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A new protection group strategy for cellulose in an ionic liquid: simultaneous protection of two sites to yield 2,6-di-*O*-substituted mono-*p*-methoxytrityl cellulose

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ABSTRACT

Increased reactivity of cellulose in ionic liquids was revealed when cellulose was protected with a 4-methoxytrityl moiety in the imidazolium-based ionic liquid, 1-allyl-3-methylimidazolium chloride ([amim]Cl). Selectively protected 2,6-di-*O*-(4-methoxytrityl)cellulose was obtained in one reaction step with a *DS* of close to 2, and was characterised by NMR.

Regioselectively substituted cellulose derivatives are of increasing interest due to their unique properties compared to those of statistically substituted analogues. These tailored derivatives can be used as components or additives in industrial products such as adhesives, films, membranes and fibres.[1] However, the poor solubility of cellulose in common organic solvents and water has held back the development of efficient uses for cellulose. Recently, it has been shown that ionic liquids can dissolve cellulose, and further provide an inert and homogeneous reaction media for this macromolecule.[2]

Selective modification of cellulose often requires the use of protecting group (PG) chemistry. The most commonly used method for the regioselective synthesis of cellulose derivatives employs the following synthetic strategy. First, a bulky protecting group (e.g., a trityl group) is selectively introduced at C-6, followed by chemical modification of the free C2–OH and C3–OH groups.[3] The final step is removal of the PG. This approach works well when synthesising 2,3-disubstituted cellulose derivatives.[1,4] However, when selective modification of only one of the secondary OH groups (either C2–OH or C3–OH) is desired, the above-mentioned strategy has to be changed in such a way that the introduced PG has to be attached not only at the C-6 position, but also at the C-2 position, leaving C3–OH available for further modification.[1,5] The reason for the successful protection only at C2–OH, additionally to C-6, is due to the reactivity differences between C2–OH and C3–OH, which is typically in the order of C2–OH > C3–OH,[6] and also, in this case, the choice of the PG is important. Herein, it is shown that the *p*-methoxytrityl group can be used as a PG, providing the reaction is carried out in an ionic liquid. The increased reactivity needed for extensive substitution of cellulose will also be discussed here. The reaction led to protection at both C-6 and C-2, in the imidazolium-based ionic liquid (IL), 1-allyl-3-methylimidazolium chloride ([amim]Cl), and gave a degree of substitution (*DS*) value of 1.8 (Scheme 1). The average molecular weight (M_w) and polydispersity of the cellulose derivative were investigated by size-exclusion chromatography (SEC) using chloroform as eluent at a flow rate of 0.4 mL min^{-1} at 24 °C. Injection volume was 10 μL and the concentration of the sample was 1 mg mL^{-1}. The SEC system was calibrated with polystyrene standards in the molecular weight range of 890–1.24 × 10^6 g mol^{-1}. In addition, deprotection of the tritylated derivative was studied using common organic solvents such as THF and CH_2Cl_2 as reaction media.

Interestingly, in a previous publication on the tritylation of cellulose with a *p*-methoxytrityl group, the *DS* did not exceed 1.3 even when the equivalency of the reagents was increased.[7] These reactions were carried out in DMA/LiCl solvent system. In the present study, for the highest possible *DS* (∼2), the ratio of the reagents was optimised to: 1 equiv of cellulose, 3 equiv of *p*-methoxytrityl chloride and 14 equiv of pyridine, the reaction time being 6 h with a reaction temperature of 60 °C.[8] Excess pyridine was used to

