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$Cu(ClO_4)_2 \cdot 6H_2O$ catalyzed solvent free per-*O*-acetylation and sequential one-pot conversions of sugars to thioglycosides†

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The solvent free per-*O*-acetylation of various reducing and non-reducing sugars has been carried out using stoichiometric amounts of acetic anhydride and copper(II) perchlorate hexahydrate as the catalyst. The reactions with various reducing monosaccharides have also been followed by a one-pot sequential conversion to the corresponding thioglycosides in high yields.

Introduction

Per-*O*-acetylation is perhaps the most used primary protecting group reaction in carbohydrate synthesis. Its importance stems from the fact that the introduction of the acetyl protecting group can be carried out under a variety of conditions, the products are very stable under many reaction conditions and they can be used as glycosyl donors under Lewis acidic conditions. Again the acetate protecting group can be easily cleaved using catalytic amounts of NaOMe (Zemplen's method). They are also used routinely for their conversion to glycosyl halides and thioglycosides which have found widespread use as glycosyl donors, the latter particularly for iterative glycosylations.[1] The classical method for carrying out the per-*O*-acetylation reaction uses pyridine as the solvent as well as the base. Sometimes, to accelerate the reactions DMAP is also added.[2] However, several issues with this such as the use of a large excess of the toxic and foul smelling pyridine have led to the development of many improved catalytic methods. Among the various catalysts used for the conversion are (i) bases such as NaOAc,[3] NaOH/TBAB,[4] imidazole[5] and DABCO[6] (ii) protic acids such as H_2SO_4,[7] H_3BO_3/H_2SO_4 (ref. 8) and *p*-toluene sulfonic acid[9] (iii) Lewis acids such as $ZnCl_2$,[10] $FeCl_3$,[11] BF_3–Et_2O,[12] $Cu(OTf)_2$,[13] $Sc(OTf)_3$,[14] $In(OTf)_3$,[15] $Ce(OTf)_3$,[16] $LiClO_4$,[17] and $Fe_2(SO_4)_3$ (ref. 18) (iv) heterogeneous catalysts such as montmorillonite K-10,[19] H-β-zeolite,[20] Amberlyst-15,[21] H_2SO_4–SiO_2,[22] $HClO_4$–SiO_2,[23] molecular sieves,[24] Al_2O_3,[25] sulphonic acid fuctionalized γ-Al_2O_3 (ref. 26) and other catalysts such as I_2 (ref. 27) and *N*-bromosuccinimide.[28]

Although effective many of these methods suffer from a few limitations such as the use of large excess of acetic anhydride, use of volatile organic solvents (VOSs) and on many occasions the toxicity and high cost of the catalysts. Therefore effective catalysts that are economically more feasible, environmentally more sustainable and use stoichiometric amounts of acetic anhydride and avoids the use of VOSs are desirable. Towards this objective, we have explored a few cheap and easily available Cu^{2+} salts for carrying out the per-*O*-acetylation of free sugars and report that $Cu(ClO_4)_2 \cdot 6H_2O$ is a very effective catalyst for carrying out the desired reaction under solvent free conditions at room temperature using only stoichiometric amounts of Ac_2O. We have also followed up the solvent free, $Cu(ClO_4)_2 \cdot 6H_2O$ catalyzed per-*O*-acetylation of free reducing monosaccharides using stoichiometric Ac_2O with the sequential one pot thioglycosylation reaction using BF_3–Et_2O to generate the corresponding thioglycosides. The one-pot per-*O*-acetylation–thioglycosylation strategy for the synthesis of thiosugars has previously been employed with *p*-toluene sulfonic acid,[9] $Cu(OTf)_2$,[13] I_2,[27] and $SnCl_4$ (ref. 29) in conjunction with BF_3–Et_2O. However these methods suffer from the limitation that the catalysts are often very corrosive, have a very short shelf life and often are very costly.

