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Synthesis and stability of mixed nonfluorinated 1,1,1-trihalo-alkanes

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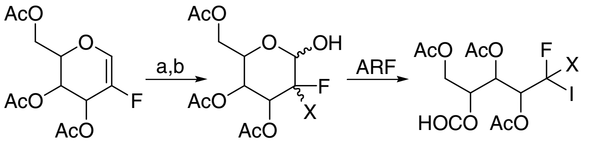
Abstract—1,1,1-Trihaloalkanes of the types R–CCl_2I, R–CClBrI, and R–CBr_2I belonging to 1,1,1-trihalo-1-deoxy-D-arabinitol series of alditols were prepared and fully characterized by anomeric alkoxyl radical fragmentation of the corresponding 2,2-dihalo-2-deoxy-D-*arabino*-hexopyranose derivatives. The analogous diiodohalo compounds R–$CClI_2$ and R–$CBrI_2$ could not be prepared by this methodology. The results strongly suggest that the stability of the mixed trihalo alditols decreases with increasing bulkiness of the halogen atoms.

1,1-Dihalo-alkanes and alkenes have now attracted much interest for their role as important intermediates in organic synthesis, for example, in the reactions of Takai and Corey or in the sp^2–sp^2 coupling via de formation of vinyl halides.[1] In contrast, the chemistry of trihalides, especially mixed 1,1,1-trihalo-alkanes of the types R–CXYZ and R–CXY_2, has comparatively received much less attention.[2] This is somewhat surprising given that most of the mixed trihalomethane compounds CHXYZ and $CHXY_2$ have been prepared and characterized.[2,3] Some studies on the absolute configuration of bromochlorofluoromethane, one of the simplest chiral molecules, are worth highlighting.[4] As another point of interest, polyhalogenated carbons have been uncovered in a growing number of naturally occurring compounds, that in recent years have assumed an important role in natural products and environmental chemistry.[5]

A careful search revealed, to our surprise, that very little information about the preparation and properties of five nonfluorinated systems of the R–CBrIX and R–CClIX types (R = alkyl, X = Cl, Br, I) is available in the open literature.[6] Indeed, with the exception of R–CCl_2I,[6a] compounds belonging to the other four systems are hitherto practically unknown. Although some reports claimed the formation of a very few compounds belonging to the R–$ClBr_2$,[6b] R–CClBrI,[6c] R–$CClI_2$,[6d] and none for R–$CBrI_2$[6e] systems, in some cases, they were obtained as byproducts and in general have been poorly characterized. This may be attributable to the incompatibility between the low stability of these compounds and to the relatively hard conditions required for the methodologies reported up to now.

Earlier research from our laboratory has shown the facile formation of mixed 1,1,1-fluoroiodohalo alditols by reaction of appropriate 2-deoxy-dihalohydrins from carbohydrates with hypervalent iodine reagents in the presence of iodine through an alkoxyl radical fragmentation (ARF) (Scheme 1).[7] The necessary 2-deoxy-dihalohydrins (**2** and **3**) were prepared by halohydroxylation of



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2 X = F
3 X = Br

4 X = F
5 X = Br

Scheme 1. Reagent and conditions: (a) F–TEDA–BF_4 (Selectfluor), CH_3NO_2/H_2O (4:1), rt, 14 h and then refluxed 30 min; (b) NBA, THF/H_2O (10:1), rt, 1 h. ARF = alkoxyl radical fragmentation reaction.

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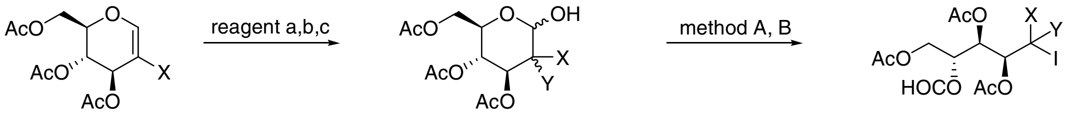
Table 1. Synthesis of nonfluorinated 1,1,1-trihalo-alditols



Entry		X	Reagent[a]		X	Y	Yield (%)	Method[b]		X	Y	Yield[c] (%)
1	**6**	Br	a	**8**	Br	Cl	79	B	**13**	Br	Cl	65
2	**6**	Br	b	**9**	Br	Br	85	A	**14**	Br	Br	65[d]
3	**7**	Cl	a	**10**	Cl	Cl	69	A	**15**	Cl	Cl	69
4	**6**	Br	c	**11**	Br	I	87	A, B	**16**	Br	I	—
5	**7**	Cl	c	**12**	Cl	I	84	A, B	**17**	Cl	I	—

[a] (a) NCS, THF/H_2O, reflux, 2–4 h; (b) NBA, THF/H_2O, rt, 1 h; (c) NIS, THF/H_2O, rt, 14 h.