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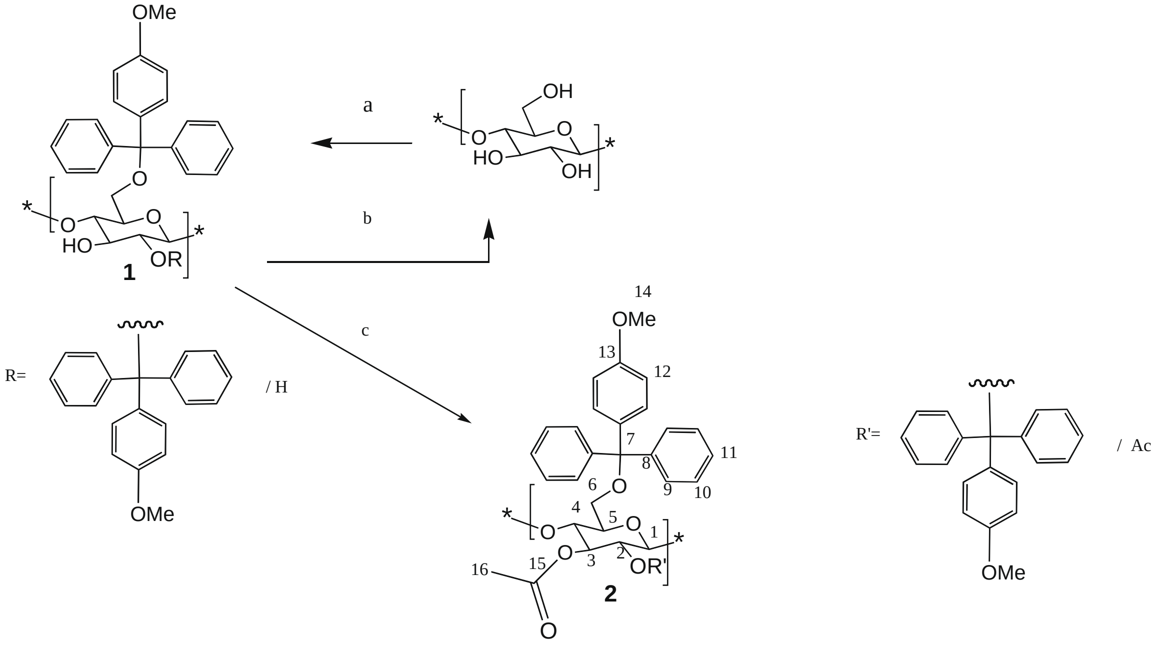

Scheme 1. General synthetic route: (a) 4-methoxytriphenylmethyl chloride, pyridine, [amim]Cl, (b) concd HCl, THF/Fe(III)Cl·$6H_2O$, CH_2Cl_2/1% I_2/MeOH, CH_2Cl_2, (c) acetic anhydride, pyridine, [amim]Cl.

dilute the fairly viscous reaction mixture. Tritylated derivatives were regenerated from the mixture of water and methanol (1:1). Further purification was achieved by continuous extraction with methanol. When the equivalency of the reagents was decreased from these values to 1:2.5:6 and 1:2:3, respectively, a lower *DS* (average of 0.8) was obtained in the former case, whereas in the latter case, the reaction gave an insoluble product, which according to IR showed limited substitution. Obviously, the solvents as well as the correct equivalency of reagents are determining factors for this particular reaction. The ionic liquid, [amim]Cl, clearly affects the reactivity of this reaction by increasing the accessibility of the C2–OH position. This can be speculated to result from two reasons. Firstly, the ionic liquid may enhance the solubility of the C-6 mono-tritylated cellulose and thereby increase the accessibility of the C2–OH reaction site, as it is the next reactive site on the cellulose unit. Furthermore, when considering the mechanism of the tritylation, which is S_N1-type, the carbocation formed from *p*-methoxytrityl chloride can be activated further by the ionic environment, and can promote the reaction at C-2. This activation effect is brought about by the released chloride anion which may be bound by the imidazolium cation in the ionic liquid leaving the charge on the carbocation 'naked' without any stabilisation brought about by ionic interactions between these two species.

