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An Improved Synthesis of Per(6-Deoxyhalo) Cyclodextrins Using *N*-Halosuccinimides – Triphenylphosphine in Dimethylformamide

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Per(6-deoxy-6-halo) cyclodextrins (bromo, chloro or iodo) have been prepared in excellent yield and high selectivity by treatment of the native cyclodextrins with the corresponding *N*-halosuccinimide and triphenylphosphine in *N,N*-dimethylformamide.

Per(6-deoxyhalo)cyclomaltooligosaccharides (cyclodextrins, CD) constitute an important and versatile class of compounds which has already been widely exploited for the preparation of numerous useful cyclodextrin derivatives arising from either intra- [1] or intermolecular displacement reactions [2]. A number of methods for the per(C-6) halogenation of cyclodextrins have been already reported involving, as a general concept, reaction of the native CD with a Vilsmeier dimethylimidoyl halide reagent in *N,N*-dimethylformamide. In the pioneer report of Takeo et al. [3], the reagent was generated in situ from methanesulfonyl bromide and DMF. Improved results have been reported with the Evans' et al. [4] methanesulfonyl chloride in DMF reagent, alone [5] or in the presence of imidazole [6]. In situ formation of the Vilsmeier iodide or bromide from triphenylphosphine and iodine or bromine in DMF was a further convenient improvement for the preparation of per(6-deoxyiodo) and per(6-bromodeoxy) α- and β-CD [1, 7] although prior isolation of the Vilsmeier bromide was subsequently claimed to be preferred for the preparation of **1–3** [8]. The more stable and easier to handle bromo- or chloromethylenemorpholinium bromide and chloride were quite recently proposed [9] for the preparation of per(6-bromodeoxy) **1–3** and per(6-chlorodeoxy) **4–6** cyclodextrins.

We now report an even more general and high yielding methodology for the preparation of per(6-bromodeoxy)- **1–3**, per(6-chlorodeoxy)- **4–6**, and per(6-deoxyiodo)cyclomaltooligosaccharides **7–9** based on the use of commercially available *N*-halosuccinimides (bromo-, chloro-, or iodo-) in the presence of triphenylphosphine, a reagent previously introduced by Hanessian et

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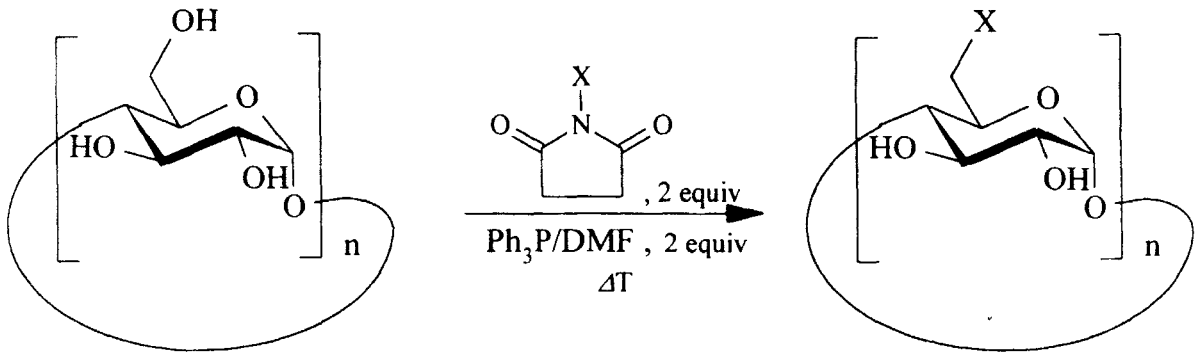

	n=6	n-7	n=8
CD	α	β	γ

	n=6	n-7	n=8
X=Br	**1**	**2**	**3**
X=Cl	**4**	**5**	**6**
X=I	**7**	**8**	**9**

SCHEME 1

al. [10] for the halogenation of monosaccharides and nucleosides. (SCHEME 1) Reaction of cyclomaltooligosaccharides (-hexaose, -heptaose, or -octaose) in DMF with 2 equiv of each *N*-bromo- or *N*-chlorosuccinimide and triphenylphosphine at 70–80 °C for 3–4 h, followed by the addition of methanol in order to destroy the excess of reagent and subsequent alkalinisation to pH 9 of the reaction mixture, yielded the corresponding per(6-bromo) or per(6-chloro) cyclodextrins as almost pure amorphous powders by pouring the solution into water, and washing out the residual triphenylphosphine oxide with methanol from the recovered precipitate.

