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A Novel Protocol for the Regioselective Bromination of Primary Alcohols in Unprotected Carbohydrates or Glycosides

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The regioselective and efficient bromination of primary hydroxyl groups in unprotected carbohydrates or glycosides is successfully achieved by using (chloro-phenylthio-methylene)dimethylammoniumchloride (CPMA) in the presence of tetrabutylammonium bromide (TBAB) in dry DMF.

Keywords regioselective, bromide, CPMA, free sugars, glycosides

Introduction

The conversion of alcohols into the corresponding alkyl halides is a significant conception of broad utility in the synthetic procedures. Halides that act as pivotal precursors find widespread application in the preparation of other functionalized compounds such as nitriles, azides, amines, and thioethers. Practical procedures available, which can be widely applied to regioselectively substitute primary alcohols in the presence of secondary ones, remain fairly limited. Especially in glycochemistry selective substitution of the primary hydroxyl groups of polyhydroxylated substrates is much more challenging. The control of the synthetic regioselectivity is usually complicated by the requirement of using a protection-deprotection strategy for differentiation of hydroxyl groups of similar reactivity which makes the synthetic routes lengthy, laborious, time consuming and in low yield.[1] Therefore, the direct introduction of a substituent at a specific position is more desired. Based on higher reactivity of primary alcohols than secondary ones, the direct replacement of primary hydroxyls of free saccharides and their derivatives has been successfully achieved.[2] Most of the examples involved the use of reagent systems containing triphenylphosphine. In addition, CH_3SO_2Br and diverse Vilsmeier-Haack reagents have been applicable for the totally monofacial bromination of the primary hydroxyl rim in cyclodextins.[3] These halides function as building blocks for branched glyconjugates, especially the ability of cyclodextrins (CDs) to include spatially compatible molecules (guest molecules) in their hydrophobic cavity to yield inclusion complexes[4] makes these monofacially substituted analogues adequate candidates to serve as scaffolds of multicovalent systems of many bioactive molecules.[5] Although the reagents succeed in regioselective conversion, there remain several obstacles. The most significant problem concerns the unsatisfactory yield, in particular when monosaccharides or disaccharides serve as substrates of the substitution reaction. In addition, a large port of triphenylphosphine oxide as byproduct has to be laboriously removed. CH_3SO_2Br has the high toxicity and Vilsmeier salts show fair sensitivity to moisture so that both of them are relatively difficult to handle. Therefore, there remains a strong need or the development of alternative approaches to address issues of reactivity, scope, and the use or generation of undesirable reagents or byproducts.

Wagner *et al*. found that selective and mild conversion of primary hydroxyl groups to corresponding halides could be achieved using a readily accessible reagent (chloro-phenylthio-methylene)dimethylammonium chloride (CPMA)[6] when unprotected secondary ones are present. The protocol led us to envisage that the reagent may be capable of direct regioselective halogenation of primary hydroxyls in unprotected saccharide derivatives. We recently developed an efficient method for the preparation of per(6-bromo-6-deoxy)-cyclodextrins and demonstrated their usefulness in cyclodextrin chemistry.[7] As our continuous efforts on seeking facile and efficient regioselective methodologies in glycochemistry, we herein would like to document our further study that the approach is extended to the substitution of free sugars or glycosides, which have potential significance for the total functionalization of the primary hydroxyl groups in carbohydrates.

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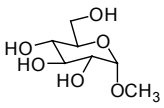
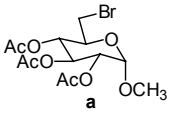
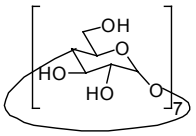
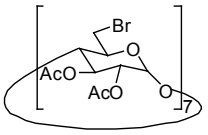
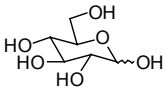
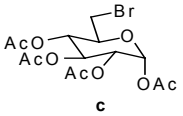
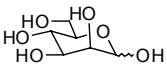
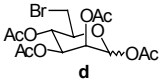
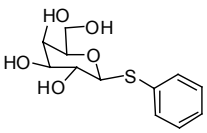
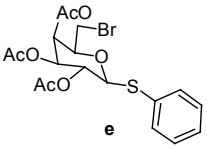
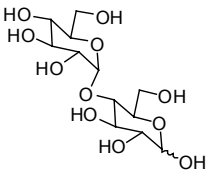
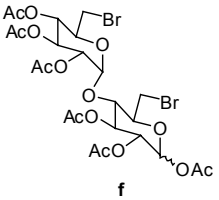
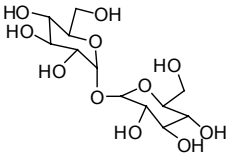
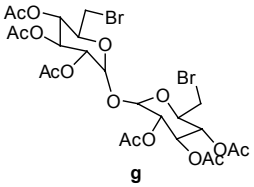
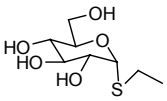
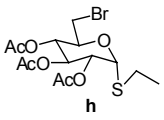
Results and Discussion