Results and discussion

The preliminary experiments for the solvent free per-*O*-acetylation reaction was carried out using D-glucose (**1a**) and Ac_2O with a few commercially available hydrated Cu(II) salts (Table 1). The experiments with 10 mol% of $Cu(OAc)_2 \cdot H_2O$, $CuCl_2 \cdot 2H_2O$ and $Cu(NO_3)_2 \cdot 3H_2O$ using an excess of Ac_2O under solvent free conditions yielded very poor results. In each case the reactions were very slow and less than 50% of the per-*O*-acetylated product **2a** could be isolated after 6 days (entries 1–3, Table 1). The reaction using $CuSO_4 \cdot 5H_2O$ as catalyst at 10 mol% was slightly better but once again the reaction yielded only about 79% of **2a** after 3 days (entry 4, Table 1). In contrast to all the above, the reaction with 10 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$ afforded **2a** in quantitative yield after only 30 minutes (entry 5, Table 1). In an effort to lower the catalyst loading, the reaction was then

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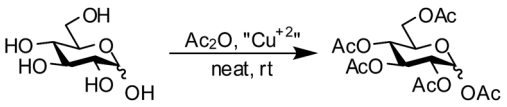
Table 1 Screening of various Cu^{2+} salts as catalysts for the per-*O*-acetylation reaction[a]



1a 2b

Entry	Catalyst (mol%)	Ac_2O equiv.	Time	Yield[b]
1	$Cu(OAc)_2 \cdot H_2O$ (10)	7.5	6 days	58
2	$CuCl_2 \cdot 2H_2O$ (10)	7.5	6 days	46
3	$Cu(NO_3)_2 \cdot 3H_2O$ (10)	7.5	6 days	28
4	$CuSO_4 \cdot 5H_2O$ (10)	7.5	4 days	79
5	$Cu(ClO_4)_2 \cdot 6H_2O$ (10)	7.5	0.5 h	97
6	$Cu(ClO_4)_2 \cdot 6H_2O$ (5)	5.05	0.5 h	95
7	$Cu(ClO_4)_2 \cdot 6H_2O$ (1)	5.05	0.5 h	97

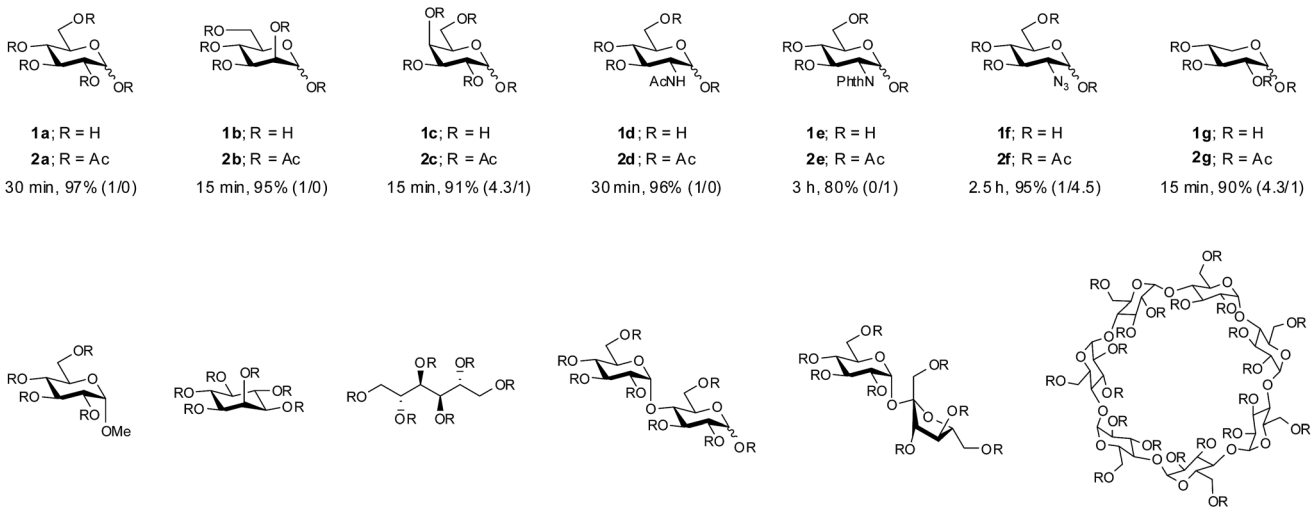
[a] The reactions were carried out with 1 g of **1a** in neat. [b] Isolated yields.

carried out using only 5 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$ with only 5.05 equivalents of acetic anhydride when it was observed that the catalyst retained its activity without any decrease in the yield (entry 6, Table 1). In the final effort towards optimizing the conditions for the reaction, it was carried out using only a stoichiometric amount of Ac_2O and 1 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$ when it was found that the yield was once again nearly quantitative (entry 7, Table 1).

