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COMMUNICATION

2,4,6-Trichloro-1,3,5-triazine (TCT) mediated one-pot sequential functionalisation of glycosides for the generation of orthogonally protected monosaccharide building blocks†

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Orthogonally protected monosaccharide building blocks have been prepared using TCT in a one-pot multicomponent transformation. The process involves successive steps of arylidene acetalation, esterification and regioselective reductive acetal cleavage. High regioselectivity, scope for using a broad range of substrates, functional group tolerance, mild reaction conditions, easy handling process and wide application range are a few advantages of the current process.

A renaissance in glycobiology and glycochemistry has made carbohydrates and their derivatives integral components of modern drug discovery programmes.[1] In synthetic organic chemistry, monosaccharides act as the principle chiral pool for natural product synthesis.[2] However, the structural complexity and diversity along with the polyfunctionality of carbohydrates have always hampered their biological studies and chemical applications.[3] Chemical and chemoenzymatic synthesis provide an alternative to exploit the biological and medicinal significance of carbohydrates.[4] Chemical synthesis involves the reaction between selectively protected monosaccharide units, one with a strategically positioned free hydroxyl group (a nucleophilic acceptor) and one bearing a labile group at the anomeric carbon (a donor), in a chemo-, regio- and stereoselective fashion.[5] Thus, stereospecific glycosylation and orthogonal protection are the two main challenges before carbohydrate chemists. Although more advances have been made in the former,[6] the synthesis of differentially protected monosaccharide scaffolds is still waiting for more satisfactory processes. In the last few years elegant Lewis acid-catalysed one-pot regioselective protection strategies have been reported by the groups of Hung,[7] Beau,[6,8] and others.[9] Even then, development of catalytic synthetic strategies for the efficient generation of monosaccharide building blocks remains a pressing requirement in carbohydrate chemistry. In particular, development of a catalytic process, which envisages two distinct transformations promoted by a single catalyst in a single reaction vessel, would make the process more advantageous, atom economic and environmentally benign.[10] Protection of a pair of appropriately oriented 1,2- or 1,3-hydroxyls as cyclic acetals is one of the most frequently used reactions in polyhydroxy compounds like carbohydrates and cyclitols.[11] The use of 4,6-*O*-arylidene acetalation in combination with esterification at C-2 and C-3 as a protecting group strategy is widely practised on carbohydrate templates as it provides a versatile orthogonal protection that allows for regio- and stereo-control in oligosaccharide assembly.[6a,9e,12] 4,6-*O*-Arylidene acetals can either undergo regioselective ring opening to provide a free OH at 4 or 6 position or make both the hydroxyl groups free, *via* acetal hydrolysis or hydrogenolysis.[11] Transformations of benzylidene acetal to a benzyl or benzoyl group are useful conversions in the synthesis of oligosaccharides. However these transformations (both arylidenation and arylidene deprotection) are often associated with several shortcomings like use of harsh acidic conditions and expensive reagents making the processes inconvenient for large scale production, incompatibility with other functional groups and generation of side products.[13] The use of a milder Lewis acid to catalyse these reactions is rarely reported. Very recently Galan *et al.*[9e] reported the application of $Cu(OTf)_2$ for the one-pot preparation of orthogonally protected glycosides from unprotected ones.

Inexpensive and readily available catalysts that bring about organic transformations in operationally simple ways are always an attractive approach for an organic chemist. Careful tuning of catalysts in a synchronized manner can lead to new synthetic transformations possessing significant chemoselectivity in functionally complex systems. To exemplify this concept, cyanuric chloride (TCT) has emerged as a catalyst of choice in organic transformations owing to its easy commercial availability, combined with stable, non-volatile, inexpensive, and easy to handle nature.[14] For example, it reacts with alcohols and acids to furnish the corresponding alkyl halides[15] and activated cyanurate esters respectively, which serve as useful starting materials in organic synthesis. Its adduct with DMF is used in the Beckman rearrangement[16] and for formyl protection of the primary hydroxyl group,[17] while that with DMSO is used in the classical Swern oxidation.[18] Syntheses of some important heterocycles such as xanthene derivatives[19] and polysubstituted quinolines[20]

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are also catalyzed by TCT. Very recently Chauhan *et al.*[14] reported a TCT catalyzed mild protocol for the synthesis of biologically active dihydro/spiro quinazolinones and quinazolinone-glycoconjugates. But in carbohydrate chemistry its use is limited to the preparation of glycosyl chlorides.[21]

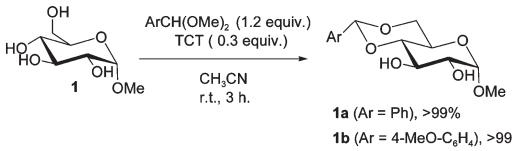
With our recent success in the development of a one-pot atom-economic approach in carbohydrate chemistry,[22] particularly for orthogonally protected carbohydrate building blocks, we speculated that TCT could be a catalyst of choice for the generation of orthogonally protected building blocks from glycosides while providing a mild reaction medium. In order to extract practical evidence in favour of our hypothesis, the potential of TCT to activate methylene arylidene acetals was evaluated. Thus, methyl-α-D-glucopyranoside **1** was allowed to undergo 4,6-*O*-arylidene acetalation in the presence of TCT (0.3 equiv.) and methylene arylidene acetal (1.2 equiv.) in CH_3CN at r.t. (Scheme 1).

