The *tertiary*-butyl group: Selective protection of the anomeric centre and evaluation of its orthogonal cleavage

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ABSTRACT

The *tertiary*-butyl group has not been examined extensively as a protecting group. In this work, we describe the synthesis of *tert*-butyl glycosides via the Fischer glycosylation protocol. Furthermore, its utility as a temporary anomeric protecting group was evaluated. A range of differentially protected monosaccharides was used to investigate the stability of the *tert*-butyl group upon the introduction of other protecting groups; and compatibility of its cleavage in the presence of the latter.

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Carbohydrates are well known for their complexity and diversity in nature.[1] This facilitates their roles in biological systems and hence makes them attractive synthetic targets for a variety of medicinal purposes.[2,3] In constructing mimics of naturally occurring glycoconjugates and oligosaccharides, glycoside bond formation is a common challenge.[1,4] Consequently, there is always a demand for alternative glycosylation strategies and a critical step in such techniques is the choice of protection for the anomeric centre on the donor molecule. Some anomeric protecting groups are bifunctional since they can also act as a leaving group upon activation to facilitate glycosylation.[5] More commonly however, the anomeric protection is removed, subsequent to which an appropriate leaving group is installed. In this latter case, an ideal candidate should be: (1) selectively and easily installed; (2) stable to further modifications on the molecule and; (3) deprotected relatively easily, yielding the hemiacetal while preserving the remaining groups.[6]

Currently, there are a number of anomeric protecting groups that are employed in oligosaccharide synthesis. Some of the more popular ones include the *O*-methyl,[7] *O*-allyl,[8] *p*-methoxyphenyl,[9] *p*-nitrobenzyl,[10] *n*-pentenyl,[11] TMSEt,[12] thioglycosides,[13] *O*-benzyl,[14] and more recently the *N,O*-dimethylhydroxylamine,[15] and the 1-methyl 1′-cyclopropylmethyl.[16] Each of these has their relative advantages and associated drawbacks. The lack of an ideal anomeric protecting group is what spurs research in this area. One of the major problems encountered with many of these groups

involves the need to perform multistep protocols to allow for their installation with differential protection around the molecule.[17] Depending on the nature of the reactions involved, this can result in a significantly low overall yield. Among the groups listed, the methyl, allyl and benzyl allow for selective introduction on a free sugar via a Fischer glycosylation pathway. This acid catalyzed reaction in the presence of excess alcohol is attractive and indispensable, due to its anomeric selectivity.[18]

The *tert*-butyl group, like most ethers, is stable to many conditions encountered. It can however be cleaved under milder conditions when compared to other alkyl ethers. Despite this, it is not among the more popular protecting groups.[19] Its utility has been demonstrated for the protection of alcohols in non-carbohydrate systems, using isobutylene together with different combinations of reagents such as: (1) $BF_3.Et_2O$, H_3PO_4;[20] (2) Amberlyst H-15;[21] (3) H_2SO_4;[22] as well as using *t*-BuOC(=NH)CCl$_3$ and $BF_3.Et_2O$.[23] The systems protected include cyclic ketones, halohydrins, acetylenic alcohols, esters and ethers. Various methods have also been developed for its selective cleavage under acidic conditions. Some of these include: (1) anhydrous CF_3COOH;[24] (2) HBr/AcOH;[25] (3) TBDMSOTf;[26] (4) HCO_2H;[27] and $CeCl_3/NaI$.[28] There exist very little precedent for its usage in carbohydrate derivatives. In most cases, *tert*-butanol has been employed as an acceptor in evaluating new glycosylation protocols. Lindberg described the synthesis of a *tert*-butyl glucoside via the Koenigs-Knorr method of glycosylation using $Hg(O_2CCH_3)_2$ as the promoter.[29] Further work done in investigating the action of strong acids on these acetylated glucosides indicated that selective deprotection of the *tert*-butyl group was achieved using BCl_3 in moderate yields.[30] A similar study was also

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undertaken using instead silver salicylate as the promoter, and selective cleavage of the glycoside was achieved with CF_3COOH.[31] Other activators also investigated include: Ag_2O;[29] HgO;[32] and $Hg(CN)_2/HgBr_2$.[33]