Following the initial success for the per-*O*-acetylation reaction using $Cu(ClO_4)_2 \cdot 6H_2O$, the optimized reaction conditions were employed for the per-*O*-acetylation of a series of unprotected sugars. The reactions were carried out under solvent free conditions using stoichiometric amounts of Ac_2O and 1 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$. The products of the per-*O*-acetylation reactions with various substrates are shown in Table 2. The per-*O*-acetylation of the corresponding fully unprotected reducing sugars such as mannose, galactose and xylose resulted in the formation of the fully acetylated products **2b** (95%), **2c**, (91%) and **2g**, (90%). The reactions were very fast and were completed in only about 15 minutes. The procedure was also applied for the synthesis of several per-*O*-acetylated derivatives of non-reducing monosaccharides such as the 2,3,4,6-tetra-*O*-acetyl-α-methyl glucopyranoside (**2h**, Table 2), per-*O*-acetyl-*myo*-inositol (**2i**, Table 1) and per-*O*-acetyl-D-mannitol (**2j**, Table 2). Various reducing amino sugars and their derivatives such as *N*-acetyl-glucosamine, *N*-phthalimidoglucosamine and 2-deoxy-2-azidoglucose were also per-*O*-acetylated under the standard conditions in very good yields (**2d–f**, Table 2). However, the reactions with *N*-phthalimidoglucosamine and 2-deoxy-2-azidoglucose were slower and required 3 hours and 2.5 hours respectively for completion. The per-*O*-acetylation reaction was also successful with disaccharides such as maltose and sucrose leading to products **2k** and **2l** in almost quantitative yields as also the cyclic sugar β-cyclodextrin **2m**. All the products were characterized by ^1H and ^{13}C spectrometry and the data corresponded well with the literature values.

The plausible mechanism of the reaction appears to be through the acylium perchlorate intermediate **B** (Scheme 1) formed by the reaction of $Cu(ClO_4)_2$ and Ac_2O.[31] Intermediate **B** would be able to acetylate the free alcohol moieties very efficiently. Again the efficiency of the copper perchlorate in the reaction is possibly due to the solubility of the former in acetic anhydride which may be ascribed to the reaction between the two, especially since the acylium perchlorate intermediate has

Table 2 Per-*O*-acetylation of various sugars. The isolated yields are given along with the α/β ratios in parenthesis[a]



1a; R = H
2a; R = Ac
30 min, 97% (1/0)

1b; R = H
2b; R = Ac
15 min, 95% (1/0)

1c; R = H
2c; R = Ac
15 min, 91% (4.3/1)

1d; R = H
2d; R = Ac
30 min, 96% (1/0)

1e; R = H
2e; R = Ac
3 h, 80% (0/1)

1f; R = H
2f; R = Ac
2.5 h, 95% (1/4.5)

1g; R = H
2g; R = Ac
15 min, 90% (4.3/1)

1h; R = H
2h; R = Ac
30 min, 98%

1i; R = H
2i; R = Ac
10 min, 95%

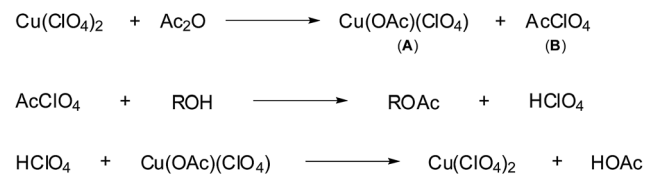
1j; R = H
2j; R = Ac
10 min, 99%

1k; R = H
2k; R = Ac
15 min, 99% (1/1.4)

1l; R = H
2l; R = Ac
30 min, 97%

1m; R = H
2m; R = Ac
15 min, 98%

[a] Reagents and conditions for the per-*O*-acetylation reactions: Ac_2O (1.01 equivalents per –OH), $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%), neat, rt.



