123–128

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Direct aqueous synthesis of non-protected glycosyl sulfoxides; weak inhibitory activity against glycosidases

Stewart R. Alexander [a], Andrew J.A. Watson [a], Antony J. Fairbanks [a, b, *]

[a] Department of Chemistry, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand
[b] Biomolecular Interaction Centre, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand

ARTICLE INFO

Article history:
Received 29 May 2015
Accepted 4 June 2015
Available online 14 June 2015

Keywords:
Glycosyl sulfoxide
Thioglycoside
Oxidation
Biomimetic catalysis
Glycosidase inhibition

ABSTRACT

A flavinium catalyst, in conjunction with hydrogen peroxide as stoichiometric oxidant, allowed the aqueous conversion of non-protected thioglycosides into the corresponding glycosyl sulfoxides. These glycosyl sulfoxides displayed only very weak inhibitory activity against corresponding glycosidases.

1. Introduction

Glycosyl sulfoxides, first introduced by Kahne and co-workers,[1] have found significant utility as highly reactive glycosyl donors. In particular they have been used to perform glycosylation reactions with large or unreactive glycosyl acceptors in cases where other donors had failed.[2–4] Typically they are produced by oxidation of the corresponding thioglycoside with *meta*-chloroperoxybenzoic acid (*m*-CPBA), although this reagent does suffer from limitations, including a propensity to cause over-oxidation to the sulfone, and also the formation of by-products that are difficult to remove. Other strategies that have been developed to circumvent the use of *m*-CPBA may also result in the formation of undesired by-products,[5] use equally difficult to work with reagents,[6–8] or complex procedures.[9] The development of a catalytic procedure that can effect the clean conversion of thioglycosides into the corresponding glycosyl sulfoxides would be advantageous, particularly if a low cost and easy to handle 'green' stoichiometric oxidant, such as hydrogen peroxide,[10–15] could be used.

Besides their utility as glycosyl donors, glycosyl sulfoxides may be interesting synthetic targets for a variety of other reasons. Electrostatic interactions play an important part of the binding of glycosidase inhibitors[16] to carboxylate residues in the enzyme active site. In this respect, whilst it has been known for a long time that the positive charge of protonated imino sugars is important for their inhibitory activity, more recently sulfonium ions, such as salacinol,[17] together with an increasing number of other zwitterionic species in which sulfur or selenium[18] bears a positive charge,[19,20] have also been demonstrated to act as potent inhibitors of glycosidases.[21] Since the anomeric sulfur atom of a glycosyl sulfoxide bears a partial positive charge, one may analogously postulate that a glycosyl sulfoxide could possess electrostatic features[22] that may favour binding to the active site of a glycosidase. In this vein, the sulfoxides of several thiosugars[23,24] have been reported to display weak activity against glycosidases, and the two previous reports[25,26] on the inhibitory activity of glycosyl sulfoxides also indicated inhibitory activity at the millimolar level. In this paper, we report the development of a catalytic aqueous oxidation procedure for the conversion of un-protected thioglycosides to their corresponding glycosyl sulfoxides using hydrogen peroxide as the stoichiometric oxidant. Also reported are the activities of some glycosyl sulfoxides against corresponding glycosidases.

2. Results and discussion

2.1. Investigation of catalysis

There has been considerable recent interest in the development of flavin and flavinium species[27] as biomimetic catalysts, which, in conjunction with hydrogen peroxide or oxygen, may be used for a

* Corresponding author.
E-mail address: antony.fairbanks@canterbury.ac.nz (A.J. Fairbanks).

http://dx.doi.org/10.1016/j.carres.2015.06.003
0008-6215/

variety of chemoselective oxidation processes,[28–32] including the oxidation of thioethers to sulfoxides.[33–37] It was reasoned that flavin-based systems might prove useful for the conversion of thioglycosides into glycosyl sulfoxides and provide an effective and useful alternative to existing procedures.

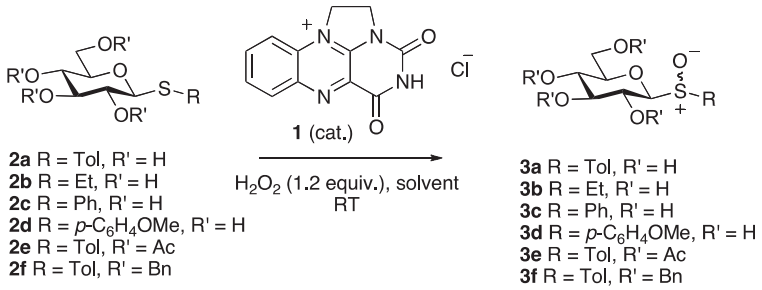
Flavinium salt **1** was selected as a candidate catalyst, and was synthesised as previously reported.[38] A variety of known thioglycosides **2a**–**f**, **4a**,[39] **5a**[40] and **6a**[41] were also synthesised as substrates for oxidation. Although thioglycosides can be made in one step from the reducing sugars in water, using the methodology of Shoda,[42] the current procedure is not completely stereoselective, and separation of the mixture of anomers of completely de-protected thioglycosides proved to be extremely problematic. Therefore, for the current study conventional literature routes, starting from the corresponding per-acetylated sugar, were used to access these substrates.

