ORGANIC LETTERS

2000
Vol. 2, No. 20
3135−3138

The Mild Cleavage of 2-Amino-2-deoxy-D-glucoside Methoxycarbonyl Derivatives

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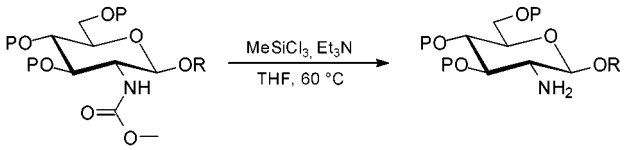
Received July 15, 2000

ABSTRACT



The conversion of methyl carbamate to the corresponding free amine is described for a series of 2-amino-2-deoxy-D-glucosamine derivatives. Cleavage of methoxycarbonyl moiety with $MeSiCl_3$ and triethylamine in dry THF at 60 °C and subsequent aqueous hydrolysis yields the free amine in 54 to 93% yields. The selective cleavage of methyl carbamates with $MeSiCl_3$ in the presence of a 2,2,2-trichloroethoxycarbonyl group or 2-azido glycosides affords selectively, orthogonal *N*-deprotected carbohydrates.

N-Acetylglucosamine-containing oligosaccharides are ubiquitous in biological systems and are major constituents of mucopolysaccharides, peptidoglycans, glycoproteins, and blood group antigens.[1] Consequently, and because of their biological importance, *N*-acetylglucosamine oligosaccharides are important synthetic targets.[2] In general, the successful chemical synthesis of these species requires careful selection of the *N*-protecting group on the 2-amino-2-deoxy sugar that is compatible with the glycosylation methodology employed and is readily removed in the presence of other carbohydrate functionality. In general, 2-acetamido glycoside derivatives are not directly employed because of poor solubility in organic solvents, and formation of the methyloxazoline[3] is oftentimes the major product isolated, thus making them poor glycosyl donors.[4]

Carbamates that act as protecting groups find widespread use in the synthesis of *N*-acetylglucosamine-containing oligosaccharides.[2] Among these, CBz- and TROC-carbamates are commonly employed, although the use of other carbamates is limited in generality and scope.[5] For example, methoxycarbonyl has not been widely employed, as *N*-deprotection typically involves a strong base and/or elevated reaction temperatures.[6] However, recent reports demonstrated that the methoxycarbonyl moiety is readily cleaved in the presence of a Lewis acid such as TMSI,[7] $HSiCl_3$,[8,9] or H_2SiI_2.[10] Additionally, different chlorosilanes were shown to activate carbamates differently, leading to multilevel selectivity in the cleavage of carbamates to isocyanates.[9] This latter

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(3) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167.

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(6) A single report exists on the base-induced cleavage of methoxycarbonyl monosaccharide derivatives. See: Kobayashi, Y.; Tsuchiya, T.; Ohgi, T.; Taneichi, N.; Koyama, Y. *Carbohydr. Res.* **1992**, *230*, 89.

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(8) (a) Greber, G.; Kricheldorf, H. R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 941. (b) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781. (c) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **19747**, *39*, 3904. (d) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1978**, *43*, 3808.

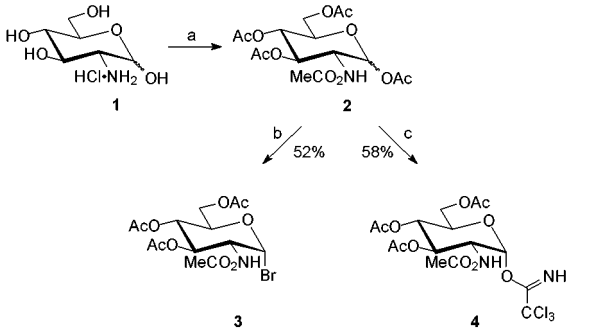
10.1021/ol0063353 CCC: $19.00
Published on Web 09/09/2000

observation is of particular importance, as the synthesis of many nitrogen-containing carbohydrates requires the orthogonal protection of multiple nitrogen centers. Demonstration that methyl carbamates are useful in the synthesis of complex carbohydrates has yet to be accomplished.

