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Efficient synthesis of thioglycosides via a Mitsunobu condensation

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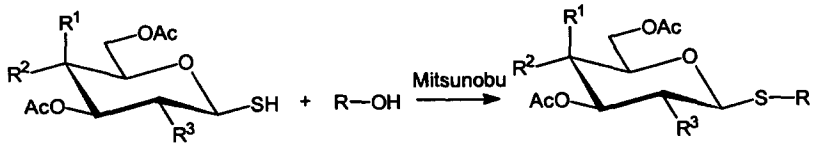
Abstract

Thioglycosides were synthesised from 1-thiosugars and a series of alcohols under Mitsunobu conditions using 1,1′-(azodicarbonyl)dipiperidine and trimethylphosphine. The conditions were found to be compatible with a wide range of functionalities and protecting groups.

Keywords: Mitsunobu reactions; thiosugars; glycosylation; glycolipids.

Thioglycosides are key intermediates for oligosaccharide synthesis and are of importance in biological systems due to their increased stability towards enzymatic degradation. There are several methods[1] to synthesise such compounds, for example, reaction of a sugar peracetate with a thiol under Lewis acid catalysis and the reaction of an acetylated glycosyl halide with a thiolate ion. Here, we report the facile synthesis of thioglycosides using a Mitsunobu condensation[2] (Scheme 1). The ability to react an alcohol directly with a thiosugar is a significant advantage, particularly in the assembly of glycoamino acids, thus avoiding the need to synthesise halide or thio-derivatives, which often require multiple steps resulting in unsatisfactory yields.



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

3a - j

Scheme 1. General reaction outline

The Mitsunobu reaction is a versatile procedure which has long been utilised to transform alcohols under mild conditions primarily to amines but also to esters, halogens and sulphides.[2,3] The original use

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Table 1
Thioglycoside synthesis under Mitsunobu conditions

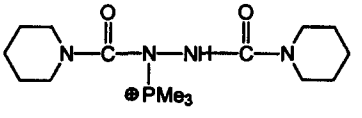
Entry	ThioSugar	Alcohol	Product	Yield[a] (%)
1	**1b**	CH_3OH	**3a**	85%
2	**1c**	CH_3CH_2OH	**3b**	73%
3	**1c**	$CH_3(CH_2)_7OH$	**3c**	61%
4	**1a**	$N_3(CH_2)_{20}OH$	**3d**	74%
5	**1a**	$AcS(CH_2)_{20}OH$	**3e**	63%
6	**1c**	$NC(CH_2)_2OH$	**3f**	79%
7	**1a**	BocHN—CH(CH$_2$OH)—COOMe	**3g**	66%
8	**1a**	BocHN—CH(CH(OH)CH$_3$)—COOMe	**3h**	40%
9	**1a**	BocHN—CH((CH$_2$)$_9$CH$_3$)—CH$_2$OH	**3i**	81%
	1b		**3j**	79%

[a] Isolated yield

of the combination of diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and triphenylphosphine frequently leads to an inability to separate the triphenylphosphine oxide by-product from the reaction mixture. In addition, it commonly co-elutes with the desired product on purification by column chromatography. It has been suggested that this is due to hydrogen bonding and hydrophobic effects.[4] Various methods have been devised to combat this problem, including the use of modified phosphines (e.g. 1,2-bis[diphenylphosphino]ethane)[5] as a substitute for triphenylphosphine, which has been used in approximately 90% of reported Mitsunobu reactions.[3] An alternative system, using 1,1′-(azodicarbonyl)dipiperidine[6] (ADDP) and trimethylphosphine represents a considerable improvement, since trimethylphosphine oxide can be removed from the reaction mixture on aqueous work-up.

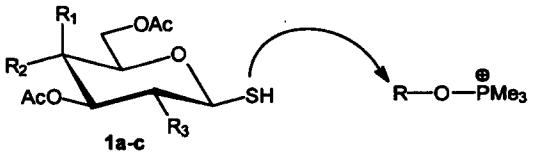
1-Thiosugars of fully acetylated glucose **1a**, galactose **1b** (both with β-configuration) and a Dde[7]-protected glucosamine **1c** (α/β mixture) were synthesised from their respective halosugars.[8] These were then coupled with a series of alcohols, including lipids, lipoamino alcohols[9] and hydroxy-amino acids with suitable protection, using THF as solvent (Table 1).

It is generally accepted that, initially, an ADDP/PMe_3 adduct **2** is formed.[10] The formation of this azaphosphonium salt can be easily monitored, as a yellow coloured solution becomes colourless over approximately 30 min. This was allowed to proceed in the absence of the alcohol and thiosugar to prevent nucleophilic addition of the thiol to ADDP.



2

On addition of the alcohol, an oxyphosphonium ion is formed, which then undergoes nucleophilic substitution by the thiol (Scheme 2).



Scheme 2.

