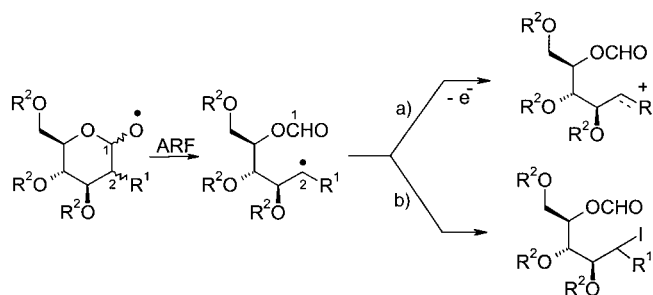


Fragmentation of Carbohydrate Anomeric Alkoxy Radicals: A New Synthesis of Chiral 1-Halo-1-iodo Compounds**

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1,1-Dihaloalkanes, and specifically the highly reactive 1,1-diiodoalkanes, are versatile compounds in organic synthesis.^[1] Several methods for the synthesis of these compounds have been developed.^[2] Among them are the iodolysis of 1,1-bis(diisobutylaluminio)alkanes,^[2a] the alkylation of diiodomethylthium or diiodomethylsodium with reactive electrophiles,^[2b] and the reaction of 1,1-bis(trifluoromethyl)sulfonyloxy-alkanes with magnesium iodide.^[2c] None of these approaches can be easily applied to the preparation of complex or sensitive molecules. Consequently, in the majority of cases the 1,1-diiodoalkanes obtained are derivatives of relatively simple hydrocarbons.^[3] A similar situation is found for the synthesis of mixed halo-iodo species, for example 1-fluoro-1-iodo,^[4] 1-chloro-1-iodo,^[5] and 1-bromo-1-iodo compounds.^[6] Moreover, there are sufficient drawbacks to most of these procedures to justify the need for a general and practical method of generating these types of compounds under mild conditions.

Earlier research from our laboratory^[7] has shown the facile formation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals by reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine. The reactions presumably proceeds through an alkyl hypiodite intermediate.^[8] Subsequently the alkoxy radical undergoes fragmentation of the C1–C2 bond and gives rise to a C2 radical (Scheme 1). The substituent at C2 may have a strong influence on the ultimate fate of the radical. When the substituent is an ether group the radical is rapidly oxidized by an excess of the hypervalent iodine reagent to give an oxycarbenium ion (path a). Inter- or intramolecular trapping by nucleophiles leads to a variety of modified carbohydrate derivatives with one carbon atom less.^[7] The presence of a stronger electron-withdrawing group at C2 (e.g., an ester group, path b) decreases the electron density at this position and oxidation of the radical should be more difficult. This opens the possibility of competitive trapping of the intermediate radical by atoms of iodine from the reaction medium.



Scheme 1. The mechanism of alkoxy radical fragmentation (ARF). a) R¹ = O-alkyl; R² = protecting group. b) R¹ = OC(O)-alkyl, halogen; R² = protecting group. See text for details.

The α -iodoalkyl esters thus formed may be interesting chiral synthons.^[7f]

With the above results in mind, we decided to introduce a halogen atom at C2 in order to develop an advantageous methodology for preparing 1-halo-1-iodo compounds. We carried out the synthesis of 1,2-halohydrins of carbohydrates in pyranose and furanose form as outlined in Table 1. 1,2-Chlorohydrins, 1,2-bromohydrins, and 1,2-iodohydrins were prepared from the corresponding 2-deoxy-hex-1-enitol by reaction with *N*-chlorosuccinimide,^[9] *N*-bromoacetamide,^[10]

Table 1. Synthesis of 1-halo-1-iodo compounds.^[a]

Entry	Substrate	<i>t</i> [h]	Product	Yield [%] (<i>dr</i>)
1	1 R = F	1	5 R = F	96 (1:1)
2	2 R = Cl	3	6 R = Cl	95 (1:1)
3	3 R = Br	1.5	7 R = Br	99 (1:1)
4	4 R = I	0.75	8 R = I	92
5	9 R = Cl	1.5	12 R = Cl	96 (1:1)
6	10 R = Br	2	13 R = Br	98 (1:1)
7	11 R = I	0.5	14 R = I	84
8	15 R = Cl	1	18 R = Cl (<i>R</i> and <i>S</i>)	92 (3:2)
9	16 R = Br	1.5	19 R = Br (<i>R</i> and <i>S</i>)	93 (3:2)
10	17 R = I	1	20 R = I	90
11	21 R = Cl	0.5	24 R = Cl	83 (3:2)
12	22 R = Br	0.5	25 R = Br	92 (3:2)
13	23 R = I	0.5	26 R = I	69

[a] Halohydrin (1 mmol) in CH₂Cl₂ (50 mL) containing DIB (1.5 mmol) and iodine (1.5 mmol) was irradiated with two 80-W tungsten filament lamps at reflux temperature.