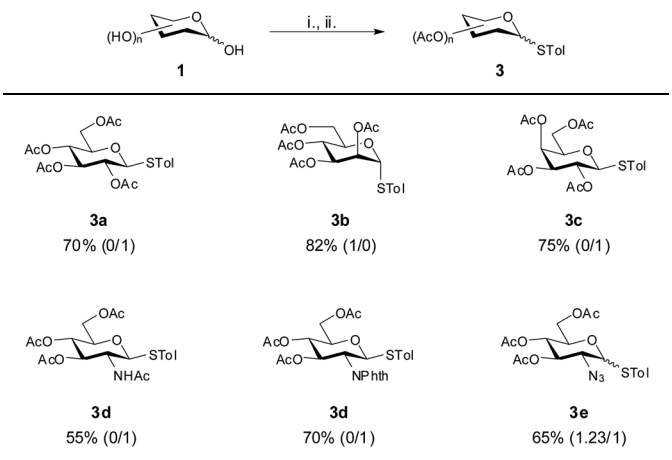
Scheme 1 Plausible mechanism of the per-*O*-acetylation reaction using $Cu(ClO_4)_2 \cdot 6H_2O$.

been detected by NMR previously.[31] The other Cu^{2+} salts are much less soluble in the reaction medium and probably are not able to form sufficiently long lived acylium intermediates to enable the acetylation reaction.

After the success with the solvent free per-*O*-acetylation of the fully unprotected monosaccharides using stoichiometric amounts of acetic anhydride and $Cu(ClO_4)_2 \cdot 6H_2O$, we turned our attention towards the sequential one-pot thioglycosylation reaction with monosaccharides. Thioglycosides have come to be widely accepted and used as glycosyl donors due to their long shelf life, stability and ease of activation with easily available promoters.[30] Again the thioglycosides are the most useful donors in iterative glycosylation strategies which enable the synthesis of oligosaccharides rapidly in one-pot.[1] The thioglycosylation of anomeric acetates is traditionally carried out using excess of Lewis acids such as $ZnCl_2$,[32] BF_3–Et_2O[33] or $SnCl_4$.[34] We employed the second one for our reaction and carried out the sequential one-pot per-*O*-acetylation–thioglycosylation for a series of fully unprotected sugars. The results are summarized in Table 3. A typical procedure involved treating the unprotected monosaccharide with stoichiometric amount of Ac_2O in the presence of 1 mol% of $Cu(ClO_4)_2 \cdot 6H_2O$. After completion of the per-*O*-acetylation reaction, as evidenced by TLC, *p*-thiocresol was added to the reaction mixture followed by addition of 2 equivalents of BF_3–Et_2O. The reaction mixture was then allowed to stir at room temperature for the appropriate time till complete disappearance of the acetylated product.

The sequential one-pot per-*O*-acetylation–thioglycosylation with glucose afforded the corresponding thioglycoside exclusively as the β isomer **3a** in an overall yield of 70%. Mannose yielded the α-thioglycoside **3b** in an overall yield of 82%. The reaction with galactose afforded the β-thiogalactopyranoside **3c** exclusively in 75% yield. The one-pot peracetylation was also successful with various aminosugars. *N*-Acetylglucosamine exclusively yielded the per-*O*-acetylated β-*N*-acetylthioglycoside **3d** in a yield of 55%. The reaction with 2-deoxy-2-phthalimidoglucose yielded the per-*O*-acetylated β-thioglycoside **3e** exclusively in a yield of 70%, while 2-azido-2-deoxyglucose yielded a mixture of the per-*O*-acetylated α- and β-thioglycosides **3f** in a ratio of 1.23/1 and an overall yield of 65%.

Table 3 One-pot per-*O*-acetylation and sequential thioglycosylation of various reducing monosaccharides[a]



[a] Reagents and conditions: (i) Ac_2O, $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol%), neat, rt.; (ii) *p*-TolSH, BF_3–Et_2O (2 equivalents).

Experimental

General methods

All the starting sugars were either purchased from commercial sources or prepared according to the standard procedures. Anhydrous solvents were prepared using standard methods. TLC was performed on precoated aluminium plates of silica gel 60 F254. Flash column chromatography was carried out with silica gel 60 (230–400 mesh, E. Merck) at medium pressure. NMR spectra were recorded either on a 400 MHz or a 500 MHz spectrometer in solution of $CDCl_3$ using tetramethylsilane as the internal standard, δ values are reported in parts per million (ppm) and coupling constants (J) in Hertz (Hz).