The pattern of substitution was initially investigated with ^1H–^{13}C HMBC, despite several trials, we were unable to record a good quality HMBC spectrum due to the high molecular weight of the derivative. Therefore, 2D HSQC (Fig. 1) and NOESY (Fig. 2) experiments were utilised for structural characterisation. The HSQC experiment made the signal assignments possible for the anhydroglucose unit (AGU) of cellulose which correlated well with previously published assignments for 6-*O*-(4-methoxytrityl) cellulose.[9]

The substitution pattern of the acetylated and tritylated derivative **2** is evident from the NOESY spectrum as the NOE correlations from the aromatic region (6.6–7.4 ppm) to C-6 (4.2 ppm) and C-5 (4.8 ppm) indicate substitution at the C-6 position. Correlations from the aromatic region to C-2 (3.0 ppm) can also be seen, which confirm the substitution at C-2 (Fig. 2). Moreover, correlations between the aromatic and methoxy protons can be seen. In addition to the NOESY spectrum, the substitution pattern and the *DS* were also investigated using a known method for calculating the *DS* from the ^1H spectrum.[10] This was achieved by firstly detritylating **2**, followed by propionylation.[11]

Size-exclusion chromatography (SEC) with UV-detection was used to determine the molecular weight distribution (M_w) and the polydispersity (D) of the tritylated derivative **1** (Fig. 3). It should be noted that these values are only approximations as it is impossible to determine absolute values. The M_w of **1** was found to be approximately 82,200 g/mol, which is significantly larger than that reported for unmodified microcrystalline cellulose (MCC, M_w = 58,600 g/mol),[12] as well as for alkoxytritylated cellulose derivatives having *DS* values of almost 1 (M_w in the range from 54,000 to 62,200 g/mol).[13] Furthermore, the degree of polymerisation (*DP*) was determined to be around 126 for compound **1**, which is considerably higher than that determined for alkoxytritylated cellulose derivatives with *DP* values ranging from 69 to 79.[13] However, the *DP* is lower than that of unmodified MCC (*DP* = 361).[12] The polydispersity of compound **1** was 4.4. This is again in good agreement with the values reported for alkoxytritylated derivatives, which range from 3.2 to 4.4.[13] However, the majority of commercial MCCs have fairly low polydispersity in the order of 1.56.[12]

In cellulose chemistry, the trityl group has been used widely as a PG for the selective protection of the OH group at C-6.[6] However, it can be problematic to remove this group completely, especially from samples of tritylated cellulose with high *DP* values.[9] With cellulose, deprotection of the trityl moieties often results in low yields and formation of by-products, and may even cause glycosidic bond cleavage which arises when acid-catalysed detritylation is used.[14] The introduction of methoxy groups to trityl molecules at the *para*-position is known to increase the rate of hydrolysis by about one order of magnitude for each *p*-methoxy-substituent.[15] Therefore, cleavage of *p*-methoxy-substituted trityl groups is anticipated to be more facile than that of trityl groups. Moreover, there are other methods for deprotection of *p*-methoxy-substituted trityl groups, for example, using molten salt hydrates such as $LiClO_4·3H_2O$ and $ZnCl_2·4H_2O$.[16] This motivated us to investigate the