Methyl- and ethyl-thioglycosides **3a** and **3b** (Table 2), common intermediates in oligosaccharide synthesis, were synthesised in very high yields. Compounds **3d**, **3e** and **3f** demonstrate that the mild conditions of the Mitsunobu reaction are compatible with a wide range of functionalities, including esters, thioesters, azides and isonitriles. Of significant importance in our laboratory was the ability to synthesise glycoamino acids **3g** and **3h** and novel glycolipids **3i**[11] and **3j**[12] in good yields without the need to synthesise halide derivatives of the alcohols. The yields of the serine and threonine derivatives were slightly lower than those obtained with the simpler alcohols, possibly due to their more hindered structures and in the case of threonine due to its secondary hydroxyl group. As expected with secondary alcohols, this reaction proceeded with complete Walden inversion.[3] The yields of the reactions to prepare glycolipids **3i** and **3j** proved more satisfactory in our hands than producing the tosyl-derivative of the lipoamino alcohol and reacting that with either the sugar thiol (in the presence of base) or the sugar thiolate. The products each inherited the sugar configuration of the respective starting 1-thiosugar.

In summary, we have demonstrated a facile procedure for preparing thioglycosides under mild conditions in high yields. The Mitsunobu reaction allows the one-step coupling of a 1-thiosugar and an alcohol, in the presence of a wide range of functionalities and protecting groups.

Table 2
Synthesised thioglycosides

	R	R^1	R^2	R^3
3a	CH_3-	OAc	H	OAc
3b	CH_3CH_2-	H	OAc	NHDde
3c	$CH_3(CH_2)_7$-	H	OAc	NHDde
3d	$N_3(CH_2)_{20}$-	H	OAc	OAc
3e	$AcS(CH_2)_{20}$-	H	OAc	OAc
3f	$NC(CH_2)_2$-	H	OAc	NHDde
3g	BocHN—CH(—CH_2)—COOMe	H	OAc	OAc
3h	BocHN—CH(—CH(—CH_3)—)—COOMe	H	OAc	OAc
3i	BocHN—CH(—$(CH_2)_9$—CH_3)—CH_2—	H	OAc	OAc
3j	BocHN—CH(—$(CH_2)_9$—CH_3)—CH_2—	OAc	H	OAc

1. General procedure

Trimethylphosphine (2 mmol of a 1.0 M solution in THF) was added to a solution of ADDP (2 mmol) in abs. THF (10 ml) at 0°C and stirred for 30 min. The alcohol (1 mmol) and the 1-thiosugar (1.3 mmol) were then added to the solution, with further stirring at room temperature for 2 h. Any precipitate was then filtered off and the solution evaporated to dryness. The residue was dissolved in ethyl acetate and the remaining hydrazide was precipitated from hexane and removed by filtration. Following evaporation, the residue was taken up in CH_2Cl_2 (50 ml), washed with water (2×25 ml) and with $NaHCO_3$ (sat. aq.) (25 ml), dried with $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography. The compounds were characterised by elemental analysis, mass and NMR spectroscopy.

Acknowledgements

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11. ^{1}H NMR (500 MHz, $CDCl_3$) for **3i** (gluco): δ 0.86 (t, 3H, CH_3), 1.24–1.39 (m, 18H, $9CH_2$), 1.43 (s, 9H, Boc CH_3), 1.99, 2.03, 2.05, 2.08 (4s, 12H, 4OAc), 2.73, 2.76 (2m, 2H, CH_2), 3.72 (m, 2H, αCH, H-5), 4.09–4.25 (2m, 2H, H-6, H-6′), 4.49 (d, 1H, H-1, $J_{1,2}$=10.1 Hz), 4.97–5.11 (m, 2H, H-3, H-4), 5.20 (t, 1H, H-2); ^{13}C NMR: δ 14.1, 20.6, 22.9, 25.9, 28.4, 29.4, 31.9, 33.8, 35.4, 36.7, 50.3, 62.1, 66.4, 69.9, 70.2, 73.9, 75.8, 76.5, 83.8, 84.8, 155.2, 169.4, 170.0, 170.2, 170.3; FAB-MS for **3i** ($C_{31}H_{53}O_{11}NS$) 647 *m/z* (%) 549 $[M–Boc+H]^+$ (48), 648 $[M+H]^+$ (40), 670 $[M+Na]^+$ (38).
12. ^{1}H NMR (500 MHz, $CDCl_3$) for **3j** (galacto): δ 0.86 (t, 3H, CH_3), 1.25–1.37 (m, 18H, $9CH_2$), 1.44 (s, 9H, Boc CH_3), 1.97, 2.03, 2.06, 2.15 (4s, 12H, 4OAc), 2.77, 2.86 (2m, 2H, CH_2), 3.51 (m, 1H, αCH), 3.95 (m, 1H, H-5), 4.11–4.19 (m, 2H, H-6, H-6′), 4.48 (d, 1H, H-1, $J_{1,2}$=9.6 Hz), 5.03, 5.20 (2t, 2H, H-2, H-3), 5.42 (t, 1H, H-4); ^{13}C NMR: δ 14.0, 20.5, 22.6, 25.9, 26.4, 29.5, 31.5, 33.4, 34.2, 35.3, 36.6, 49.9, 53.0, 61.2, 66.1, 67.3, 71.6, 74.4, 76.4, 84.1, 85.4, 155.3, 169.1, 169.6, 170.1, 170.2; FAB-MS for **3j** ($C_{31}H_{53}O_{11}NS$) 647 *m/z* (%) 548 $[M–Boc+H]^+$ (97), 648 $[M+H]^+$ (5), 670 $[M+Na]^+$ (20).