In glycosylations which employ the anomeric acetate as a leaving group, the formation of ortho esters inevitably results in low yields of the target glycoside.[34] Pavia et al. described the synthesis of *tert*-butyl glycosides in yields of 60–90% using isobutylene on acetylated reducing sugars.[35] Cleavage of the glycosides was effected using $FeCl_3$, both in the presence and absence of acetic anhydride.[35]

We report herein a straightforward synthesis of *tert*-butyl glycosides via the Fischer glycosylation method; using *tert*-butyl alcohol with catalytic amounts of Lewis acid. Its stability under conditions necessary for the introduction of common protecting groups was also investigated. Furthermore, we evaluated its selective removal in the presence of these protecting group patterns. To the best of our knowledge this is the first report: (i) detailing the synthesis of *tert*-butyl glycosides using the Fischer glycosylation; and (ii) functionalizes the remaining hydroxyls on the *tert*-butyl glycoside beyond an ester protection and testing for the latter's orthogonal cleavage.

The impact of temperature, time, equivalents of catalyst, as well as the volume of the alcohol were examined. Below 150 °C, extended reaction times (>48 h) were required for solubilization of the free sugar. Refluxing beyond 48 h did not yield any appreciable improvement in product yield. The deoxy sugars, L-Rha and L-Fuc, were the most soluble in the *tert*-butanol followed by D-Xyl. D-Glc demonstrated a much lower solubility than D-Man and as a result, a larger volume of the alcohol was required for solvation. The other sugars exhibited poor solubility in the *t*-BuOH. In an attempt to facilitate their dissolution and hence reaction, an equal volume of DMF was added. With D-Gal, D-Maltose and D-Gentiobiose, homogenous solutions were formed within 2 h. However, with D-GlcNAc and D-GlcNH2.HCl, no apparent solubilization was observed, even when DMSO was used instead. This is not surprising as solubility problems exist with these sugars even with the simpler alcohols.[36]

Acetylation of the crude mixture was undertaken to aid in purification of anomers (Table 1).[37] The α anomer of the glucopyranoside **1a** was the major product, with minor quantities of the β anomer and furanosides being detected. Recrystallization from methanol afforded the pure β anomer. The mannoside, **2a**, was obtained exclusively in the α configuration. It is likely that the bulkiness of the *tert*-butyl group destabilizes the *cis*-glycosidic linkage, a common observation with D-Man.[38] Interestingly, both these hexopyranoses yielded the 1,6 di-substituted compound, **1b** and **2b** respectively. Such products have never been reported under typical Fischer conditions. A plausible explanation revolves around the stability of a *tert*-butyl carbocation which is unfavourable with the simple commonly used alcohols. Nucleophilic attack by the 6-OH on the cation is facilitated because of the former's sterically accessible nature.

The rhamnopyranoside, **3a**, was obtained exclusively as the β anomer in 61% yield. L-Fuc yielded both anomers with the β being higher yielding. Xyloside, **5a** was obtained in 43% yield of the α isomer and 22% of the β. The resulting glycoside of D-Lyx, **6a**, was produced only as the α anomer. Though the D-Gal was soluble in the *t*-BuOH/DMF system, no reaction occurred. For the disaccharides, hydrolysis of the glycoside bond took precedence over formation of the Fischer product. Significant amounts of glucose were produced indicating that hydrolysis was faster than glycoside formation. Glycosides **1a**–**6a** were obtained in yields ranging from 58 to 65% (Table 1). These lower than usual yields (for a Fischer

Table 1
Synthesis of *tert*-butyl Glycosides.

HO—[sugar]—OH →(1. $(CH_3)_3COH$, AcCl, 150 °C, 48h; 2. Ac_2O, C_5H_5N, rt, 24h)→ AcO—[sugar]—O^{t}Bu
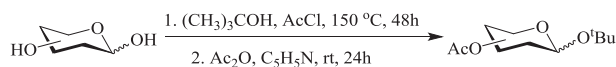
Entry	Substrate	Product	Yield%	Ratio α:β
1	D-Glucose	**1a** / **1b**	58 (**1a**) 8 (**1b**)	3:1 (**1a**) α exclusively
2	D-Mannose	**2a** / **2b**	65 (**2a**) 10 (**2b**)	α exclusively
3	L-Rhamnose	**3a**	61	β exclusively
4	L-Fucose	**4a**	64	0.7: 1
5	D-Xylose	**5a**	65	1: 0.5
6	D-Lyxose	**6a**	61	α exclusively