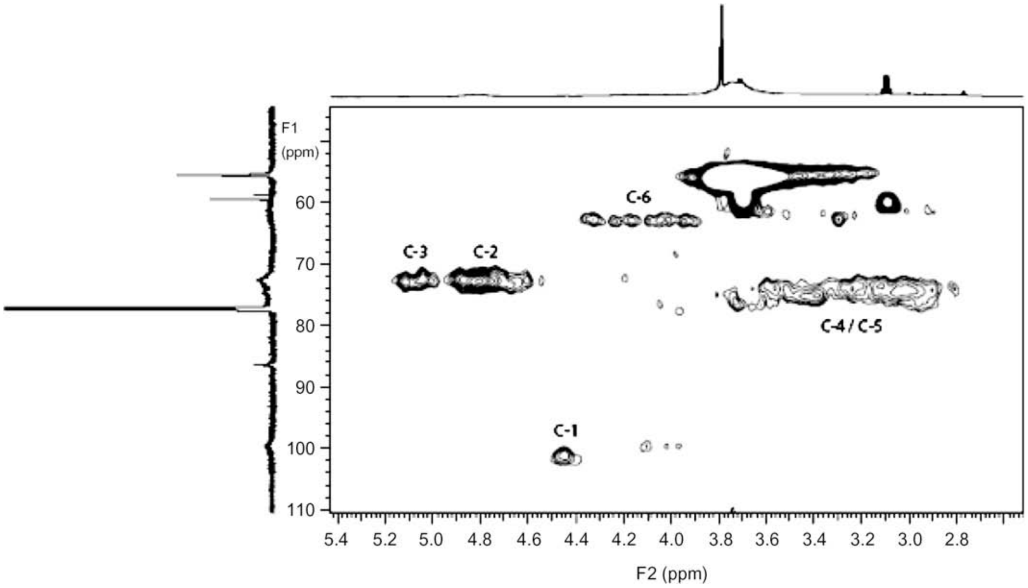

Figure 1. The ^{1}H NMR–^{13}C HSQC spectrum of 3-*O*-Ac-2,6-di-*O*-(4-methoxytrityl)cellulose **2** showing signal assignments for the cellulose anhydroglucose unit (AGU).

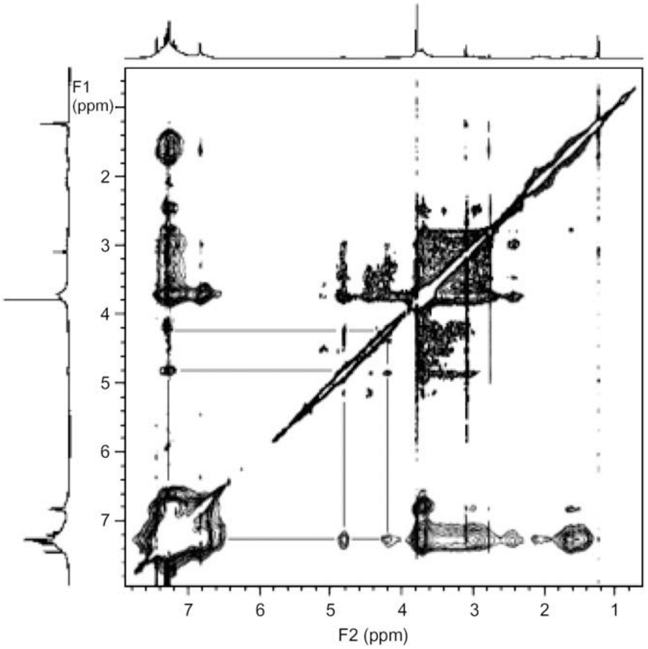

Figure 2. The NOESY spectrum of 3-*O*-Ac-2,6-di-*O*-(4-methoxytrityl)cellulose **2**. The lines indicate NOE correlations from the aromatic region (6.6–7.4 ppm) to C-6 (4.2 ppm) and C-5 (4.8 ppm) and also to C-2 (3.0 ppm).

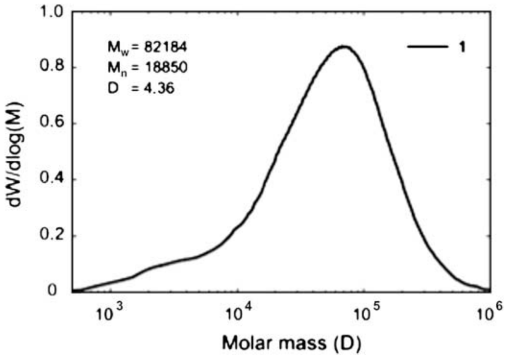

Figure 3. SEC chromatogram of tritylated derivative **1** showing the values for M_w, average molecular weight (M_n) and polydispersity (D).

deprotection of *p*-methoxy-tritylated cellulose using Lewis acids such as ferric chloride hexahydrate.

