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The *S*-xanthenyl group: potential for application in the synthesis of thioglycosides

Robert A. Falconer*

Department of Pharmaceutical & Biological Chemistry, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK

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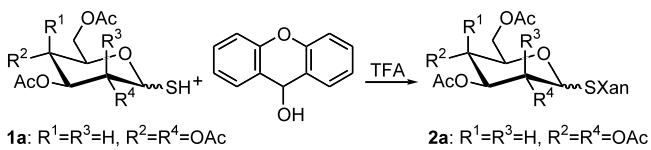
Abstract—The *S*-xanthenyl (Xan) group was demonstrated to have potential as a convenient protecting group for 1-thiosugars in the synthesis of thioglycosides. Easily introduced by reaction of a 1-thiosugar with 9-hydroxyxanthene in the presence of catalytic TFA, the *S*-Xan group is compatible with a wide range of functionalities and protecting groups.

Thioglycosides are key intermediates for oligosaccharide assembly[1] and are of importance in biological systems due to their increased chemical and enzymatic stability.[2] They are more stable to the action of glycosidases than their *O*-linked isosteres, making them candidates as enzyme inhibitors,[3] and are a potential means by which to facilitate the delivery of therapeutic peptides.[4]

The synthesis of complex thio-linked oligosaccharides and glycoconjugates demands a convenient orthogonal thiol-protecting group. This group should ideally be easily introduced and removed, and be able to withstand conditions commonly employed in the preparation of thioglycosides. In addition, the increasing importance of solid-phase methodologies in the synthesis of complex oligosaccharides and glycopeptides, means compatibility with conventional solid-phase synthesis protocols (e.g. Fmoc) would be a significant advantage.



1a: R^1=R^3=H, R^2=R^4=OAc
1b: R^1=R^4=OAc, R^2=R^3=H
1c: R^1=R^4=H, R^2=R^3=OAc

2a: R^1=R^3=H, R^2=R^4=OAc
2b: R^1=R^4=OAc, R^2=R^3=H
2c: R^1=R^4=H, R^2=R^3=OAc

Figure 1. Introduction of the *S*-xanthenyl group.

Protection of the thiol group is generally problematic in organic synthesis.[5] Many of the commonly used protecting groups suffer from the need for strongly basic conditions during introduction or strongly acidic, reductive or basic conditions during deprotection. Various thiol-protecting groups have been reported,[6] for example the 4-methoxytrityl (Mmt),[7] *tert*-butyl[8] and acetamidomethyl (Acm)[9] groups—all commonly used in solid-phase peptide chemistry. However, these protecting groups present some limitations. 1-Thiosugars have been protected using the acetate group, which presents difficulties in selective deprotection. Other candidates include the 9-fluorenylmethyl (Fm) group,[10] which requires basic conditions for its introduction, and the triphenylmethyl (Trt) group,[11] which requires strong acid for its removal. In addition, reactions to introduce both the Fm and Trt protecting groups were problematic and generally low yielding in our hands. There is therefore a need for new alternatives.

The recently reported *S*-9*H*-xanthen-9-yl (Xan) protecting group,[12] used as a temporary cysteine *S*-protecting group in the synthesis of α-conotoxin,[13] has been successfully applied here for thiol protection in thioglycoside synthesis. This represents a considerable improvement over existing options. It is easily introduced under mild conditions and can be selectively removed in the presence of a wide range of hydroxyl protecting groups. Another significant advantage is that it can be introduced cleanly in quantitative yield.[14]

The Xan group is conveniently introduced by reaction of the 1-thiosugar with 9-hydroxyxanthene, in the presence of a catalytic quantity of trifluoroacetic acid

* Tel.: +44-20-7753-5883; fax: +44-20-7753-5964; e-mail: robert.falconer@ulsop.ac.uk

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(TFA), in CH_2Cl_2 (Fig. 1). 1-Thiosugars (glucose **1a**, galactose **1b**, mannose **1c**) were synthesised from their respective bromosugars using the procedure described for glucose by Horton.[15] The reaction proceeds cleanly to completion within 1 h at room temperature and isolation of **2a**,[16] **2b** and **2c** requires only simple purification.

The *S*-Xan protected derivatives were found to be stable to a wide variety of reaction conditions, such as those required to introduce and remove various hydroxyl-protecting groups (Fig. 2). For example, treatment of **2a** with sodium methoxide in methanol led to the formation of the de-*O*-acetylated analogue **3a** in excellent yield, with no apparent removal of the *S*-Xan group. The reverse, base-catalysed acetylation was similarly high yielding. Benzylation (conversion of **3a** to **4a**), catalytic hydrogenation (**4a** to **3a**) and benzylidene acetal formation (**3a** to **6a**) were also successfully achieved in high yield without loss of the thiol protection.