While CPMA was prepared, bis(trichloromethyl)-carbonate (BTC) instead of phosgene was dissolved into toluene, a catalytic amount of triethylamine was added to the above solution, and BTC rapidly decomposed into phosgene. CPMA can be stored in the solid state at ambient temperature for one month without appreciable decomposition. We have successfully used the solid reagent when stored at −80 ℃ under nitrogen for 2 months. Pure CPMA affords clear and nearly colorless solutions when initially dissolved in dry DMF. Methyl *α*-*D*-glucopyranoside was selected as a model in order to explore the optimal condition for CPMA-mediated bromination. The reaction of model substrate (2.0 equiv.) with CPMA (2.0 equiv.) in anhydrous DMF in the presence of tetrabutylammonium bromide (TBAB) at room temperature for 2 h, followed by one-pot acetylation, provided the expected bromide **a** in 84% isolated yield. To show the generality and scope of the protocol for bromide synthesis, the reaction was examined with various structurally diverse glycosides and saccharides. These results were summarized in Table 1. In most cases, the bromination proceeded smoothly with CPMA (2 equiv. per monosaccharide unit) and anhydrous TBAB (2 equiv. per monosaccharide unit) in DMF, giving handsome isolated yields of the desired totally brominated derivatives at the position of C-6. We also observed that the reaction conditions neither lead to the anomeric inversion of glycosides and disaccharides nor cleave glycosidic bonds, so the anomeric blocking groups or glycosidic bonds were stable against the reagent. No other brominated byproducts could be detected from the crude reaction mixtures by ^{1}H and ^{13}C NMR spectroscopy. The NMR spectra reflected the nature of the substituents at the primary position, primary bromides have a particular chemical shift of around δ 3.30 for methylene protons and around δ 30 for the corresponding carbon.

Table 1 Synthesis of 6-brominated sugars

Entry	Substrate	Product	Yield/%
1		 **a**	84
2		 **b**	82[3a]
3		 **c**	80
4		 **d**	92
5		 **e**	83
6		 **f**	88
7		 **g**	95
8		 **h**	93

Experimental

General methods

All the reagents and solvents were commercial products and used as received, unless otherwise noted. NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in $CDCl_3$ unless stated. TLC was performed with the plates coated with silica gel 60-F254, visualization of spots was effected by charring with a solution of 20% (*V*/*V*) H_2SO_4 in ethanol or under UV light. High resolution mass spectra (HRMS) were recorded on a Bruker APEX II high-resolution mass spectrometer with electrospray ionization (ESI).

General procedure for the synthesis of per-6-bromo-6-deoxy-carbohydrate derivatives

To a solution of the free carbohydrates or glycosides (2 mmol of monosaccharide unit) and anhydrous tetrabutylammonium bromide (4 mmol) in dry DMF (8 mL) was slowly added CPMA (4 mmol) with stirring. The reaction mixture was stirred at room temperature for 48 h under nitrogen. Methanol (10 mL) was added, and the solution was filtered. After evaporation under reduced pressure and desiccation, the residue was acetylated with acetic anhydride (3 equiv. of hydroxyl group) in pyridine (10 mL). After the reactions were complete monitored by TLC (toluene/EtOAc or petroleum ether/EtOAc), the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with HCl (20 mL, 0.1 mol/L), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by flash chromatography on silica gel leading to products.

CHINESE JOURNAL OF CHEMISTRY

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-bromo-*α*-*D*-glucopyranoside (a) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 3.36—3.41 (m, 2H), 3.41 (s, 3H), 3.98—4.03 (m, 1H), 4.89 (dd, J=10.0, 3.3 Hz, 1H), 4.95—4.99 (m, 2H), 5.47 (t, J=9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 170.0, 169.6, 96.7, 71.2, 70.8, 69.9, 68.5, 66.5, 55.6, 31.2, 20.7, 20.6; HRMS (ESI) calcd for $C_{13}H_{19}O_8BrNa^+$ [M+Na^+] 405.0161, found 405.0188.

1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-bromo-*α*,*β*-*D*-mannopyranose (c) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.99 (s, 3H), 2.03 (s, 3H), 2.10 (s, 3H), 3.40—3.53 (m, 2H), 4.03—4.07 (m, 1H), 5.10—5.35 (m, 3H), 5.48 (d, J=2.8 Hz, 1H), 6.10 (d, J=1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 170.0, 169.8, 169.6, 169.5, 168.3, 168.0, 90.5, 90.28, 74.4, 71.8, 70.4, 68.5, 68.4, 68.1, 68.0, 30.8, 30.2, 20.8, 20.6, 20.5; HRMS (ESI) calcd for $C_{14}H_{19}O_9BrNa^+$ [M+Na^+] 433.0105, found 433.0104.