Quantitative conversions to products 4,6-*O*-benzylidene acetal derivative **1a** and 4,6-*O*-*p*-metoxybenzylidene acetal **1b** were achieved within 5 h. As acetalation processes are generally favoured by ultrasound,[13] irradiation of the reaction mixture with high intensity ultrasound was resorted to, which accomplished the acetalation of glycoside **1** within 10 min in >99% yield.

Encouraged by these results, the scope and generality of the reaction was explored by using thio-, *O*-, and silyl glycosides (entries 1–13, Table 1). In all cases, the reaction proceeded smoothly leading to the formation of the corresponding products in quantitative yield. The reaction conditions were found compatible with different protecting groups like acetyl (entry 1) or benzoyl (entry 2) esters, benzyl ethers (entry 3), and amino protecting groups (entries 10, 11), making the process more versatile. High regioselectivity was observed with the formation of 4,6-*O*-arylidene products only. Formation of no side product like 2,3-*O*-acetal in case of methylmannoside **9** (entry 8) or 3,4-*O*-acetal in case of thiogalactoside **10** (entry 9) was detected. On a larger scale (20 g substrate), the reaction proceeded in a similar manner even with a lower catalyst loading (10 mol%), thus making the process amenable to easy scale up.

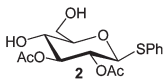
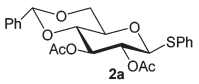
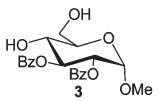
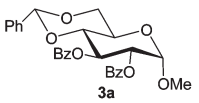
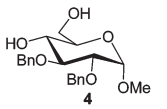
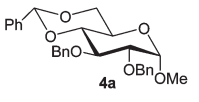
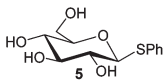
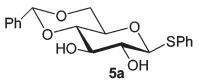
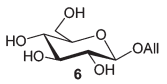
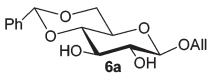
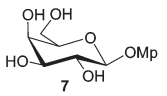
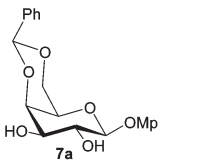
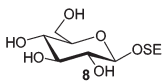
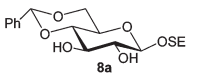
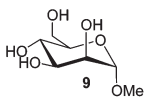
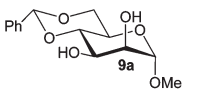
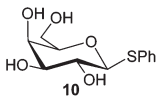
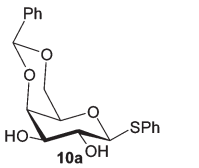
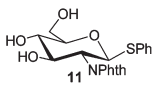
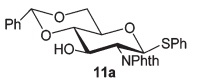
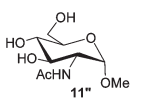
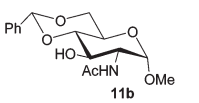
We next designed a one-pot strategy for the preparation of orthogonally protected monosaccharide building blocks, using TCT for a one-pot sequential acetalation/acetylation reaction. Thus, methyl-α-D-glucopyranoside **1** was subjected to TCT mediated acetalation using benzaldehyde dimethylacetal, and then treated with Ac_2O for acetylation under sonication (Scheme 2). Formation of product **12a** was indeed observed after 8 h. To check the feasibility of the reaction, glycosides **6–11** were allowed to react under the same conditions to obtain the corresponding acetalated acetylated products (**13a–18a**, Fig. 1). In all cases, including the amino protecting group containing substrate **11**, good to excellent yields were obtained (Fig. 1). The labile *p*-methoxybenzylidene acetal (rate of hydrolysis 10 times faster than benzylidene acetal)[9e,29] survived under the reaction conditions (Scheme 2, **12b**), underlining the mildness of the reaction conditions.

Contemporary organic synthesis demands the development of simple one-pot multicomponent organic transformations due to their advantages over sequential approaches.[22b] We, therefore proposed the opening of 4,6-*O*-benzylidene using a hydride source in the same pot keeping in view the fact that 1 mol of



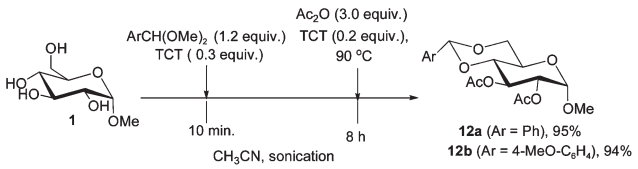
Scheme 1 TCT-catalysed 4,6-*O*-arylidene acetalation.