According to IR data, it was clear that deprotection of *p*-methoxy-tritylated cellulose was achieved completely with concd HCl,[17] ferric chloride hexahydrate[18] and 1% I_2/MeOH[19] solution. The yield (59%) of the reaction was fairly low when 1% I_2/MeOH was used as the deprotection agent compared to other deprotection agents used in this study. This is possibly due to the hydrolysis of cellulose under these reaction conditions based on two assumptions.[20] Hydrolysis may take place via electrophilic attack of iodine on the oxygen in the glycosidic bond and hence result in cleavage, or oxidation of methanol by iodine produces small amounts of HI, which in turn may cause hydrolysis of cellulose. It has been reported that in trityl group deprotection, the released trityl carbocation may undergo re-insertion.[21] It has been also shown that ferric chloride hexahydrate can prevent the re-insertion.[22] Here, ferric chloride hexahydrate acts as a Lewis acid forming adducts, most likely with the C-6 oxygen or trityl methoxy oxygen aiding release of the trityl group and also hindering re-insertion.[22] In the current case, the addition of ferric chloride hexahydrate had a dramatic effect on the reaction efficiency, improving the yield of the deprotection (100%) compared with other deprotection methods (i.e., concd HCl and 1% I_2/MeOH).

To conclude, we have been able to protect two reaction sites on cellulose simultaneously in one reaction step leaving one site available for further modification as demonstrated by carrying out acetylation at the C-3 position. It was shown that ionic liquids not only function as solvents for cellulose, but are also capable of increasing the reactivity. Additionally, new and efficient deprotection routes for tritylated cellulose were described. This protection group strategy greatly simplifies the synthesis of tailored cellulose derivatives.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.144.

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8. 4-Methoxytrityl chloride (6.2 g, 20 mmol) was dissolved in pyridine (5.0 mL, 60 mmol) and was added to a solution of cellulose (1.0 g, 6.2 mmol), dissolved in [amim]Cl (10.0 g) containing pyridine (2.5 mL, 30 mmol). The reaction mixture was stirred at 60 °C for 6 h, followed by precipitation of the crude product from a mixture of methanol and water (1:1). Yield: 1.1 g (27%); *DS* = 1.8 (determined by ^{1}H NMR using the propionylation method[11]).
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11. In order to determine the *DS* by ^{1}H NMR NMR, compound **2** was firstly detritylated using concd HCl in THF (yield: 85%, structure was confirmed by IR) as described for compound **1**,[17] and then propionylated according to Heinze et al.[10] (yield 92%, structure was confirmed by ^{1}H NMR). The *DS* was then calculated from the ^{1}H NMR NMR spectrum as described previously by Goodlett et al.[10b]: $DS = 3 - \frac{7 \times I_{\mathrm{Propyl}}}{3 \times I_{\mathrm{H,AGU}}}$.
I_{Propyl} = The integral of the chemical shift of the methyl protons of the propionoyl substituents, $I_{\mathrm{H,AGU}}$ = the integral of all the protons of anhydroglucose unit (AGU) of cellulose.
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17. Compound **1** (0.5 g, 0.77 mmol) was dissolved in THF (15.0 mL), and HCl (0.6 mL, concd) was added in three portions (3 × 0.2 mL) over 24 h. The reaction mixture was stirred at rt for 3 d, followed by work-up to give cellulose. Yield: 0.1 g (80%).IR (cm^{-1}): Identical to a commercial microcrystalline cellulose sample; 3340 (OH), 2910 (CH), 1100 (C–O).
18. Compound **1** (0.15 g, 0.23 mmol) was dissolved in CH_2Cl_2 (10.0 mL) and $FeCl_3{\cdot}6H_2O$ (0.2 g, 7.2×10^{-4} mol) was added in one portion. The reaction mixture was stirred at rt overnight, followed by work-up to give cellulose. Yield: 0.04 g (100%)IR (cm^{-1}): Identical to a commercial microcrystalline cellulose sample; 3340 (OH), 2910 (CH), 1100 (C–O).
19. 1% I_2/MeOH (2.0 mL) was added to a solution of **1** (0.14 g, 0.21 mmol) dissolved in CH_2Cl_2 (10.0 mL). The reaction mixture was stirred at rt overnight, followed by work-up to give cellulose. Yield: 0.02 g (59%).IR (cm^{-1}): Identical to a commercial microcrystalline cellulose sample; 3340 (OH), 2910 (CH), 1100 (C–O).
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