Phenyl 2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-*β*-*D*-thiogalactopyranoside (d) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.12 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 3.31—3.46 (m, 2H), 3.90—3.93 (m, 1H), 4.73—4.76 (m, 1H), 5.04—5.08 (m, 2H), 5.56 (d, J=10.1 Hz, 1H), 7.31—7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.0, 169.9, 169.8, 132.9, 132.7, 132.6, 132.4, 129.0, 128.9, 90.4, 81.3, 79.7, 71.9, 67.8, 28.1, 20.5, 20.6, 20.7; HRMS (ESI) calcd for $C_{18}H_{21}O_7BrSNa^+$ [M+Na^+] 483.0105, found 483.0083.

1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-bromo-*α*-*D*-glucopyranose (e) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 2.06 (s, 3H), 2.07 (s, 3H), 2.12 (s, 3H), 3.39—3.47 (m, 1H), 3.48—3.50 (m, 1H), 5.09—5.17 (m, 2H), 5.26 (t, J=7.2 Hz, 1H), 5.47 (t, J=7.2 Hz, 1H), 6.35 (d, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 169.6, 169.3, 169.1, 91.5, 73.4, 72.6, 70.6, 70.5, 30.2, 20.8, 20.6, 20.5; HRMS (ESI) calcd for $C_{14}H_{19}O_9BrNa^+$ [M+Na^+] 433.0105, found 433.0083.

2',3',4'-Tri-*O*-acetyl-6-deoxy-6-bromo-*α*-*D*-glucopyranosyl-(1→4)-1,2,3-tri-*O*-acetyl-6-deoxy-6-bromo-*D*-glucopyranose (f) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.99—2.12 (m, 36H), 3.43—3.44 (m, 2H), 3.64—3.67 (m, 2H), 3.74—3.76 (m, 2H), 3.77—3.80 (m, 2H), 4.04—4.11 (m, 2H), 4.13—4.18 (m, 4H), 4.84—4.88 (m, 2H), 5.07—5.09 (m, 4H), 5.28—5.50 (m, 6H), 5.80 (d, J=8.0 Hz, 1H), 6.27 (d, J=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 170.4, 170.3, 170.0, 169.9, 169.6, 169.3, 169.2, 169.1, 168.8, 95.4, 91.0, 90.9, 75.0, 74.7, 73.4, 73.1, 72.9, 72.8, 71.7, 70.5, 70.2, 70.0, 68.9, 68.6, 67.8, 33.1, 32.5, 20.3—20.8; HRMS (ESI) calcd for $C_{24}H_{32}O_{15}Br_2Na^+$ [M + Na^+] 741.0010, found 741.0026.

2,2',3,3',4,4'-Hex-*O*-acetyl-6,6'-dideoxy-6,6'-dibromo-*α*,*α*-*D*-trehalose (g) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.00 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 3.29—3.40 (m, 2H), 4.09—4.14 (m, 1H), 4.94 (t, J=10 Hz, 1H), 5.14—5.17 (m, 1H), 5.37 (d, J=3.6 Hz, 1H), 5.49 (t, J=10 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.9, 169.6, 169.4, 91.9, 71.2, 69.9, 69.8, 69.3, 30.4, 20.9, 20.6; HRMS (ESI) calcd for $C_{24}H_{36}O_{15}Br_2N^+$ [M+NH_4^+] 736.0446, found 736.0461.

Ethyl 2,3,4-tetra-*O*-acetyl-6-deoxy-6-bromo-*α*-*D*-thioglucopyranoside (h) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, J=7.5 Hz, 3H), 1.96 (s, 3H), 1.97 (s, 3H), 2.10 (s, 3H), 2.57—2.70 (m, 2H), 3.20—3.30 (m, 2H), 4.06 (d, J=10.1 Hz, 1H), 4.75—4.80 (m, 1H), 5.46—5.52 (m, 1H), 5.12 (t, J=9.6 Hz, 1H), 6.65 (d, J=3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.1, 169.5, 169.3, 91.5, 73.4, 72.6, 70.6, 70.5, 30.7, 28.6, 20.6, 20.5, 20.4, 11.8; HRMS (ESI) calcd for $C_{14}H_{21}O_7BrSNa^+$ [M+Na^+] 435.0089, found 435.0099.

Conclusions

In conclusion, a novel and convenient method has been developed, by which brominated carbohydrate derivatives have been efficiently synthesized from readily available unprotected sugars or glycosides. The reaction has a broad substrate scope and it proceeds with high regioselectivity to furnish C6-substituted products in satisfactory yields under mild conditions. This methodology is believed to have potential in a wider application in glycoconjugate chemistry than conventional ones.

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