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Radical-mediated bromination of carbohydrate derivatives: searching for alternative reaction conditions without carbon tetrachloride

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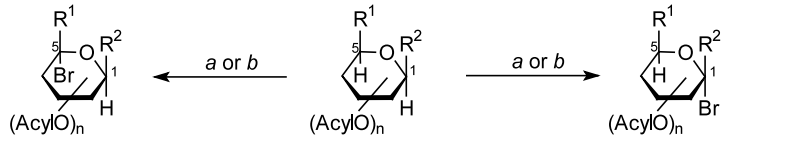
Abstract—$KBrO_3$–$Na_2S_2O_4$ in CH_2Cl_2–H_2O or $PhCF_3$–H_2O biphasic solvent systems was applied to the bromination of several monosaccharide derivatives having capto-datively substituted reaction centres. With less reactive compounds neat $PhCF_3$ was shown to be a suitable substitute of the health and environmentally hazardous carbon tetrachloride.

Radical-mediated bromination is one major procedure by which hydrogens at ring positions of carbohydrate derivatives can directly be replaced.[1–3] The regioselectivity of the transformation depends largely on the substituents at C-1 and C-5 (or C-4 in furanoid derivatives), the hydrogens bound to these carbon atoms being the subjects of the replacement,[2] as illustrated in Scheme 1. The brominated compounds offer several possibilities for further transformations either by homolytic or heterolytic pathways,[2] and many useful intermediates and biologically active products have been prepared by using this reaction as a key step in synthetic sequences.[4]

Generally bromine or NBS (methods *a* and *b*, respectively, in Scheme 1 and Table 1) are used for radical-mediated brominations either by illuminating the reaction mixture with a tungsten or heat lamp or by using benzoyl peroxide (Bz_2O_2) or AIBN as radical initiators. Refluxing carbon tetrachloride is the almost exclusively applied solvent which has sometimes been mixed with bromotrichloromethane or chloroform in reactions with carbohydrate derivatives.[2] However, accessibility of carbon tetrachloride has been seriously restricted in recent years especially because of its health hazards and ozone layer damaging property.



R^1 = H, CH_2OAc, CH_2OBz, CO_2Me
R^2 = α- or β-OAc, α- or β-OBz, β-Cl

R^1 = H, CH_2OAc, CH_2OBz
R^2 = β-Cl, β-CO_2Me, β-$CONH_2$, α- or β-CN, β-heterocycle

Scheme 1. *Reagents and conditions*: (*a*) Br_2, CCl_4, hν, reflux; (*b*) NBS, Bz_2O_2, CCl_4, reflux.

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With these concerns in mind alternative conditions were sought for typical radical-mediated brominations like those of aromatic side chains, and supercritical CO_2 was suggested as a solvent.[5] For small scale laboratory preparations the use of $NaBrO_3$–$NaHSO_3$ in the EtOAc–H_2O solvent mixture[6] seemed more appropriate, and with slight modifications this method was applied to cleave carbohydrate benzyl ethers and benzylidene acetals[7] as well as for the preparation of bis-*C*-glycosyl-1,2,4-thiadiazole derivatives.[8] The application of CH_2Cl_2, PhH, and their biphasic mixtures with water was investigated for the bromination, with bromine or NBS, of oligopyridine benzylic-methyl groups.[9] With 2,5-anhydro-aldonic esters 1,1,1-trichloroethane[4e] and with 2,6-anhydro-aldononitriles and -amides chloroform and dichloromethane[4f] were used as substitutes for CCl_4.

Given the usefulness of the bromination of carbohydrate derivatives and the environmental and health concerns of using CCl_4 as solvent, in order to find similar generally applicable reaction conditions, we have started a systematic investigation whose first results are disclosed here.

Several protocols were tried for the bromination of acetylated β-D-galactopyranosyl cyanide (Table 1): no reaction was observed with $KBrO_3$–$Na_2S_2O_4$ in the suggested[6,7] EtOAc–H_2O solvent system (method *c*), but in CH_2Cl_2–H_2O (method *d*), good to excellent yields were achieved; in order to avoid the use of the chlorinated solvents, benzotrifluoride[10] ($PhCF_3$, BTF), a hybrid organic-fluorous solvent was tried in a biphasic system (method *e*) and also as a neat medium (method *f*); bromination with NBS in CH_2Cl_2–H_2O at reflux temperature could also be performed (method *g*). Each of the tested methods gave yields comparable to those of the classical procedures using CCl_4 (methods *a* and *b*).