Physical data for per(6-bromo-6-deoxy) and per(6-chloro-6-deoxy) α-, β-, and γ-CD **1–6** agree with lit. (Table I). The purity of the compounds was confirmed by FABMS which showed in every case prominent molecular ions and absence of ions for partly derivatized CD. The ^{13}C NMR spectra displayed only one set of signals for C-11C-6 as expected from the six, seven, and eight fold symmetries expected for uniformly substituted compounds.

When, however, the same protocol as above was applied to the preparation of per(6-deoxy-6-iodo) CD **7–9**, using *N*-iodosuccinimide as halide donor, the FABMS displayed minor signals at 110 mu or multiple of 110 mu below the expected molecular ion indicating some uncomplete substitution. Kuszmann and coll. [11] have already pointed out that two pathways involving either a dimethylformamidium halide or a phosphonium halide are both operative in the *N*-halosuccinimide-triphenylphosphine reaction scheme with alcohols. Enhanced susceptibility towards hydrolysis of the formamidinium iodide salts might explain the uncomplete substitution with the *N*-iodosuccinimide reagent. In fact, when the solution of α-, β-, and γ-CD in DMF was dried by azeotropic distillation with toluene prior to the reagent addition, pure per(6-deoxy-6-iodo) α-, β-, and γ-cyclodextrins were obtained in high yield (Table I).

TABLE I Yields and physical data for per(6-deoxyhalo) cyclodextrins **1–9**

CD	*yield (%)*	*mp (°C)*	$[\alpha]_D$ (°) (*c* 1, DMF)	*FAB (glycerol) m/z* $[M + H]^+$	*Lit.*	*mp (°C)*	$[\alpha]_D$ (°) (*c* 1, DMF)
1	85	194	+92.1	1350.4	[7]	222	+124 (*c* 1.5, DMF)
2	96	202	+84.7	1576.5	[7]	214	+78 (*c* 1.8, DMF)
3	88	198	+105.5	1800.6	[2]	223	+111.6
							(*c* 0.2, Me_2SO)
4	76	256	+112.4	1104.5	[9]	254	+116.5
				$[M + Na]^{+a}$			
5	93	240	+113.8	1285.0	[5]	> 265	–
				$[M + Na]^{+a}$	[9]	245	+122.1
6	93	222	+134.8	1445.1[b]	[9]	238	+149.1
7	81	231	+64.7	1654.4	[1][7]	227	+95 (*c* 1.3, DMF)
			(*c* 0.5, DMF)	$[M + Na]^+$			
8	89	218	+66.3	1925.9	[1]	235	+66.1 (*c* 1.1, DMF)
			(*c* 0.5, DMF)	$[M + Na]^+$,	[7]	224	+79.5 (*c* 1, DMF)
9	81	213	+75.3	2198.7	[12]	231	+72.8
			(*c* 1.1, Me_2SO)	$[M + Na]^+$			(*c* 1.1, Me_2SO)

a. NBA matrix.
b. glycerol/Me2SO matrix.

General Procedure for the Preparation of Per(6-bromo-6-deoxy) and Per(6-chloro-6-deoxy) Cyclodextrins 1–6

To a solution of dried cyclomaltooligosaccharide (1 mmol) in DMF (40 mL), the corresponding *N*-halosuccinimide (12–16 mmol, 2 equiv/OH-6) and triphenylphosphine (12–16 mmol, 2 equiv/OH-6) were added at ambient temperature. The reaction mixture was protected by a drying tube ($CaCl_2$) and heated for 3–4 h at 70–80 °C. After completion (TLC, 7:7:5:4 EtOAc – 2-propanol – 25% aq NH_4Cl – water), MeOH was added at room temperature and stirring was continued for 30 min. The reaction mixture was then cooled to ~15 °C and the pH was adjusted to 9 with 3 M MeONa in MeOH, while stirring for further 30 min. It was then poured into stirred ice-water (600 mL) resulting in the formation of a precipitate which was filtered (fritted glass no. 3), washed with MeOH, and dried. Yields and physical data with reference to lit. are collected in Table I.

General Procedure for the Preparation of Per(6-deoxy-6-iodo) Cyclomaltooligosaccharides 7–9

To a solution of dried cyclomaltooligosaccharide (1 mmol) in DMF (40 mL), toluene (3 × 10 mL) was added and evaporated using a rotatory evaporator. To the resulting solution, *N*-iodosuccinimide (18–24 mmol, 3 equiv/OH-6) and triphenylphosphine (18–24 mmol, 3 equiv/OH-6) were added with stirring. The reaction mixture was heated at 90 °C for 20 h

while protected by a drying tube. Isolation of the products followed the above procedure.

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