An Improved Procedure for Regioselective Acylation of Carbohydrates: Novel Enzymatic Acylation of α-D-Glucopyranose and Methyl α-D-Glucopyranoside

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6-*O*-Monoesters of α-D-glucopyranose and methyl α-D-glucopyranoside have been prepared with high yields through a novel enzymatic reaction using oxime esters as acyl transfer agents.

The potential of lipases as acylation catalysts in organic synthesis in non-aqueous media is currently of considerable interest.[1] The biocatalyst in organic solvents has been successfully applied in regioselective acylation of carbohydrates.[2] Various papers have recently been published on the preparation of 6-acylglucopyranoses[3] and 6-acylglucopyranosides[4] using lipases. Although lipase-catalysed acylation of carbohydrates is effective, these processes require the use of activated esters[3] or special reaction conditions.[4] Recent investigations report the use of oxime esters as irreversible acyl transfer agents where the leaving group, an oxime, does not participate in the back reaction.[5] Our interest in the development of an enzymatic method for the regioselective acylation of carbohydrates in mild conditions led us to examine the reaction of α-D-glucopyranose

Table 1 Compounds **3** prepared with Lipase Amano PS

Product	R	R^1	T/°C	Solvent	Yield (%)[a]	$[\alpha]_D^{25}$ (*c*, solvent)
3a	H	Me	25	pyridine	68	49.3 (0.56, H_2O)
3b	Me	Me	25	pyridine	76	169.2 (0.06, H_2O)
3c	H	$CH_3[CH_2]_2$	25	pyridine	72	47.0 (0.84, H_2O)
3d	Me	$CH_3[CH_2]_2$	25	pyridine	78	111.16 (1.24, H_2O)
3e	H	$CH_3[CH_2]_6$	40	pyridine	86	57.5 (0.30, DMSO)
	H	$CH_3[CH_2]_6$	40	3-methylpentan-3-ol	93	
3f	Me	$CH_3[CH_2]_6$	40	pyridine	88	76.6 (0.60, DMSO)
	Me	$CH_3[CH_2]_6$	40	3-methylpentan-3-ol	92	
3g	H	$CH_3[CH_2]_8$	40	pyridine	86	58.1 (0.27, DMSO)
	H	$CH_3[CH_2]_8$	40	3-methylpentan-3-ol	91	
3h	Me	$CH_3[CH_2]_8$	40	pyridine	94	89.7 (0.45, DMSO)
	Me	$CH_3[CH_2]_8$	40	3-methylpentan-3-ol	92	

[a] All products **3** were fully characterized by spectroscopic methods (IR, ^1H and ^{13}C NMR) and microanalysis.

and methyl α-D-glucopyranoside with oxime esters in presence of lipases.

After a preliminary screening to find the desirable enzyme and reaction conditions, we selected Lipase Amano PS,* and pyridine or 3-methylpentan-3-ol as solvents. To compare the reactivity of the different acylating agents and starting sugars all the reactions were carried out in similar experimental conditions (see Experimental and Table 1). Sugars **1** do not react with oxime esters in the absence of enzyme.

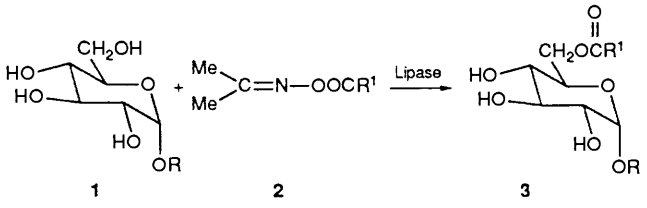
In contrast to other enzymatic acylation reactions, diacylation compounds were not detected. Moreover, the conversion found is higher than described by other groups on the enzymatic esterification of α-D-glucopyranose and methyl α-D-glucopyranoside.[3,4]

With C_8–C_{10} oxime esters the process can be carried out in less polar solvents. Thus, when diisopropylether is used the yields are less than 40%, however if 3-methylpentan-3-ol is employed, the acylated sugars **3** are obtained with yields greater than 90%. Presumably this is due to an improved solubility of the sugars carrying lipophilic groups in solvents less polar than pyridine.

In conclusion, the strategy described here provides an easy method of obtaining 6-*O*-acyl esters of α-D-glucopyranose and methyl α-D-glucopyranoside. Which, to the best of our knowledge, is an improvement on methods of acylation of these sugars. The important applications of fatty acid esters of carbohydrates in various fields are noteworthy.

Experimental

A typical procedure for the synthesis of acylglucopyranoses (Table 1: **3e**) is as follows: to α-D-glucopyranose (0.45 g, 25 mmol) in dry pyridine (10 ml), *O*-octanoyl acetoxime (0.65 g, 3.25 mmol) and lipase Amano PS (2 g) were added. After 3 d, the reaction was stopped, filtered and purified to yield 6-*O*-octanoyl-α-D-glucopyranose (0.66 g, 86%). δ_C(75 MHz; DMSO), 173.2, 92.6, 73.2, 72.5, 70.8, 69.43, 64.1, 33.8, 31.4, 28.7, 24.8, 22.4 and 14.2.



1 2 3

Scheme 1

For the acylglucopyranosides the method is the same. ^{13}C NMR data of 6-*O*-octanoyl-α-D-glucopyranoside (Table 1: **3f**), (75 MHz; DMSO), 173.1, 100.0, 73.5, 72.1, 70.7, 69.9, 63.9, 54.6, 33.8, 31.5, 28.7, 24.8, 22.4 and 14.2.

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References

1 See for example, A. M. Klibanov, *Trends in Biochem. Sci.*, 1989, **14**, 141; C-S. Chen and C. J. Sih, *Angew. Chem., Int. Ed. Eng.*, 1989, **28**, 695; A. M. Klibanov, *Acc. Chem. Res.*, 1990, **23**, 144.
2 P. Ciuffreda, D. Colombo, F. Roncheti and L. Toma, *J. Org. Chem.*, 1990, **55**, 4187.
3 M. Therisod and A. M. Klibanov, *J. Am. Chem. Soc.*, 1986, **108**, 5638; M. Therisod and A. M. Klibanov, *J. Am. Chem. Soc.*, 1987, **109**, 3977.
4 F. Björkling, S. E. Godtfrendsen and O. Kirk, *J. Chem. Soc., Chem. Commun.*, 1989, 934; K. Adelhorst, F. Börkling, S. E. Godtfredsen and O. Kirk, *Synthesis*, 1990, 112.
5 A. Ghogare and G. S. Kumar, *J. Chem. Soc., Chem. Commun.*, 1989, 1533; A. Goghare and G. S. Kumar, *J. Chem. Soc., Chem. Commun.*, 1990, 134.

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* An improved method for identification of enzymes developed by the Amano Pharmaceutical Co. has shown that the lipase Amano P from *Pseudomonas fluorenscens* is now more similar to lipase from *Pseudomonas cepacia*. For this reason it is convenient to change the trade name to lipase Amano PS.