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[**] This work was supported by the Investigation Programme no. PB96-1461 of the Dirección General de Investigación Científica y Técnica, Spain. C.C.G. and C.R.-F. thank the Ministerio de Educación y Ciencia, Spain, and the Dirección General de Universidades e Investigación del Gobierno de Canarias, respectively, for fellowships.

Supporting information for this article is available on the WWW under <http://www.angewandte.com> or from the author.

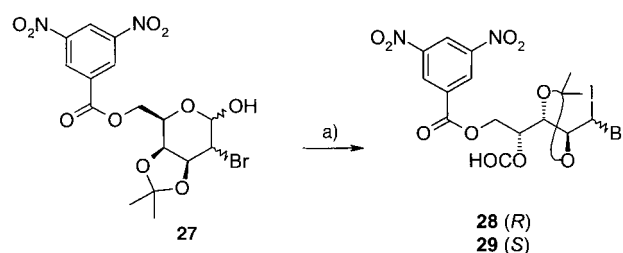
and *N*-iodosuccinimide,^[11] respectively, in THF/water. The fluorohydrin **1** was synthesized by reaction of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-*D*-arabino-hex-1-enitol with xenon difluoride,^[12] followed by acid hydrolysis of the anomeric fluoride, peracetylation, and selective anomeric *O*-deacetylation with hydrazine acetate.^[13] As detected spectroscopically, the halohydrins were diastereoisomeric mixtures in most cases.^[10] Chromatographically homogeneous products which gave correct elemental analyses were used in the fragmentation reaction.

The alkoxy radical fragmentation (ARF) reactions were performed under the conditions stated in Table 1, with (diacetoxyiodo)benzene and iodine in CH₂Cl₂ at reflux temperature and irradiation with two 80-W tungsten filament lamps. Complete consumption of the starting material was observed in all cases. In entries 1–4 of Table 1 we compare the reaction of several halohydrins of the 2-deoxy-2-haloglucopyranose type. The reaction proceeded smoothly in excellent yield to give 1-halo-1-iodo-arabinitol derivatives **5**–**8**, without affecting the stereogenic integrity of the adjacent center. As expected, diastereoselection was very low for the mixed halogen compounds, which were obtained as a chromatographically inseparable mixture of isomers. These compounds seem to be stable for long periods of time and were handled without any special precautions apart from avoiding overexposure to light or heat. The *galacto* halohydrins **9**–**11** provided a new series of 5-halo-5-iodo-arabinitol derivatives **12**–**14**, also in excellent yields and without any diastereoselectivity (entries 5–7).

Several differently protected galactopyranose halohydrins, **15**–**17**, were prepared in order to study the influence of the protecting groups on the selectivity of the fragmentation reaction (entries 8–10). A modest increment in the diastereoselectivity is observed as the steric demand of the starting halohydrin increases (compare entries 5 vs. 8 and 6 vs. 9). The mixed 1-chloro-1-iodo and 1-bromo-1-iodo diastereoisomers **18** and **19** can now be separated by chromatotron chromatography. The configuration at C1 was tentatively assigned on the basis of the significant deshielding of the C3 resonance ($\delta_S - \delta_R = 1.8$ – 2.8) observed in the ¹³C NMR spectra of the *S* series (see below).

To further extend the scope of the described method, we investigated the feasibility of applying it to the five-membered glucofuranose halohydrins **21**–**23** (entries 11–13). In all cases the reaction proceeded analogously to give a new set of halo-iodo-arabino derivatives **24**–**26** with a very different protection pattern.

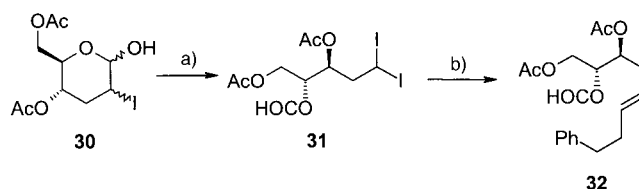
Since neither of the diastereoisomers of **18** or **19** could be crystallized, we prepared 3,5-dinitrobenzoate **27** (Scheme 2) in order to establish the absolute configuration at C1 by X-ray diffraction experiments. The diastereoisomeric mixture obtained (dr 2:1) after the ARF reaction was separated by chromatography to provide the 5-bromo-5-iodo-arabinitol derivatives **28** and **29**. Crystallization of **28** from EtOAc/*n*-hexane yielded colorless crystals suitable for X-ray studies, which confirmed the *R* configuration at C1.^[14] The observed deshielding of the C3 signal in the ¹³C NMR spectrum of **29**, possibly due to restricted rotation around the C1–C2 bond, allowed us to tentatively assign the



Scheme 2. Alkoxy radical fragmentation of halohydrin **27**. a) DIB (1.5 equiv), iodine (1.5 equiv), CH₂Cl₂, *hν*, reflux, 1 h, 93%. DIB = (diacetoxyiodo)benzene.

configuration at C1 for the mixed 1-halo-1-iodo compounds prepared previously.

