Iodine(III)-Initiated Bromoacetoxylation of Olefins

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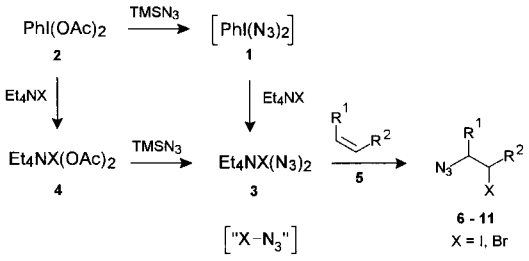
Abstract: A new and mild method for the bromoacetoxylation of olefins is presented, which is initiated by iodine(III). α-Acetoxy bromides **6-11** are generated from olefins **5** in the presence of tetraethylammonium bromide (**1**) and (diacetoxyiodo)benzene (**2**). The 1,2-addition to carbohydrate-derived enol ethers results in 2-deoxy-2-bromo-pyranosyl acetates which are versatile glycosyl donors for the synthesis of 2´-deoxy-2´-bromo glycosides **16**.

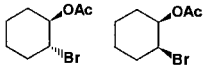
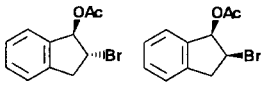
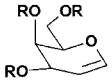
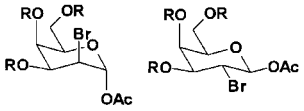
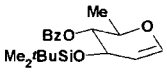
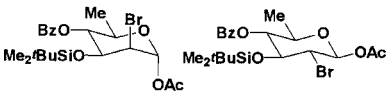
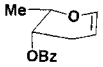
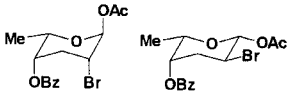
The versatility of polycoordinated iodine compounds in the oxidation state III is well recognized.[1] A notable feature of these molecules is their ability to transfer ligands that are bound to the central iodine atom onto appropriate electrophiles. Under these conditions iodine(III) reagents behave like transition metals, as they undergo reductive elimination and subsequently iodobenzene is formed as a by-product. Recently, we initiated an investigation on ligand transfer reactions from iodine(III) onto iodide anions.[2] The species generated under these conditions are believed to be iodate(I) salts[3] which have found only few applications in organic synthesis.[4] It was thought, that the analogous ligand transfer onto the bromide anion would create the corresponding bromate(I) anions.[5]

Based on this assumption, we developed a new method for the bromoacetoxylation of olefins.[6] When tetraethylammonium bromide (**1**) was mixed with (diacetoxyiodo)benzene (**2**) in dichloromethane at rt, a clear yellow solution developed within 15 minutes. It can be reasoned that tetraethylammonium [di(acyloxy)bromate (I)] (**3**) is formed under these conditions (Scheme 1). Alternatively, acetylhypobromite (**4**) may be responsible for the yellow colour. In fact, when olefins **5** were added to this solution, formal addition of **4** to the olefinic double bond took place, affording α-acetoxy bromides **6-11** in good yield (Table 1). Cyclic enol ethers **5c-f** were transformed quantitatively (>90 %);[7] chromatographic separation of all stereoisomers led to reduction in isolated yields.[8] Electron withdrawing protecting groups on glycal **5c** resulted in very slow conversion to 1,2-adducts **8 a-d**. In dichloromethane and acetonitrile the yields were further reduced due to formation of elimination products **12a**[9] and **12b** (23%; 2 : 1).