Deprotection of the *S*-Xan group, in for example compound **2a**, was easily achieved using 2% TFA in CH_2Cl_2 to give the free thiol **1a** (Fig. 3) in essentially quantitative yield.[17]

Barany and co-workers originally used the *S*-Xan protecting group as a means by which to de-block cysteine thiol groups selectively in order to produce cyclic peptides linked via disulphide bridges.[13] Application of this compatibility with standard Fmoc solid-phase synthesis protocols has provided a potential means by which to anchor an orthogonally masked thiosugar onto a solid support.

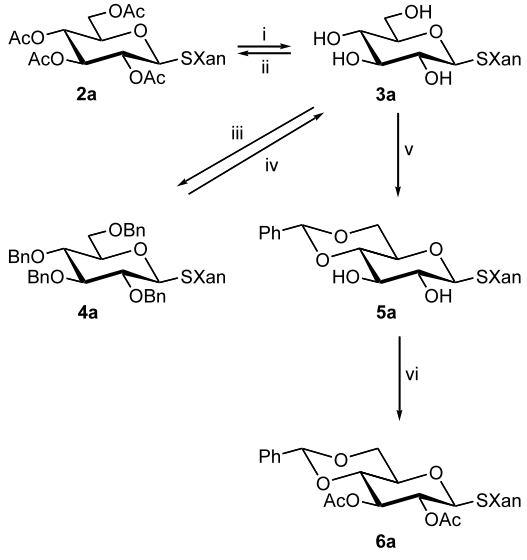

Figure 2. *Reagents and conditions*: (i) NaOMe, MeOH, rt, 91%; (ii) Ac_2O, pyr, rt, 93%; (iii) NaH, BnBr, DMF, rt, 74%; (iv) H_2, Pd/C, MeOH, rt, 79%; (v) HCOOH, PhCHO, rt, 92%; (vi) Ac_2O, pyr, rt, 89%.

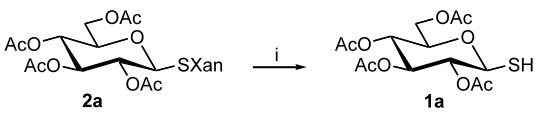

Figure 3. *Reagents and conditions*: (i) TFA:Et_3SiH:CH_2Cl_2, 2:1:97, rt, quant.

Glycopeptides in which the sugar component is linked via an unnatural linkage (e.g. thio-linked glycopeptides) have potential utility in therapeutic peptide and drug delivery. In previous work in our laboratory, a glycosyl azide was immobilised onto a solid support, allowing extension of the peptide chain via an *N*-linkage in a modified Staudinger reaction.[18] The versatility of the *S*-Xan protecting group is further demonstrated by the preparation of protected thioglycoside building blocks **9a–c** and **10a–c**, which were synthesised as a means by which to anchor the thiosugar to the solid support via the 6-OH (either directly or via a linker, depending on the nature of the derivatised resin being used). This would allow the extension of a peptide chain via a thioether linkage.

The *S*-Xan protected derivatives **2a–c** were de-*O*-acetylated under standard Zemplen conditions. The 6-OH was then protected with a *tert*-butyldimethylsilyl (TBDMS) group. Introduction of this group to mannose derivative **2c** proved facile, simply stirring the *S*-Xan protected derivative with TBDMS–Cl and imidazole in pyridine at room temperature to give **7c**. Introduction to glucose derivative **2a** (Fig. 4) and galactose derivative **2b** proved more problematic, requiring the use of triethylamine and DMAP while refluxing in 1,2-dichloroethane to give **7a** and **7b** in high yield. This is most likely to be due to the relative steric inaccessibility of the primary hydroxyl group in the glucose and galactose derivatives, where the *S*-Xan group is in the β-configuration, as opposed to the predominantly α-configuration of mannose.[19]

Following re-*O*-acetylation (**8a–c**), the TBDMS group was removed using tetra-butylammonium fluoride