General procedure for per-*O*-acetylation of carbohydrate substrates

To a mixture of sugar (1 g scale) and stoichiometric acetic anhydride (1.01 equivalents per –OH of sugar) was added $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mol% of sugar) under nitrogen and the mixture was kept stirring at room temperature. When TLC showed complete conversion of the starting material, the reaction mixture was diluted with ethyl acetate and the mixture was washed with aqueous $NaHCO_3$ followed by brine. The ethyl acetate extract was then dried over anhydrous Na_2SO_4, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the expected compound.

Compound characterization data

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranoside[15] (2a). Isolated as white solid following elution of the column with 20% ethyl acetate (EA) in petroleum ether (PE); yield 97%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.33 (d, $J = 3.6$ Hz, 1H), 5.48 (dd, $J = 10.0$ and 9.6 Hz, 1H), 5.17–5.08 (m, 2H), 4.27 (dd, $J = 4$ and 4.4 Hz, 1H), 4.14–4.08 (m, 2H), 2.19 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 170.2, 169.6, 169.4, 168.8, 89.0, 69.8, 69.2, 67.8, 61.4, 20.9, 20.7, 20.6, 20.5, 20.4.

1,2,3,4,6-Penta-*O*-acetyl-α-D-mannopyranoside[9] (2b). Isolated as white solid following elution of the column with 20% EA–PE; yield 95%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.02 (d, J = 1.8 Hz, 1H), 5.28 (dd, J = 10.0 and 9.6 Hz, 2H), 5.20 (dd, J = 2.3 and 2.0 Hz, 1H), 4.22 (dd, J = 4.9 and 4.9 Hz, 1H), 4.04 (dd, J = 2.4 and 2.4 Hz, 2H), 2.12 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 169.8, 169.6, 168.1, 90.6, 70.6, 68.8, 68.3, 65.5, 62.1, 20.9, 20.8, 20.73, 20.67, 20.65.

1,2,3,4,6-Penta-*O*-acetyl-D-galactopyranoside[9] (2c). Isolated as thick yellow oil following elution of the column with 30% EA–PE; yield 91%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.38 (d, J = 2.3 Hz, 1H, α-anomer), 5.71 (d, J = 8.3 Hz, 0.23H, β-anomer), 5.43 (d, J = 4.3 Hz, 1H), 5.34–5.33 (m, 3H), 5.11–5.07 (m, 1H), 4.37–4.34 (m, 1H), 4.15–4.06 (m, 3H), 2.17–2.00 (m, 27H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.9, 168.9, 99.0, 92.1, 89.6, 71.6, 70.8, 69.2, 68.7, 67.8, 67.4, 67.3, 66.4, 61.2, 61.0, 20.9, 20.64, 20.62, 20.59, 20.52.

1,3,4,6-Tetra-*O*-acetyl-2-*N*-acetyl-α-D-glucosamine[15] (2d). Isolated as white solid following elution of the column with 50% EA–PE; yield 96%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.17 (d, J = 3.6 Hz, 1H), 5.59 (d, J = 8.8 Hz, 1H), 5.23 (dd, J = 4.8 and 2.4 Hz, 2H), 4.50 (dd, J = 3.6 and 3.2 Hz, 1H), 4.31 (dd, J = 4.0 and 4.0 Hz, 1H), 4.07 (dd, J = 2.4 and 2.4 Hz, 1H), 4.00 (bs, 1H), 2.20 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 1.95 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.9, 170.7, 170.0, 169.1, 168.7, 90.6, 70.6, 69.7, 67.5, 61.5, 51.0, 23.0, 20.9, 20.7, 20.6.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside[35] (2e). Isolated as white crystals following elution of the column with 20% EA–PE; yield 80%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 3.0 and 3.0 Hz, 2H), 7.77 (dd, J = 3.0 and 3.0 Hz, 2H), 6.53 (d, J = 8.9 Hz, 1H), 5.89 (dd, J = 9.1 and 9.1 Hz, 1H), 5.23 (dd, J = 9.2 and 9.2 Hz, 1H), 4.48 (dd, J = 8.9 and 8.9 Hz, 1H), 4.38 (dd, J = 4.4 and 4.4 Hz, 1H), 4.16 (dd, J = 2.1 and 2.1 Hz), 4.06–4.02 (m, 1H), 2.13 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.88 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 169.5, 168.7, 168.2, 167.4, 134.5, 131.2, 123.8, 89.7, 72.6, 70.5, 68.3, 61.5, 53.5, 20.8, 20.7, 20.6, 20.4.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-azido-D-glucopyranoside[9] (2f). Isolated as white solid following elution of the column with 20% EA–PE; yield 95%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.30 (d, J = 4.0 Hz, 0.22H, α-anomer), 5.55 (d, J = 8.8 Hz, 1H, β-anomer), 5.11–5.02 (m, 2H), 4.33–4.28 (m, 1H), 4.10–4.07 (m, 1H), 3.82–3.78 (m, 1H), 3.69–3.65 (m, 1H), 2.19–2.03 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5, 169.8, 169.6, 168.5, 92.5, 89.9, 72.7, 72.6, 70.7, 69.7, 67.8, 67.7, 62.5, 61.4, 60.3, 20.9, 20.7, 20.6, 20.5.