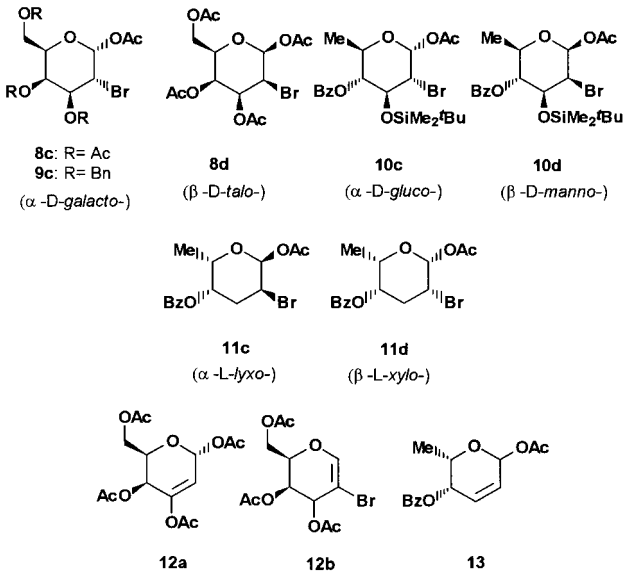


Scheme 1

Table 1. Bromoacetoxylation of olefins

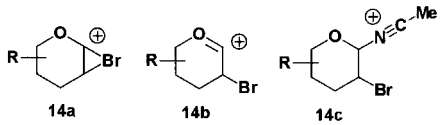
	olefin 5a - f		conditions	α-acetoxy bromides 6 - 11		ratio[a] a:b:c:d	yield (%)[b]
1		**5a**	**1** and **2**, CH_2Cl_2, rt, 2h		*rac*-**6a,b**	14 : 1	59[c]
2		**5b**	**1** and **2**, CH_2Cl_2, rt, 2h		*rac*-**7a,b**	> 20 : 1	67
3		**5c**	**1** and **2**, CH_2Cl_2, rt, 24h		**8a,b,c,d**	3 : 1.5 : 3 : 1	42
4		(R= Ac)	**1** and **2**, CH_3CN, rt, 40h			4 : 2 : 1 : 4	61
5			**1** and **2**, toluene, TMSOTf, rt, 12h			3 : 1 : -- : --	78
6		**5d**	**1** and **2**, CH_2Cl_2, rt, 2h		**9a,b,c**	1 : 2.7 : 1.6 : --	74
7		(R= Bn)	**1** and **2**, CH_3CN, rt, 2h			1 : 1.7 : 1.8 : --	45
8			**1** and **2**, toluene, TMSOTf, rt, 6h			5 : 9 : 1 : --	71
9		**5e**	**1** and **2**, CH_3CN, rt, 1.5h		**10a,b,c,d**	2 : 1.5 : 1 : 1	79
10			**1** and **2**, toluene, TMSOTf, rt, 12h			1 : 1.5 : -- : --	73
11		**5f**	**1** and **2**, CH_2Cl_2, rt, 16h		**11a,b,c,d**	6 : 6 : 1 : 5	70
12			**1** and **2**, CH_3CN, rt, 17h			5 : 5 : 1 : 5	53
13			**1** and **2**, toluene, TMSOTf, rt, 30h			1 : 4.5 : -- : 4	45

[a] from the crude ^1H NMR. [b] yields refer to separated isomers.
[c] volatile product. [d] traces of 2-enopyranosyl acetate **13** detected.



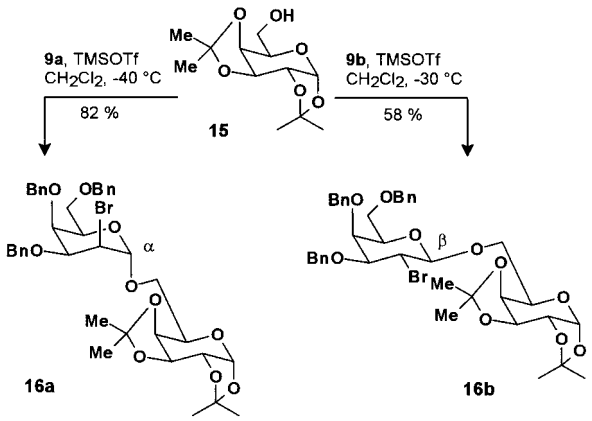
For cyclohexene **5a** and indene **5b** (entries 1 and 2) the 1,2-addition was highly *trans* selective. In contrast, the diastereoselectivity in reactions with glycals is dependent on the conditions employed. When the active agent was generated in dichloromethane (entries 3, 6 and 11) or acetonitrile (entries 4, 7, 9 and 12), up to all four possible 2-bromo-2-deoxy-glycosyl acetates **8**-**11** were formed, which could be separated by column chromatography. With the exception of 3-deoxyglycal **5f**, formation of 1,2-*cis* adducts was suppressed by employing **1** and **2** (3 equiv.) in toluene in the presence of 0.2 equivalents of TMSOTf (entries 5, 8 and 10) . The Lewis acid is partly needed for overcoming lack of solubility of **1** and **2** in toluene, thereby accelerating formation of the active agent. In contrast to iodo acetoxylation of glycals,[10] using excess of NIS and HOAc in propionitrile, higher yields of rare β-1-*O*-acetyl-2-bromo-2-deoxy pyranoses were obtained with our reagent system.