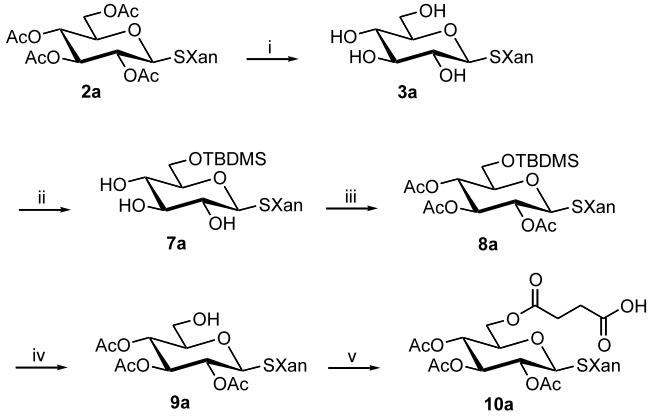

Figure 4. *Reagents and conditions*: (i) NaOMe, MeOH, rt, 91%; (ii) TBDMS–Cl, DMAP, Et_3N, $ClCH_2CH_2Cl$, reflux, 76%; (iii) Ac_2O, pyr, rt, 89%; (iv) TBAF, THF, rt, 93%; (v) succinic anhydride, DMAP, pyr, rt, 72%.

(TBAF) in THF to give **9a–c**, with no apparent loss of the *S*-Xan group.

Compounds **9a–c** can be directly anchored to a solid support via the free primary hydroxyl group, or alternatively attached through a linker bearing a free carboxyl group, such as that formed by reaction with succinic anhydride to give **10a–c**. Once immobilised, the *S*-Xan protection is easily removed providing a free thiol from which to synthesise glycopeptides through a thioether linkage.[20]

In conclusion, considering the relative lack of suitable temporary thiol-protecting groups of use in carbohydrate synthesis, the *S*-Xan protecting group has proved to be stable to a wide variety of conditions frequently employed in carbohydrate chemistry, such as acylation, de-acylation, alkylation, catalytic hydrogenation, acetal formation, silylation and de-silylation. In addition, it is compatible with standard solid-phase protocols and can be selectively cleaved in the presence of commonly used protecting groups while attached to the solid support.

It is introduced in quantitative yield under mild conditions and can be selectively removed in the presence of a range of other protecting groups. It is therefore extremely useful in the synthesis of thio-linked glycoconjugates.

Acknowledgements

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14. 2,3,4,6-Tetra-*O*-acetyl-1-thio-glucopyranose (1 g, 2.75 mmol) was stirred in 4% TFA in abs. CH_2Cl_2 (50 ml) for 15 min and then treated with 9-hydroxyxanthene (816 mg, 4.12 mmol). After 90 min at rt, the solution was concentrated, and the residue dissolved in CH_2Cl_2, (50 ml). The solution was washed with satd $NaHCO_3$ (2×25 ml), dried ($MgSO_4$) and concentrated. Column chromatography (hexane:ethyl acetate, 1:2 v/v) gave the pure product as an oil.
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16. ^{1}H NMR (500 MHz, assigned using 2D-COSY, $CDCl_3$) for **2a** (gluco): δ 1.84, 1.93, 1.98, 2.06 (4×s, 12×H, 4× OAc), 3.39 (m, 1×H, H-5), 3.85 (m, 1×H, H-6′), 4.14 (m, 1×H, H-6), 4.17 (d, 1×H, H-1, $J_{1,2}$=9.9 Hz, β), 4.91, 4.99–5.02 (2×m, 3×H, H-2, H-3, H-4), 5.54 (s, 1×H, CH), 7.10–7.14 (m, 4×H, ArH), 7.26–7.31 (m, 2×H, ArH), 7.35–7.40 (m, 2×H, ArH). FAB-MS for **2a** ($C_{27}H_{28}O_{10}S$) 544 *m*/*z* (%) 567 $[M+Na]^+$ (100), 677 $[M+Cs]^+$ (40).
17. *S*-Xan derivative **2a** (50 mg, 0.0919 mmol) was stirred in TFA:Et_3SiH:CH_2Cl_2 (2:1:97, 5 ml) for 60 min at room temperature. The solution was then concentrated and purified by column chromatography to give **1a**.
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19. ^{1}H NMR (400 MHz, assigned using 2D-COSY, $CDCl_3$) for **2c** (manno): δ 1.92, 1.99, 2.06, 2.08 (4×s, 12×H, 4×OAc), 4.07–4.16 (m, 3×H, H-5, H-6, H-6′), 5.03 (d, 1×H, H-1, $J_{1,2}$=1.5 Hz, α), 5.11–5.18 (m, 2×H, H-2, H-3), 5.22–5.28 (m, 1×H, H-4), 5.46 (s, 1×H, CH), 7.07–7.15 (m, 4×H, ArH), 7.25–7.32 (m, 2×H, ArH), 7.40–7.44 (m, 2×H, ArH).
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