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Glycosylative transcarbamylation: efficient transformation of *tert*-butyl carbamates to novel glycoconjugates

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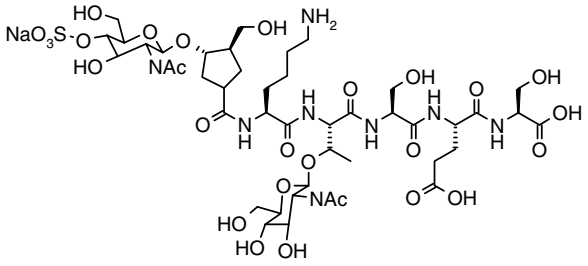
Abstract—Reaction of a variety of *tert*-butyl carbamates under glycosylation conditions gives rise to anomeric 2-deoxy-2-amino sugar carbamates in a good to excellent yields. The reaction exhibits good tolerance to several common protecting groups, and has been used to generate unnatural glycopeptide building blocks.

Protecting group strategies are central to the successful synthesis of glycopeptides. It has long been recognized that *tert*-butyl carbamates (Boc groups) are sometimes poor protecting groups for glycosylation reactions,[1] although there have been examples where the Boc group has efficiently survived. Jiaang et al. have reported an example where glycosylation in the presence of the electron-rich *p*-methoxybenzyl carbamate (Moz) group resulted in carbamate exchange; giving rise to an anomerically linked glycosyl carbamate in an excellent yield, and it was surmised that the same process could occur with a Boc group.[2]

As part of a synthesis of the peptide fragment of the natural product SQ-28546,[3] we attempted to glycosylate the threonine residue of the protected tetrapeptide **1**.[4] Glycosylation with *N*-trichloroethoxycarbonyl-glucosaminyl trichloroacetimidates has been well studied.[5] Their ease of synthesis, high selectivity for β-linkages, and facile refunctionalization makes them a premier choice for glycosyl donors. Glycosyl donor **2** was prepared for this study by the published method.

Peptide **1** was treated with 2 equiv of donor **2** and catalytic TMS-OTf (10%) in dichloromethane at −40 °C for 20 min, at which time the starting material was consumed as judged by TLC. In addition to a modest yield of the desired product **3**, we also isolated an equivalent amount of the unexpected product **4**, which arose from the glycosylation of the threonine residue, and subsequent exchange of the *tert*-butyl group of the carbamate by a second sugar group (Eq. 1). It is worth noting that Schmidt has reported very efficient glycosylation of the free hydroxyl of Boc-threonine benzyl ester under conditions which were nearly identical to ours with the exception that a single equivalent of glycosyl donor was used. It seems likely therefore, that the unexpected formation of **4** is solely due to the presence of an excess of reagent, and the yield of **3** could have been substantially improved by using a stoichiometric amount of donor. Nevertheless, this intriguing suboptimal result prompted us to further examine the reaction of Boc groups with **2**.



SQ-28546

The proton NMR spectrum of **4** was expectedly complex, and the assignment was made primarily on the basis of the parent ion in the mass spectrum, and on the lack of a *tert*-butyl carbamate resonance in the

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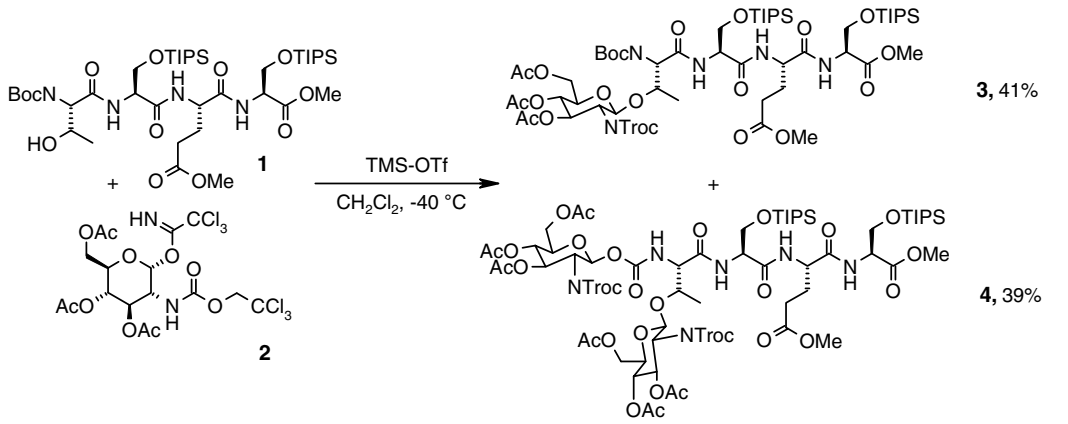
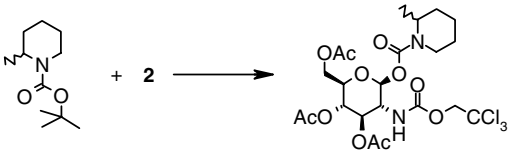


(1)

proton NMR.[6] Therefore, the result was corroborated with a much simpler substrate. When the *tert*-butyl carbamate of 2-methylpiperidine (**5**) was treated under similar conditions (1.5 equiv of donor **2**, 10% TMS-OTf, powdered 4 Å molecular sieves, dichloromethane, −35°C), glycosyl carbamate **6** was isolated in an 85% yield (Eq. 2) as an inseparable mixture of isomers. Carbon NMR of **6** and subsequent derivatives clearly showed two sets of carbamate resonances, which further solidified the assignment of the new compound as a glycosyl carbamate.