Formation of 1-*O*-acetyl bromides is initiated by an electrophilic bromonium species which adds both to the α- as well as the β-face of the olefinic double bond. When the electrophilic agent is activated by TMSOTf in toluene (Table 1), formation of the cyclic intermediate halocarbonium ion **14a** is strongly favoured. Under these conditions only 1,2-*trans* products are formed after capture of **14a** by nucleophiles like acetate. Under most other conditions, oxonium ion **14b** is present in equilibrium with **14a** which also results in 1,2-*syn* addition products.[11] In acetonitrile nitrilium ion **14c** has to be considered for further stabilization, thus accounting for generation of elimination product **12b**.[9]



Various groups have championed 1-*O*-acetyl-2-deoxy-2-iodo-pyranoses[10,12] as glycosyl donors for the construction of 2-deoxygenated oligosaccharides.[13] Therefore, we studied the ability of bromine at C-2 to exert anchimeric assistance in the glycosidation process (Scheme 2). Reaction of glycosyl acetate **9a** with the galactosyl acceptor **15** in CH_2Cl_2 in the presence of TMSOTf afforded the corresponding disaccharide **16a** as a single isomer. Likewise, **9b** was transformed under similar reaction conditions into **16b**,[14] again in a highly stereocontrolled manner.

In conclusion, we presented the *in situ* preparation of bromate(I) salts by ligand transfer of acetoxy groups from iodine(III) onto the bromide anion. These new reagents can efficiently be utilized for the bromoacetoxylation of olefins under very mild conditions.



Scheme 2

Acknowledgement: We thank the Deutschen Akademischen Austauschdienst for a fellowship for Md. A. H. Financial support by the Deutsche Forschungsgemeinschaft (grant Ki 397/4-2) and the Fonds der Chemischen Industrie is grateful acknowledged.

References and Notes

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(6) For a review on cohalogenations see: Rodriguez, J., Dulcère, J.-P., *Synthesis*, **1993**, 1177-1205.

(7) The corresponding tetrabutylammonium salts, generated from Bu_4NBr and $PhI(OAc)_2$, gave similar diastereomeric ratios. However, the reaction was only complete after more than one to two days and the α-bromoacetates were isolated in slightly reduced yields (48-54 %).

(8) *Typical Experimental Procedure:* $PhI(OAc)_2$ (0.58 g,1.8 mmol) was suspended in CH_2Cl_2 (10 mL) under nitrogen at rt and Et_4NBr (0.378 g, 1.8 mmol) was added in one portion. Stirring was continued for 35 min at ambient temperature until a clear yellow solution was obtained. Glycal **5d** (0.25 g, 0.6 mmol) was added and stirring was continued for 2 h at rt. For work-up, the phases were separated after addition of saturated $NaHSO_3$ solution. The aqueous phase was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$)

and concentrated *in vacuo* to afford 0.48 g of crude product. Flash chromatography using PE/EE (85:15) gave three fractions: ^{1st}fraction: **9b**: 123 mg (37 %), colorless crystals; m.p. 82 °C; $[\alpha]^{26}_D$ = +44 (*c* = 1.02, $CHCl_3$); ^{2nd}fraction: **9c**: 77 mg (23 %), colorless oil; $[\alpha]^{27}_D$ = +80 (*c* = 1.01, $CHCl_3$);. ^{3rd}fraction: **9a**: 47 mg (14 %), colorless oil; $[\alpha]^{26}_D$ = -9.5 (*c* = 1.03, $CHCl_3$).

(9) Selected ^{1}H- and ^{13}C NMR data for 2-enopyranosyl acetate **12a**: 6.53 (1-H), 5.81 (2-H); $J_{1,2}$= 3.2, $J_{4,5}$= 2.4 Hz; 147.3 (C-3), 119.6 (C-2), 89.8 (C-1) and **12b**: 6.73 (1-H), 5.68 (3-H); $J_{1,3}$= 1.2, $J_{4,5}$= 4.8 Hz; 145.5 (C-1), 96.7 (C-2); EI-MS, *m*/*z* =352, 350 (1:1) [M^+]. For additional data on unsaturated sugars like **12a** refer to: Harders, J., Garming, A., Jung, A., Kaiser, V., Monenschein, H., Ries, M., Rose, L., Schöning, K.-U., Weber, T., Kirschning, A., *Liebigs Ann. Chem*., **1997**, 2125-2132.