Preliminary attempts to use these compounds in a Takai (*E*)-olefination^[15] of aldehydes were unsuccessful. For example, when compounds **8** and **20** were treated with hydrocinnamaldehyde with the complex chromium(II) chloride–DMF as reagent, only a mixture of the corresponding (*Z*)- and (*E*)-1-iodoalkenes was obtained by β elimination. Nevertheless, when pentitol **31**^[16] was submitted to the above conditions the expected (*E*)-olefin **32** was obtained in good yield (Scheme 3). It is worth noting the stability of the highly



Scheme 3. Alkoxy radical fragmentation of halohydrin **30**. a) DIB (1.5 equiv), iodine (1.5 equiv), CH₂Cl₂, *hν*, reflux, 30 min, 94%; b) CrCl₂ (4 equiv), hydrocinnamaldehyde (Ph(CH₂)₂CHO; 2 equiv), DMF (4 equiv), THF, RT, 30 min, 70%.

sensitive formyl ester under the reaction conditions. In the majority of cases, this reaction has been used in synthetic organic chemistry as an (*E*)-ethylenation of aldehydes with diiodoethane.^[17]

The new ARF reaction presented here offers special advantages for the synthesis of *gem*-dihalo compounds, including high efficiency, procedural simplicity, and mild reaction conditions that are compatible with the protecting groups most frequently used in carbohydrate chemistry.^[18] It is hoped that these 1-halo-1-iodo compounds will be powerful building blocks for organic synthesis since the carbohydrate would potentially be amenable to prior manipulation to provide more specific or complex systems.

Received: December 28, 2000
Revised: March 27, 2001 [Z16345]

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A Schizophrenic Water-Soluble Diblock Copolymer**

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Recently we reported the first example of a water-soluble diblock copolymer capable of existing in three states in aqueous solution, namely, as conventional micelles, reverse micelles, and molecularly dissolved (non-micellar) chains.^[1] This diblock copolymer was based on two tertiary amine methacrylates, 2-(diethylamino)ethyl methacrylate (DEA) and 2-(N-morpholino)ethyl methacrylate (MEMA), and was synthesized using group transfer polymerization,^[2, 3] a type of anionic polymerization which is particularly well suited to the living polymerization of methacrylates at room temperature. Formation of micelles with DEA cores was achieved merely by adjusting the solution pH value, but formation of the reverse micelles with MEMA cores required the addition of a large amount of electrolyte to selectively “salt out” the MEMA chains. To date, this remains the only well-documented example of such a “schizophrenic” block copolymer.^[4]

Since its discovery in 1995,^[5] atom-transfer radical polymerization (ATRP) has proved to be a reliable and versatile method for the synthesis of functional, controlled-structure copolymers.^[6] This free-radical polymerization chemistry is “pseudo-living” and particularly tolerant of monomer functionality; it has been used to polymerize a wide range of hydrophilic monomers with narrow molecular weight distributions and controlled architectures.^[7]

Herein we describe the facile ATRP synthesis of a new diblock copolymer based on poly(propylene oxide) (PPO) and DEA (Scheme 1a). This diblock copolymer dissolves molecularly in cold aqueous solution but undergoes reversible micellar self-assembly to give either PPO-core micelles or DEA-core micelles. Unlike the DEA–MEMA diblock copolymer reported previously, both types of micelles can be formed solely by the judicious selection of solution pH value and solution temperature.

It is well known that PPO with an M_n of around 2000 dissolves in cold, dilute aqueous solution but becomes insoluble at 20 °C; its lower critical solution temperature (LCST) lies between 10 °C and 20 °C, depending on the solution concentration.^[8] Similarly, we have recently shown that DEA homopolymer is soluble in acidic solution as a weak cationic polyelectrolyte (due to protonation of the tertiary amine residues), but precipitates from solution at around neutral pH. We have recently published several papers

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[**] We thank EPSRC for a post-doctoral fellowship for S.Y.L. (GR/N17409). Dr. P. McKenna of Laporte Performance Chemicals, Hythe (UK), is thanked for the gift of the monohydroxy-capped PPO. The reviewers are thanked for their helpful and constructive comments.

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