Un-protected tolyl thioglycoside **2a**[43,44] was selected as an initial substrate for a study into the efficacy of the catalytic oxidation process. Unfortunately the low aqueous solubility of **2a** precluded the use of water as solvent. However, reaction of **2a** in methanol with 1.2 equiv of H_2O_2 as stoichiometric oxidant, in the presence 1.8% of catalyst **1**, at room temperature for 6 h resulted in 78% conversion to the corresponding glycosyl sulfoxide **3a** (Table 1, entry 1); no over-oxidation to the glycosyl sulfone was observed. The use of MeCN as an alternative solvent resulted in the formation of a mixture of products, so that assessment of reaction efficiency was difficult (Table 1, entry 2). A study into the effect of catalyst loading indicated that conversion was more efficient when using 5% catalyst (Table 1 entry 3), though the use of a considerably higher catalyst loading did not significantly increase the conversion (Table 1, entry 4). A catalyst loading of 5% was therefore used in all subsequent experiments.

The reaction was then applied to other thioglycosides. Ethyl thioglycoside **2b**[45] was converted into sulfoxide **3b** with 93% conversion in MeOH. However, as **2b** was aqueous soluble, water was assessed also as the reaction solvent. Pleasingly conversion of **2b** into **3b** in water was complete; no residual starting material could be observed by NMR. It therefore appeared that water was an appropriate solvent for this particular catalytic oxidation process. Extension of the oxidation process to the aryl thioglycosides **2c**[46,47] and **2d**,[42,48] the solubility properties of which required the use of MeOH as reaction solvent, did not result in any improvement in synthetic efficiency. The process was also found to be considerably less efficient using protected thioglycosides **2e**[27] and **2f**[49] as substrates; in these two cases solubility properties necessitated the use of MeCN as solvent. In all of these cases, the low conversion simply reflected the persistence of unreacted starting material, rather than substrate degradation, the formation of other products, or any issues of low substrate solubility.

Catalyst **1** would therefore appear to be effective in conjunction with H_2O_2 for production of completely de-protected glycosyl sulfoxides, using water as the reaction solvent. A control reaction of oxidation of ethyl thioglycoside **2b** in water with hydrogen peroxide in the absence of catalyst **1** did not result in the formation of any sulfoxide, confirming the essential role of the catalyst (Table 1, entry 7). The reaction was subsequently applied to the *gluco* **2b**,[45] *manno* **4a**,[39] and *galacto* **5a**[40] ethyl thioglycosides, and in all cases the corresponding glycosyl sulfoxides **3b**, **4b** and **5b** were produced with complete conversion of the starting material, and in good to moderate yields[50] (Scheme 1). The *gluco* **3b** and *galacto* **5b** ethyl glycosyl sulfoxides were obtained as mixtures of diastereoisomers, whilst in contrast the *manno* ethyl glycosyl sulfoxide **4b** was obtained as a single diastereoisomer, tentatively assigned as the (R_S)-isomer on the basis of previous glycosyl sulfoxide syntheses.[51,52] Additionally the reaction was found to be equally applicable to a disaccharide; the *lacto* ethyl thioglycoside **6a**[41] was converted into the corresponding glycosyl sulfoxide **6b**, as a 1:1 mixture of diastereoisomers, under identical conditions. Additionally in this latter case the use of other solvents, such as MeOH, was not possible due to the limited solubility of the non-protected disaccharide.

Table 1
Oxidation of *gluco* thioglycosides to glycosyl sulfoxides



Entry[a]	Substrate	Product	Solvent	Catalyst loading (%)	Conversion[b] (%)
1	**2a**	**3a**	MeOH	1.8	78
2	**2a**	**3a**	MeCN	1.8	Not clean
3	**2a**	**3a**	MeOH	5	87
4	**2a**	**3a**	MeOH	20	92
5	**2b**	**3b**	MeOH	5	93
6	**2b**	**3b**	H_2O	5	**>99**
7	**2b**	**3b**	H_2O	**0**	**0**
8	**2c**	**3c**	MeOH	5	30
9	**2d**	**3d**	MeOH	5	64
10	**2e**	**3e**	MeCN	5	30
11	**2f**	**3f**	MeCN	5	<10

[a] Reaction conditions were 6 h at rt with 1.2 equiv. of H_2O_2 as stoichiometric oxidant.
[b] Percentage assessed by ^1H NMR of the crude reaction mixture.