1,2,3,4-Tetra-*O*-acetyl-D-xylopyranoside[18] (2g). Isolated as colourless oil following elution of the column with 20% EA–PE; yield 90%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J = 3.6 Hz, 1H, α-anomer), 5.72 (d, J = 6.9 Hz, 0.23H, β-anomer), 5.47 (t, J = 10.0 Hz, 1H), 5.38–5.21 (m, 1H), 5.05–5.01 (m, 3H), 4.65 (d, J = 8 Hz, 0.49H), 4.27–4.21 (m, 1H), 3.95–3.92 (m, 1H), 3.74–3.69 (m, 1H), 3.56–3.51 (m, 0.24H), 2.18–2.03 (m, 24H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.5, 170.1, 169.8, 169.7, 169.6, 169.0, 168.2, 168.1, 98.7, 92.7, 91.9, 89.2, 79.8, 79.4, 74.2, 69.3, 68.6, 62.7, 62.3, 61.6, 60.6, 21.0, 20.8, 20.7, 20.64, 20.57, 20.53, 20.47, 20.40.

1-*O*-Methyl-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside[18] (2h). Isolated as white solid following elution of the column with 20% EA–PE; yield 98%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.41 (dd, J = 10.0 and 9.2 Hz, 1H), 5.00 (dd, J = 9.6 and 9.6 Hz, 1H), 4.86 (dd, J = 10.4 and 2.4 Hz, 2H), 4.20 (dd, J = 4 and 4 Hz, 1H), 4.04 (d, J = 12 Hz, 1H), 3.92 (d, J = 7.6 Hz, 1H), 3.35 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 170.0, 169.6, 96.7, 70.7, 70.0, 68.5, 67.1, 61.9, 55.4, 20.71, 20.66, 20.60.

Hexa-*O*-acetyl-*myo*-inositol[36] (2i). Isolated as white solid following elution of the column with 20% EA–PE; yield 95%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.59 (dd, J = 2.4 and 2.0 Hz, 1H), 5.49 (dd, J = 8.0 and 8.0 Hz, 2H), 5.17 (dd, J = 8.0 and 8.0 Hz, 1H), 5.08 (dd, J = 2.0 and 2.0 Hz, 2H), 2.20 (s, 3H), 2.03–1.99 (5 s, 15H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.8, 169.7, 169.5, 71.0, 69.4, 68.5, 68.2, 20.8, 20.6, 20.5.

Hexa-*O*-acetyl-D-mannitol[22] (2j). Isolated as white solid following elution of the column with 20% EA–PE; yield 99%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.44 (d, J = 6.6 Hz, 2H), 5.08–5.05 (m, 2H), 4.21 (dd, J = 2.1 and 2.1 Hz, 2H), 4.06 (dd, J = 4.1 and 4.1 Hz, 2H), 2.08–2.04 (s, 18H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 169.7, 67.8, 67.4, 61.8, 20.9, 20.7, 20.6.

