Selective 1-O-Deacetylation of Carbohydrates Using Polymer-Bound Benzylamine

Richard Johnsson, Ulf Ellervik*

Organic Chemistry, Center for Chemistry and Chemical Engineering, Lund University, P.O. Box 124, 221 00 Lund, Sweden
Fax +46(46)2228209; E-mail: ulf.ellervik@organic.lu.se

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Abstract: A new method for highly effective and selective 1-O-deacetylation of peracetylated carbohydrates using polymer-bound amines is presented.

Key words: polymer-bound reagents, carbohydrates, deacetylation, regioselectivity, protective groups

Protected carbohydrates with a free anomeric hydroxyl group are versatile and important synthetic intermediates, useful for the synthesis of trichloroacetimidates,[1] glycosyl fluorides and iodides,[2] as well as for nucleophilic glycosylation.[3]

Common methods for anomeric deacetylation of peracetylated carbohydrate derivatives suffer from disadvantages, such as highly toxic reagents (e.g. hydrazine acetate[4]) or heavy metal salts [e.g. bis(tributyltin) oxide,[5] tributyltin methoxide,[6] or mercuric chloride/mercuric oxide[7]]. More environmentally friendly methods include benzylamine,[8] sodium methoxide,[9] ammonia,[10] ammonium carbonate,[11] piperidine,[12] Al_2O_3[13] or MgO.[14] Unfortunately, most techniques are accompanied with time-consuming purification steps.

In order to perform high-yielding anomeric deacetylation without the necessity of purification we decided to investigate the use of commercially available polymer-bound benzylamine (i.e. aminomethylated polystyrene resin).

Peracetylated glucose was used as a model system. The conversion into the hemiacetal was analyzed using NMR after two days reaction at ambient temperature in a variety of solvents (Table 1).

Table 1 Conversion of Peracetylated Glucose[a]

Solvent	Conversion (%)
N,*N*-Dimethylformamide	79
Tetrahydrofuran	76
Ethanol	70
Diethyl ether	67
Ethyl acetate	55
Toluene	51
Dioxane	47
Dichloromethane	22
Acetonitrile	4

[a] Reaction time: 44 h at 22 °C; conversion estimated by NMR.

The highest conversion was found in *N*,*N*-dimethylformamide and tetrahydrofuran followed by ethanol and diethyl ether. The conversion was also acceptable in ethyl acetate, toluene and dioxane. Dichloromethane and acetonitrile gave slow conversion. We decided to continue our experiments using the easily removed tetrahydrofuran as solvent. Initial experiments using different carbohydrates showed differences in the ease of anomeric deprotection; $Xyl(OAc)_4 > Glc(OAc)_5 > Gal(OAc)_5 > Lac(OAc)_8$.

However, even after two days reaction time the conversion of peracetylated glucose was far from completion, though increased temperature (75 °C in a sealed tube) gave 78% conversion. We reasoned that the incomplete reaction might result from poor diffusion due to charge buildup on the resin, and addition of three equivalents of triethylamine resulted in an excellent conversion of 96% in 18 hours (Table 2).

In order to verify the method we selected a number of peracetylated carbohydrates according to Table 3, which were subjected to the deacetylation conditions.[15]

The deacetylation of the peracetylated monosaccharides (entries 1–5) gave excellent conversion (90–96%) whereas the disaccharide lactose resulted in only 67% conversion. However, when the reaction was allowed to run for two days, the conversion increased to 88%. The more easily deprotected glucose was run at ambient temperature, which resulted in 79% conversion after two days, making this method suitable even for sensitive carbohydrates. 1,2,3,4,6-Penta-*O*-benzoyl-β-D-glucopyranose was tested under the same conditions but did not result in anomeric deprotection.

Table 2 The Conversion of Glucose at Different Reaction Conditions

Reaction conditions	Conversion (%)
44 h, 22 °C	76
44 h, 22 °C, Et_3N	79
18 h, 75 °C	78
18 h, 75 °C, Et_3N	96

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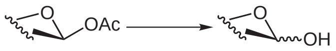
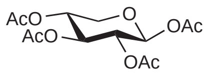
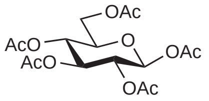
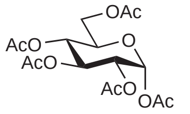
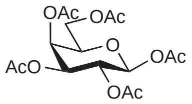
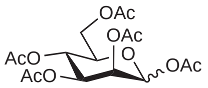
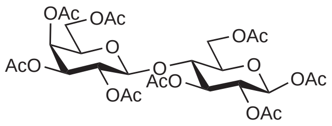
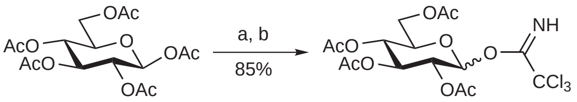
Table 3 Anomeric Deacetylation of Peracetylated Carbohydrates by Polymer-Bound Benzylamine[16]



Entry	Starting material	Conversion (%)[a]	α/β
1		96	5:3
2		96	3:1
3		96	2:1
4		90	5:2
5		95	1:0
6		88	4:3

[a] The reactions were run for 18 h (entries 1–5) or 44 h (entry 6), filtered and concentrated. The conversion was estimated by NMR.

To verify the usefulness of our method peracetylated glucose was deprotected and subsequently converted to the trichloroacetimidate by reaction with trichloroacetonitrile and DBU (Scheme 1).[17] 2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate was isolated in 85% yield, which is comparable to yields reported for synthesis from the hemiacetal.[18]



Scheme 1 Synthesis of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl trichloroacetimidate. *Reagents and conditions*: (a) aminomethylated polystyrene, Et_3N, THF; (b) Cl_3CCN, DBU, CH_2Cl_2.

To summarize, we have introduced a new method using polymer-bound amines for highly effective and selective 1-O-deacetylation of peracetylated carbohydrates without the need for subsequent purification.

Acknowledgment

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(15) **Representative Experimental Procedure.**
1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (11 mg, 0.028 mmol) and aminomethylated polystyrene resin (60 mg, 0.90 mmol/g) were mixed in THF (1 mL) in a sealed tube. Then, Et_3N (0.011 mL, 0.0078 mmol) was added and the mixture was heated to 75 °C for 18 h. The mixture was filtered with CH_2Cl_2 and concentrated from $CHCl_3$. NMR showed 96% product and 4% starting material.

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