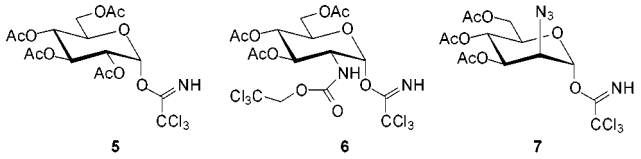
We now report the use of methyl carbamate as an *N*-protecting group for 2-amino-2-deoxyglycosides and its compatibility with commonly employed carbohydrate protecting groups. Methyl carbamate derivatives of 2-amino-2-deoxyglycosides are shown to be useful glycosyl donors and acceptors and provide β-glucosides via C-2 participation under Koenigs−Knorr and Schmidt trichloroacetimidate glycosylations. The methoxycarbonyl moiety is readily converted to the corresponding free amine in the presence of acid-sensitive protecting groups such as acetals and bisketals. Finally, we establish that methyl carbamates provide orthogonal nitrogen protection in the presence of TROC-carbamates and azides.

Preparation of the Glycosyl Donors. The methyl carbamate glycosyl donors were prepared from D-glucosamine·HCl (**1**), a solution of methyl chloroformate, and sodium bicarbonate in chloroform/water (1:1) to afford the corresponding methyl carbamate (Scheme 1). Subsequent per-

Scheme 1[a]



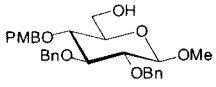
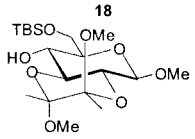
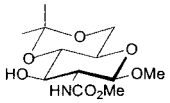
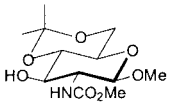
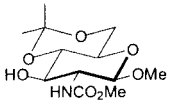
[a] (a) (1) Methyl chloroformate, $NaHCO_3$, $CHCl_3$:H_2O (1:1), 25 °C, 1 h; (2) Ac_2O, pyridine, 25 °C; (b) 30% HBr in AcOH, 25 °C, 12 h; (c) (1) NH_2NH_2·HOAc, DMF, 25 °C, 2 h; (2) CCl_3CN, DBU, CH_2Cl_2, 25 °C, 1 h.



acetylation produced **2** in 90% yield as an anomeric mixture. Tetraacetate **2** is readily transformed into either glycosyl donor **3**[11] by treatment with 30% HBr in acetic acid or into **4** by the selective reduction of the 1-*O*-acetate with hydrazine acetate followed by treatment with trichloroacetonitrile and 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU).

Preparation of the Substrate Glycosides. The syntheses of substrate glycosides represent a range of functionality commonly employed in carbohydrate synthesis (Table 1). Glycosyl bromide **3** was used to prepare monosaccharides

Table 1. Preparation of the Substrate Glycosides

donor	acceptor	product	yield (%)
3	MeOH	**8a**	74
4	MeOH	**8a**	91
3	*i*-PrOH	**9a**	75
4	HSEt	**10a**	73
4	 **18**	**11a**	91
4	 **19**	**20**	94
5	 **21**	**13a**	58 (β-anomer)
6	 **21**	**14a**	96
7	 **21**	**15a**	30

8a and **9a**, and in all other glycosylations, trichloroacetimidates **5**−**7** were employed using either TMSOTf or BF_3·Et_2O as a catalyst.[12] The trichloroacetimidates proved more reliable than the corresponding glycosyl bromide and resulted in cleaner glycosylations in higher overall yields. C2-Methyl carbamate glycosyl donors yielded only β-glycoside derivatives, suggesting anchimeric assistance. For **13a**, where imidate **5**[13] was used as the glycosyl donor, a 1:2 mixture of α- and β-anomers was isolated, accounting for the 58% yield observed for the glycosylation step.[14]