D-Maltose octa-*O*-acetate[18] (2k). Isolated as white solid following elution of the column with 30% EA–PE; yield 99%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.22 (d, J = 3.7 Hz, 0.73H, α-anomer), 5.72 (d, J = 8.1 Hz, 1H, β-anomer), 5.41 (dd, J = 8.4 and 3.9 Hz, 1H), 5.38–5.25 (m, 5H), 5.06–4.98 (m, 2H), 4.96–4.93 (m, 2H), 4.87–4.82 (m, 2H), 4.45–4.41 (m, 2H), 4.25–4.20 (m, 4H), 4.08–3.99 (m, 4H), 3.94–3.91 (m, 2H), 3.84–3.80 (m, 1H), 2.20–1.97 (m, 44H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.4, 170.1, 169.9, 169.6, 169.5, 168.8, 95.7, 91.2, 88.8, 76.7, 75.2, 72.9, 72.4, 70.9, 69.2, 68.6, 62.5, 61.4, 21.0, 20.94, 20.88, 20.82, 20.7, 20.6, 20.5, 20.4.

Sucrose octa-*O*-acetate[37](2l). Isolated as thick oil following elution of the column with 20% EA–PE; 97%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.69 (d, J = 3.7 Hz, 1H), 5.47–5.42 (m, 2H), 5.37 (t, J = 5.9 and 5.9 Hz, 2H), 5.07 (dd, J = 9.7 and 8.7 Hz, 1H), 4.87 (dd, J = 3.7 and 2.4 Hz, 1H), 4.37–4.13 (m, 8H), 2.18 (s, 3H), 2.12–2.10 (s, 15H), 2.05 (s, 3H), 2.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 170.2, 170.1, 170.0, 169.9, 169.7, 169.6, 104.0, 89.9, 79.1, 75.6, 74.9, 70.2, 69.6, 68.5, 68.1, 63.6, 62.8, 61.7, 20.74, 20.71, 20.67, 20.63, 20.60, 20.58.

Per-*O*-acetylated β-cyclodextrin[9] (2m). Isolated as white solid following elution of the column with 20% EA–PE; yield 98%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.30 (dd, J = 8.2 and 8.2 Hz, 7H), 5.09 (dd, J = 3.9 and 3.9 Hz, 7H), 4.80 (dd, J = 3.9 and 3.9 Hz, 7H), 4.56 (d, J = 11.2 Hz, 7H), 4.27 (dd, J = 4.2 and 4.2 Hz, 7H), 4.14 (m, 7H), 3.70 (dd, J = 8.2 and 8.1 Hz, 7H), 2.13–2.06 (3s, 63H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.4, 169.5, 96.7, 70.8, 70.4, 69.6, 62.5, 20.8.

General procedure for one-pot per-*O*-acetylation–thioglycosylation of sugars

Per-*O*-acetylation of sugar was carried out as described above. When reaction was completed according to TLC, *p*-thiocresol (2 equiv.) and BF_3–Et_2O (2 equiv.) were sequentially added to the

reaction solution, and the mixture was allowed to stir for 2 days. The reaction was quenched by addition of aqueous $NaHCO_3$ and the mixture was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue through flash column chromatography gave the desired thioglycoside.

Compound characterization data

***p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[9] (3a).** Isolated as white solid following elution of the column with 20% EA–PE; yield 70%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 5.21 (dd, J = 9.6 and 9.2 Hz, 1H), 5.02 (dd, J = 9.6 and 9.2 Hz, 1H), 4.94 (dd, J = 10.0 and 9.6 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 4.24–4.16 (m, 2H), 3.70 (ddd, J = 2.8, 4.4 and 10.1 Hz, 1H), 2.40 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 170.2, 169.4, 169.3, 138.8, 133.8, 129.7, 127.5, 85.8, 75.7, 74.0, 69.9, 68.1, 62.1, 21.2, 20.79, 20.76, 20.6.

***p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside[9] (3b).** Isolated as colorless thick oil following elution of the column with 20% EA–PE; yield 82%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 5.49 (dd, J = 1.7 and 1.7 Hz, 1H), 5.42 (d, J = 1.4 Hz, 1H), 5.33–5.32 (m, 1H), 4.60–4.53 (m, 1H), 4.30 (dd, J = 5.9 and 5.9 Hz, 1H), 4.10 (dd, J = 2.4 and 2.3 Hz, 1H), 2.33 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0, 169.9, 169.8, 138.5, 132.6, 129.7, 128.8, 86.0, 70.9, 69.39, 69.37, 66.4, 62.5, 21.2, 20.9, 20.74, 20.72, 20.67.