Taking into account the costs of the reagents as well as the simplicity of the protocols methods *d* and *e* were investigated† further with other carbohydrate derivatives (Table 2). It can be seen that bromination of capto-datively substituted reaction centres[2] (entries 1–10) gives similar yields by methods *a*, *b*, and *d*, and the yields are somewhat lower with method *e*. Bromination of acetylated β-D-glucopyranosyl azide (entry 11) by method *d* resulted in a much lower yield than with method *b*. Non-captodative centres (entries 12 and 13) were unreactive under conditions used in methods *d* and *e*, while the use of neat BTF (method *f*) allowed C-5 bromination only with the benzoylated substrate.

In conclusion, we have shown that bromination of a wide range of carbohydrate derivatives is possible by using the $KBrO_3$–$Na_2S_2O_4$/CH_2Cl_2–H_2O reagent–solvent system. The chlorinated solvent can be replaced by benzotrifluoride which, applied as a neat solvent, can also facilitate bromination of rather unreactive centres.

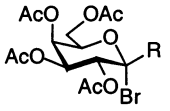
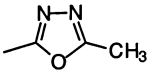
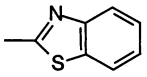
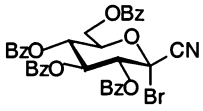
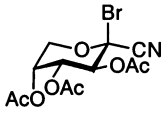
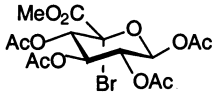
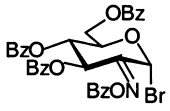
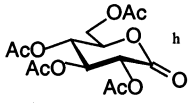
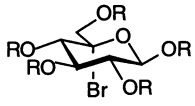
Table 1. Bromination of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl cyanide[a]

	Method	Reaction time (h)	Yield (%)
a	Br_2, CCl_4, hν, reflux	0.5	88
b	NBS, Bz_2O_2, CCl_4, reflux	2	73
c	$KBrO_3$–$Na_2S_2O_4$ (6–6 equiv.) EtOAc–H_2O, rt	240	No reaction
d	$KBrO_3$–$Na_2S_2O_4$ (6–6 equiv.) CH_2Cl_2–H_2O, rt	24	79
		72[b]	99[b]
e	$KBrO_3$–$Na_2S_2O_4$ (6–6 equiv.) $PhCF_3$–H_2O, rt	27	88
f	Br_2, $PhCF_3$, hν, K_2CO_3, reflux	1	69
g	NBS, CH_2Cl_2–H_2O, AIBN, hν, reflux	3	75

[a] The reactions were performed with 0.1 g substrate.
[b] With 5 g substrate.

† General procedure: The sugar derivative (0.1 g) was dissolved in CH_2Cl_2 (3 ml, Method *d*) or BTF (3 ml, Method *e*), and $KBrO_3$ (6 equiv.) and $Na_2S_2O_4$ (6 equiv.) in aqueous solutions (3 ml of each) were added in one portion (in the case of larger scale reactions as in entries 1 and 7 of Table 2 the $Na_2S_2O_4$ solution was added dropwise to the other components). The mixture was stirred at room temperature until disappearance of the starting material (TLC), then diluted with CH_2Cl_2 in both Methods. A 1 M aqueous solution of $Na_2S_2O_5$ (3 ml) was added, well shaken, and then separated. The organic phase was further washed with satd. aqueous $NaHCO_3$ (2×5 ml), and water (5 ml), then dried with $MgSO_4$. After filtration and removal of the solvent(s) in vacuo the residue was purified by crystallization if necessary. The materials obtained exhibited NMR spectra identical with those reported.

Table 2. Bromination of carbohydrate derivatives[a]

Entry	Product	R	Isolated yield [%] (Reaction time [h]) Method[b]				
			a[2]	*b*[2]	*d*	*e*	*f*
1.		-CN	88 (0.5)	73 (2)	79 (24) 99[c] (72)	88 (27)	69 (1)
2.		-CONH$_2$		50 (1)	68 (64)		
3.				75 (1)	89 (30)		
4.				67 (1)	61 (24)		
5.		-COOPCP[d]	99[e] (0.5)		no reaction	91 (139)	
6.		-COOMe	65[e] (1)		69 (6)		
7.			95[4f] (2.5)	62[4f] (2)	90 (32) 97[c] (168)		
8.				78 (0.5)	96[f] (22)		
9.				68 (1.3)	61 (240)	51 (54)	
10.				85 (0.3)	95[g] (5.5)	78 (6)	
11.				45[11] (1)	22 (100)		
12.		Ac		82 (2)	no reaction (120)		decomposition
13.		Bz	77 (8.5)	43 (4)	no reaction (288)	no reaction (48)	54 (2.5)

[a] The reactions were performed on 0.1–0.3 mmol scales unless otherwise indicated.
[b] For methods see Table 1.
[c] With 5 g starting material.
[d] PCP = pentachlorophenyl.
[e] In $CHCl_3$.
[f] Pure crude product (yield: 75% after crystallization from ethanol).
[g] Pure crude product (yield: 80% after crystallization from ethanol).
[h] From 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide.

Acknowledgements

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