Scheme 2

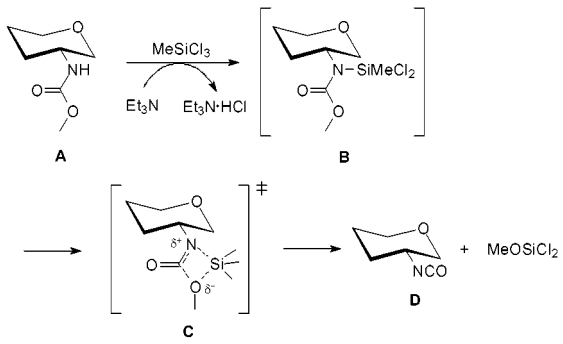
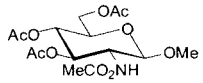
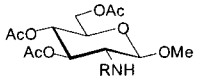
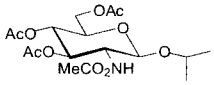
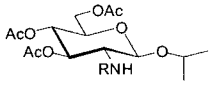
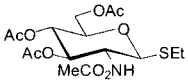
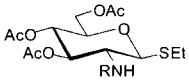
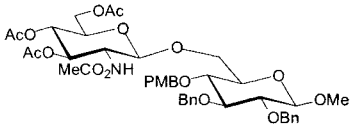
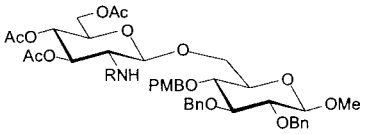
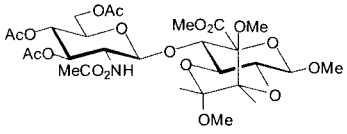
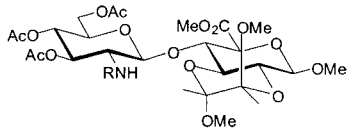
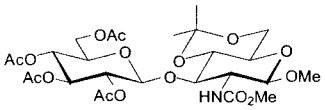
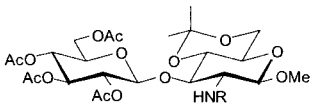
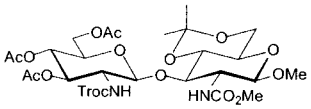
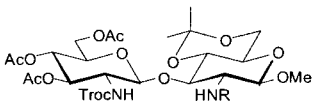
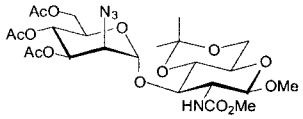
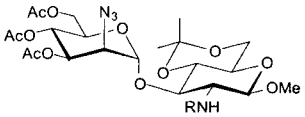
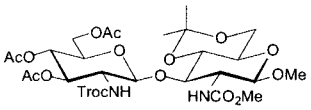
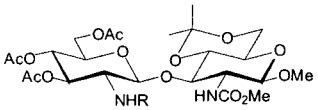
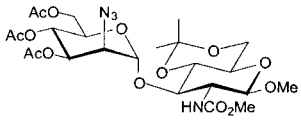
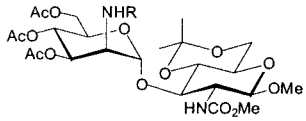


Table 2. Deprotection of Methyl Carbamate Glycosides **8a-15a**

entry	substrate	product	yield (%)[a]		time
8a			**8b**: R = H **8c**: R = Ac	93 quant.	24 h
9a			**9b**: R = H **9c**: R = Ac	82 quant.	24 h
10a			**10b**: R = H **10c**: R = Ac	68[b] 95	48 h
11a			**11b**: R = H **11c**: R = Ac	54 (91) quant.	36 h
12a			**12b**: R = H **12c**: R = Ac	67 (96) quant.	7 d
13a			**13b**: R = H **13c**: R = Ac	77 96	17 h
14a			**14b**: R = H **14c**: R = Ac	93[c] 96	48 h
15a			**15b**: R = H **15c**: R = Ac	81 (97) quant.	26 h
16a			**16b**: R = H	61 (87)[d]	4 h
17a			**17b**: R = H	quant.[e]	4 h

[a]Yields are reported for isolated, purified product uncorrected and corrected based on recovered starting material. [b]Partial direct activation of the thioacetal was observed. [c]Cleavage to the amine proceeded cleanly; Partial cleavage (23%) of the acetonide took place during SiO_2 purification. [d]TROC removal took place using Zn dust, AcOH, r.t., 4 h according to the method of Dullenkopf et al.[20] [e]Reduction of the azide moiety utilized H_2 and W2-RaNi.[21]

Deprotection of Substrate Glycosides. The chlorosilane-induced cleavage of methyl carbamates was carried out by treatment of the substrate glycoside (**A**) with $MeSiCl_3$ and Et_3N to afford isocyanate (**D**) and methoxymethyldichlorosilane (Scheme 2). In the first step, an *N*-silylated species is generated[15] (**B**), followed by formation of the four-membered ring transition state (**C**), which collapses to form the isocyanate.[16] Subsequent hydrolysis of the isocyanate during aqueous workup forms the carbamic acid, which liberates CO_2 and provides the corresponding free amine.[17]

Conversion of the methyl carbamate to the corresponding amine by the action of $MeSiCl_3$ proceeds in moderate to

(9) (a) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 8515. (b) Chong, P. Y.; Petillo, P. A. *Tetrahedron Lett.* **1999**, *40*, 2493. (c) Chong, P. Y.; Petillo, P. A. *Tetrahedron Lett.* **1999**, *40*, 4501.

(10) Gastaldi, S.; Weinreb, S. M.; Stien, D. *J. Org. Chem.* **2000**, *65*, 3239.

(11) Boullanger, P.; Jouineau, M.; Bouammali, B.; Lafont, D.; Descotes, G. *Carbohydr. Res.* **1990**, *202*, 151.

(12) Yeung, B. K. S.; Hill, D. C.; Janicka, M.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 1279.

(13) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249.