***p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside[9] (3c).** Isolated as thick yellow oil following elution of the column with 20% EA–PE; yield 75%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 5.39 (d, J = 3.0 Hz, 1H), 5.20 (dd, J = 9.9 and 9.9 Hz, 1H), 5.02 (dd, J = 3.3 and 3.3 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 4.17 (dd, J = 7.0 and 6.9 Hz, 1H), 4.09 (dd, J = 6.3 and 6.2, 1H), 3.89 (dd, J = 6.6 and 6.6 Hz, 1H) 2.33 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.5, 138.5, 133.1, 129.8, 129.7, 87.0, 74.3, 72.0, 67.2, 61.6, 21.2, 20.9, 20.70, 21.67, 20.62.

***p*-Tolyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside[9] (3d).** Isolated as white solid following elution of the column with 50% EA–PE; yield 55%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 5.52 (br d, J = 8.8 Hz, 1H), 5.18 (dd, J = 9.9 and 9.6 Hz, 1H), 5.02 (dd, J = 9.8 and 9.6 Hz, 1H), 4.75 (d, J = 10.4 Hz, 1H), 4.21–4.12 (m, 2H), 3.97 (dd, J = 10.0 and 9.6 Hz, 1H), 3.69–3.65 (m, 1H), 2.32 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 170.0, 169.4, 138.4, 133.3, 129.7, 128.4, 86.7, 75.7, 73.8, 68.4, 62.4, 53.3, 23.4, 21.2, 20.8, 20.7, 20.6.

***p*-Tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[38] (3e).** Isolated as white crystals following elution of the column with 20% EA–PE; yield 70%. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 3.2 and 3.2 Hz, 2H), 7.76 (dd, J = 3.0 and 3.0 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 5.78 (dd, J = 9.3 and 9.3 Hz, 1H), 5.65 (d, J = 10.5 Hz, 1H), 5.12 (dd, J = 10.0 and 9.4 Hz, 1H), 4.35–4.22 (m, 3H), 3.90–3.86 (m, 1H), 2.33 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 1.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.2, 169.9, 167.8, 167.0, 138.8, 134.5, 134.3, 133.9, 129.7, 128.2, 127.0, 126.9, 123.7, 83.2, 75.8, 71.7, 68.7, 62.2, 53.6, 21.2, 20.8, 20.6, 20.4.

***p*-Tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-azido-1-thio-D-glucopyranoside[39] (3f).** Isolated as thick brown oil following elution of the column with 10% EA–PE; yield 65%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.50–7.14 (m, 8H), 5.58 (d, J = 5.5 Hz, 1.23H, α-anomer), 5.36 (dd, J = 9.2 and 9.2 Hz, 1H), 5.10–5.03 (m, 2H), 4.92 (t, J = 9.8 and 9.8 Hz, 1H), 4.65–4.61 (m, 1H), 4.44 (d, J = 10.1 Hz, 1H, β-anomer), 4.28 (dd, J = 5.1 and 5.1 Hz, 1H), 4.22 (dd, J = 4.8 and 2.4 Hz, 1H), 4.08 (dd, J = 5.6 and 5.5 Hz, 2H), 4.03 (d, J = 2.2 Hz, 1H) 3.71–3.68 (m, 1H), 3.38 (dd, J = 9.9 and 9.9 Hz, 1H) 2.39 (s, 3H), 2.35 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.54, 170.52, 169.9, 169.8, 169.7, 139.4, 138.5, 134.7, 132.8, 130.0, 129.9, 128.6, 126.1, 86.9, 85.7, 76.8, 75.7, 74.5, 72.0, 68.8, 68.4, 68.1, 62.4, 62.0, 61.9, 61.6, 21.23, 21.15, 20.74, 2.67, 20.63, 20.58.

Conclusions

In summary, we have reported a very convenient method of the per-*O*-acetylation of unprotected sugars using the very cheap and easily available $Cu(ClO_4)_2\cdot 6H_2O$. The per-*O*-acetylation reactions could be carried out under solvent free conditions using a stoichiometric amount of acetic anhydride. The reactions required very less time and used a very low loading of only 1 mol% of the $Cu(ClO_4)_2\cdot 6H_2O$ catalyst. Furthermore the $Cu(ClO_4)_2\cdot 6H_2O$ catalyzed per-*O*-acetylation reaction was followed by a sequential thioglycosylation reaction to afford the corresponding per-*O*-acetylated thioglycosides in good yields.

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