(2)

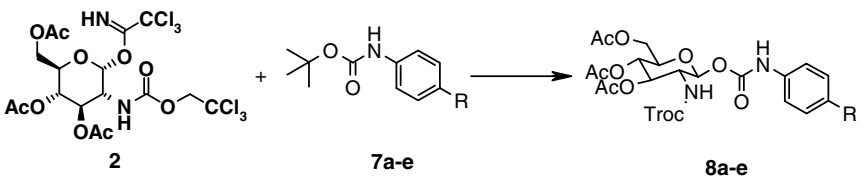
We have further examined the scope, limitations and some of the protecting group tolerances for this reaction. The reaction of a series of *tert*-butyl carbamates of simple anilines was instructive (Table 1). Consistent with a strong dependence on the electronic composition of the carbamate, an electron rich aryl group afforded a superior yield, whereas electron deficient substrates failed to react.[7] This observation suggests the likelihood that the reaction proceeds by way of electrophilic attack of the glycosyl cation on the carbonyl oxygen of the *tert*-butyl carbamate, and subsequent loss of the more stable *tert*-butyl cation.

The application to protected amino acid derivatives was also successful, affording high yields of glycosyl carbamates (Table 2). The reaction is highly selective for *t*-butyl carbamates, and fails to react with Cbz or Fmoc groups. Benzyl esters, and even *t*-butyl esters and pentafluorophenyl esters are compatible with the chemistry.

Finally, we demonstrated that the deprotection and refunctionalization of a select number of these *N*-trichloroethoxycarbonyl glucosaminyl carbamates with zinc powder and acetic anhydride following the procedure of Schmidt[5] affords the expected 2-deoxy-2-amino sugars in a good yield (Table 3).

In conclusion, we have uncovered an efficient means of converting *tert*-butyl carbamates to unnatural glycoside analogs. The reactions proceed in a very good yield, and exhibits an excellent protecting group selectivity. Furthermore, we have demonstrated that the carbamate linkage tolerates conditions for unveiling of the parent sugar. This methodology will provide access to novel unnatural glycoconjugates.

Table 1.



	R	Yield (%)
a	H	84
b	Me	95
c	OMe	98
d	NO_2	NR
e	CO_2Et	NR

Table 2.

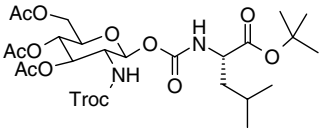
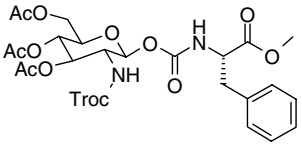
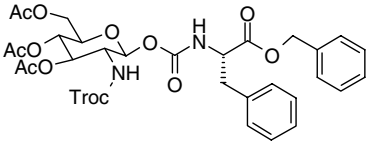
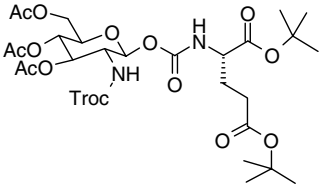
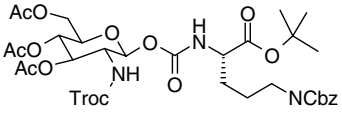
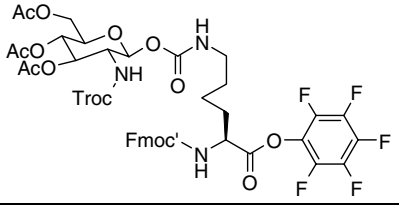
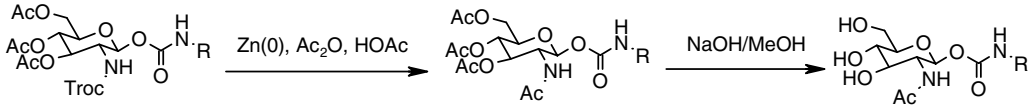
Substrate	Product	Compound (% yield)
Boc-Leu-O*t*Bu		**9** (87)
Boc-Phe-OMe		**10** (90)
Boc-Phe-OBn		**11** (90)
Boc-Glu(OtBu)-O*t*Bu		**12** (87)
Boc-Lys(*Z*)-O*t*Bu		**13** (58)
Fmoc-Lys(Boc)-OPfp		**14** (56)

Table 3.



Compound	Step 1 yield (%)	Step 2 yield (%)
6	71	89
8a	85	50
8b	76	51
8c	71	33
12	64	50
13	78	65
14	37[a]	—

[a] Low yield due in part to incomplete conversion of starting material.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.027.

References and notes

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2. Jiaang, W.-T.; Hsiao, K.-F.; Chen, S.-T.; Wang, K.-T. *Synthesis* **1999**, *9*, 1687–1690.

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4. Prepared in 7 steps by standard solution-phase peptide synthesis.
5. (a) Dullenkopf, W.; Castro-Palomino, J. C.; Manzoni, L.; Schmidt, R. R. *Carbohydr. Res.* **1996**, *296*, 135–147; (b) Saha, U. K.; Schmidt, R. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1855–1860.
6. All compounds were characterized by ^{1}H NMR and MS, and yields refer to isolated, homogeneous products.
7. It is noteworthy that our ability to perform the transcarbamylation reaction roughly mimicked the ease with which the parent amine reacted with di-*tert*-butyl dicarbonate to afford the carbamate. Ethyl *p*-aminobenzoate is only carbamylated under forcing conditions, and *p*-nitroaniline is inert to carbamylation, requiring a different route to starting material **7d**: Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, *20*, 2975.