(14) A mixture of anomers is commonly observed for this particular glycosyl donor with a C2-acetyl group. See: Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(15) (a) Kricheldorf, H. R. *Synthesis* **1970**, 649. (b) Kricheldorf, H. R. *Liebigs Ann. Chem.* **1973**, 772. (c) Kricheldorf, H. R. *Chem. Ber.* **1971**, *104*, 3146.

excellent yields and is compatible with a variety of protecting groups including the acid-labile bis-dimethyl acetal (e.g., **12a**) and acetonides (**13a**−**15a**) (Table 2). Partial cleavage of the acetonide was observed for **15b** only during column chromatography, as TLC and crude ^{1}H NMRs show no evidence of acetonide loss after carbamate cleavage. Deprotection of monosaccharides **8a**−**10a** afforded the free amine after 24 h with no starting material remaining, while disaccharide substrates **11a**−**15a** required significantly longer reaction times. Although reaction times vary greatly as a function of disaccharide, the reactions themselves are exceptionally clean with only free amine and unreacted starting material recovered in all examples with the exception of **10a**. Some decomposition of **10a** was observed, presumably due to direct activation of the thioglycoside.

Methyl carbamate cleavage carried out in the presence of other *N*-protecting groups such as azides and 2,2,2-trichloroethoxycarbonyl demonstrates the selectivity and orthogonality available with this methodology. Cleavage of the methyl carbamate in disaccharide **14a** proceeded in 93% yield with complete retention of the TROC carbamate. Although some loss of the acetonide was observed during purification, the crude reaction mixture was essentially clean and all functionality except the methoxycarbonyl moiety remained intact. Conversely, removal of the TROC carbamate in **16a** by the action of Zn dust in AcOH revealed the corresponding free amine (**16b**), with complete retention of the methyl carbamate. These observations are consistent with those observed for simple aromatic carbamates[9] and suggest that glycoside carbamates are also subject to reactivity differences as a function of silane. Finally, cleavage of the methoxycarbonyl moiety in **15a** proceeded in 81% yield (**15b**) in the presence of the alkyl azide. As expected, the reduction of the azide moiety (**17a**) occurred quantitatively, leaving the methyl carbamate untouched (**17b**).

Deprotection of methyl carbamates **8a** and **9a** initially results in the formation of a higher R_f product that corresponds to the glycosyl isocyanate **D** (Scheme 2). Interestingly, the glycosyl isocyanates are remarkably stable as demonstrated by **9a**, which was isolable and completely characterizable by IR, MS, and NMR spectroscopies. Moreover, a simple aqueous wash proved inadequate for complete isocyanate hydrolysis, and unless the reaction is quenched under dilute conditions, any free amine present quickly condenses with the remaining isocyanate to form the corresponding ureido glycoside **22** (Figure 1).[18] Only under highly dilute conditions can the isocyanate be hydrolyzed without intermolecular condensation.[19]

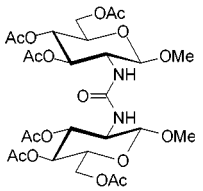


Figure 1. Ureido glycoside **22**.

In summary, we have demonstrated that methoxycarbonyl-protected 2-amino-2-deoxy glycosides are useful glycosyl donors, which can be readily *N*-deprotected in the presence of acid-sensitive protecting groups by the action of $MeSiCl_3$. Selective cleavage of the methoxycarbonyl group in the presence of other protected nitrogen centers occurs without crossover, suggesting that this methodology may be useful in the synthesis of differentially functionalized polyamino carbohydrates.

Acknowledgment. This research was generously supported by the National Institutes of Health.

Supporting Information Available: Experimental procedures and complete spectroscopic data for all substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0063353

(16) (a) Mironov, V. F.; Seludjakov, V. D.; Kozjukov, V. P.; Chatuncev, G. D. *Dokl. Akad. Nauk. SSSR* **1968**, *181*, 115. (b) Mironov, V. F.; Kozyukov, V. P.; Orlov, G. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1981**, *51*, 1555. (c) We have recently carried out a kinetic study on the formation of isocyanates from carbamates with a variety of chlorosilanes.

(17) **General procedure:** $MeSiCl_3$ (5 equiv) is added to a solution of the methyl carbamate glycoside (0.02−0.1 M) and Et_3N (5 equiv) in dry THF. The reaction flask is sealed under nitrogen and heated to 60 °C. When the starting material is consumed, the reaction is diluted (3×−20× reaction volume) with water or 1:1 THF−water and allowed to stir until the isocyanate is hydrolyzed as determined by TLC. The free amine can then be purified or directly acetylated.

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