Table 1 TCT mediated 4,6-*O*-arylidene acetalation

Entry	Ar	Substrate[a]	Product[b]	Yield[c] (%)
1	Ph			99[9e]
2	Ph			93[23]
3	Ph			98[24]
4	Ph			95[9e]
5	Ph			99[25]
6	Ph			99[26]
7	Ph			95[27]
8	Ph			98[28]
9	Ph			96[9e]
10	Ph			80[9e]
11	Ph			75[23]

[a] In all cases 1 mmol of glycoside, 1.2 mmol of a methylene arylidene acetals and 0.3 mmol of cyanuric chloride were used. [b] Characterised by ^{1}H NMR and ^{13}C NMR. [c] Isolated yield after column chromatography.

TCT generates 3 moles of HCl.[30] Consequently, methyl-α-D-glucopyranoside **1** was subjected to one-pot acetalation–acetylation under standardised reaction conditions followed by the addition of $NaCNBH_3$ as a hydride source for acetal cleavage, and



Scheme 2 TCT mediated one-pot acetalation–acetylation.

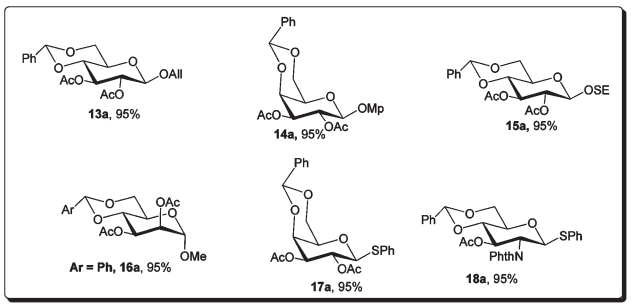
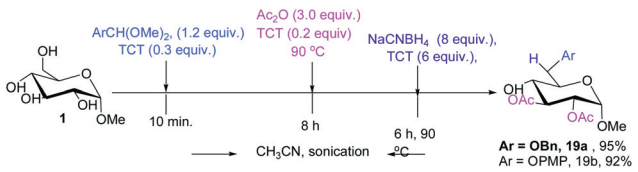


Fig. 1 Generation of TCT promoted orthogonally protected carbohydrate units.



Scheme 3 TCT mediated one-pot sequential acetalation–acetylation–reductive opening reactions.

Table 2 Suitability of different hydride donors for reductive ring opening

Entry	Hydride donor[a]	Time (h)	Yield[b] (%)
1	$NaCNBH_3$	6	95
2	Et_3SiH	8	45[c]
3	BH_3·THF	11	55[c]
4	DIBAL-H	10	30[d]

[a] In all cases 1 equiv. of methyl glycoside (**1**) was used. [b] Yield obtained after column chromatography. [c] Degraded products were found. [d] Mostly acetalated–acetylated product was isolated.

additional amounts of TCT (6 equiv.), (Scheme 3). As expected, product **19a** was obtained in good yield in the one-pot three step operation.

Checking the compatibility of other hydride donors for the TCT mediated one-pot reaction (Table 2), showed that $NaCNBH_3$ was the best hydride source among all in terms of conversion, time and yield.

Having optimised reaction conditions for one-pot acetalation–acetylation and alkylidene opening, a series of orthogonally protected useful monosaccharide building blocks for oligosaccharide synthesis were prepared using glycosides **5–10** (Fig. 2). It is noteworthy that in all cases the reaction proceeded smoothly with high regioselectivity, leading to the formation of 4-OH, 6-OBn products in good to excellent yields (Fig. 2).

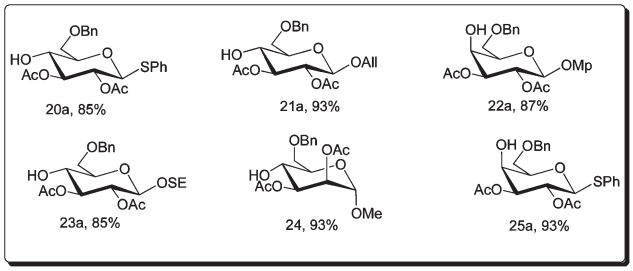


Fig. 2 Library of orthogonally protected monosaccharide acceptors prepared using current MCR.

In summary, TCT has proven to be a mild, inexpensive, non-toxic, functional group tolerant, environmentally viable catalyst for the generation of orthogonally protected monosaccharide units. The high regioselectivity and substrate diversity add to the advantages of the current methodology over the already existing ones. The process is useful for industrial purposes owing to the easy availability and low cost of TCT.

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