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(14) Selected physical and spectroscopic data for disaccharides **16a** and **16b**:
16a: colorless oil; $[\alpha]_D^{27}$: -26.8 (*c*= 1.03; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41-7.20 (m, 15H, H arom.), 5.51 (d, $J_{1,2}$= 5.2 Hz, 1H, 1-H), 5.27 (d, $J_{1´,2´}$= 1.2 Hz, 1H, 1´-H), 5.00, 4.74, 4.61, 4.51, 4.50, 4.43 (6d, $J_{A,B}$= 12.0 Hz, 6H, 3x CH_2Ph), 4.58 (dd, $J_{3,2}$= 2.4 Hz, $J_{3,4}$= 8.0 Hz, 1H, 3-H), 4.31 (m, 1H, 2´-H), 4.31 (dd, $J_{2,3}$= 2.4 Hz, $J_{2,1}$= 5.2 Hz, 1H, 2-H), 4.17 (dd, $J_{4,5}$= 1.6 Hz, $J_{4,3}$= 8.0 Hz, 1H, 4-H), 4.10 (dd, $J_{3´,2´}$= $J_{3´,4´}$= 4.8 Hz, 1H, 3´-H), 3.96 (dt, $J_{5,4}$= 1.6 Hz, $J_{5,6a}$= $J_{5,6b}$= 6.0 Hz, 1H, 5-H), 3.94 (d, $J_{5´,6a´}$= 6.8 Hz, 1H, 5´-H), 3.90 (m, 1H, 4´-H), 3.80 (dd, $J_{6a´,5´}$= 6.8 Hz, $J_{6a´,6b´}$= 10.8 Hz, 1H, 6a´-H), 3.71 (dd, $J_{6a,5}$= 6.0 Hz, $J_{6a,6b}$= 9.0 Hz, 1H, 6a-H), 3.69 (d, $J_{6b´,6a´}$= 10.8 Hz, 1H, 6b´-H), 3.66 (dd, $J_{6b,5}$= 6.0 Hz, $J_{6b,6a}$= 9.0 Hz, 1H, 6b-H), 1.51, 1.41, 1.32 (3s, 12H, 4x CH_3).
16b: colorless oil; $[\alpha]_D^{27}$: -17 (*c*= 1.01; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.43-7.22 (m, 15H, H arom.), 5.52 (d, $J_{1,2}$= 4.8 Hz, 1H, 1-H), 4.85, 4.71, 4.70, 4.55, 4.45, 4.41 (6d, $J_{A,B}$= 12.0 Hz, 6H, 3x CH_2Ph), 4.64 (d, $J_{1´,2´}$= 8.4 Hz, 1H, 1´-H), 4.58 (dd, $J_{3,2}$= 2.4 Hz, $J_{3,4}$= 8.0 Hz, 1H, 3-H), 4.30 (dd, $J_{2,3}$= 2.4 Hz, $J_{2,1}$= 4.8 Hz, 1H, 2-H), 4.29 (dd, $J_{4,5}$= 1.6 Hz, $J_{4,3}$= 2.0 Hz, 1H, 4-H), 4.18 (dd, $J_{2´,1´}$= 8.4 Hz, $J_{2´,3´}$= 10.8 Hz, 1H, 2´-H), 4.06 (dt, $J_{5,4}$= 1.6 Hz, $J_{5,6a}$= 4.8, $J_{5,6b}$= 6.4 Hz, 1H, 5-H), 4.00 (dd, $J_{6a,5}$= 4.8 Hz, $J_{6a,6b}$= 11.4 Hz, 1H, 6a-H), 3.88 (d, $J_{4´,3´}$= 2.8 Hz, 1H, 4´-H), 3.79 (dd, $J_{6b,5}$= 6.4 Hz, $J_{6b,6a}$= 11.4 Hz, 1H, 6b-H), 3.62-3.58 (m, 3H, 5´-H, 6a´-H, 6b´-H), 3.55 (dd, $J_{3´,4´}$= 2.8 Hz, $J_{3´,2´}$= 10.8 Hz, 1H, 3´-H), 1.54, 1.42, 1.33, 1.31 (4s, 12H, 4x CH_3).