[b] The ARF reactions were performed in dry CH_2Cl_2 (50 mL/mmol) containing (diacetoxyiodo)benzene (DIB) (1.5 mmol) and iodine (1 mmol) per mmol of substrate under two different conditions: Method A, by irradiation with two 80 W tungsten-filament lamps at reflux temperature for 1 h, and method B, by heating at reflux temperature with complete exclusion of light for 1 h. Overexposure to light or heat was avoided during all the purification step.

[c] Isolated yield.

[d] 2,3,5-Tri-*O*-acetyl-1,1,1-tribromo-1-deoxy-4-*O*-formyl-D-arabinitol (**18**) 8% was also obtained.

readily accessible 2-deoxy-2-fluoro-hex-1-enitol **1**.[8] This protocol works extremely well for the preparation of relatively stable systems of the R–$CFHal_2$ type, and a number of 1,1-difluoro-1-iodo- **4** and 1-bromo-1-fluoro-1-iodo-alditols **5** have been synthesized.[9]

The mildness of the reaction conditions and the high functional group tolerance observed encouraged us to extend this methodology to the preparation of the less stable 1,1,1-trihaloalkanes possessing heavier halogens commented above. Nonfluorinated systems of the type R–CBrIX and R–CClIX (R = alkyl, X = Cl, Br, I; five compounds in total) were selected.

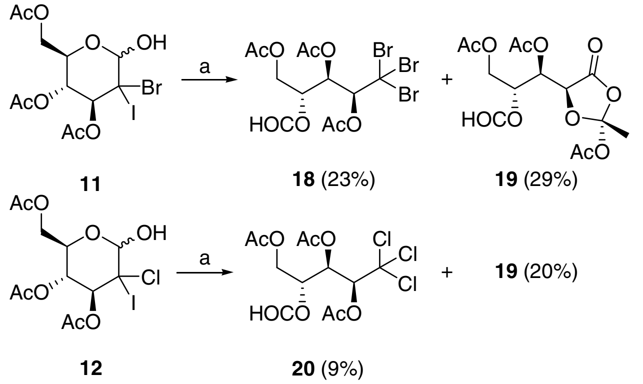
The synthesis is outlined in the scheme of Table 1. 2-Deoxy-2-bromo-hex-1-enitol derivative **6** has been prepared as previously described from 3,4,6-tri-*O*-acetyl-2-deoxy-hex-1-enitol (tri-*O*-acetyl-D-glucal).[10] Notwithstanding, 2-deoxy-2-chloro-hex-1-enitol **7** has been synthesized previously only by chlorination of tri-*O*-acetyl-D-glucal, and subsequent dehydrohalogenation of the chlorine atom at C-1.[11] Alternatively, **7** was prepared by using a more convenient method, that avoided the chlorination step and that essentially follows the route utilized for the synthesis of **6** (see Supplementary data).

Three of the required 2,2-dihalohydrins **8**, **9**, and **11** were prepared by reaction of 2-deoxy-2-bromo-hex-1-enitol **6**, respectively, with NCS, *N*-bromoacetamide (NBA), and NIS in THF/H_2O (Table 1, entries 1, 2, and 4). A similar methodology has been successfully applied to 2-deoxy-2-chloro-hex-1-enitol **7** to give the other two 2,2-dihalohydrins **10** and **12** (Table 1, entries 3 and 5). Apart from 2,2-dichloro-2-deoxy-D-*arabino*-hexopyranose **10**, the other 2,2-dihalohydrins have not been previously described.[11]

The ARF reactions were accomplished as stated in Table 1, with (diacetoxyiodo)benzene and iodine in CH_2Cl_2, either photochemically by irradiation with two 80 W tungsten-filament lamps at reflux temperature (Method A), or thermally by heating at reflux temperature under complete exclusion of light (Method B). Only the experiments giving the best yield of the expected trihaloalditol are shown in Table 1. The results summarized as entries 1–3 showed that these reactions proceeded smoothly for dihalohydrins **8**–**10** to afford the corresponding 1,1,1-trihalocompounds **13**–**15**. On the contrary, the reaction of haloiodohydrins **11** and **12** fails completely since not even traces of the expected diiodobromo **16** and diiodochloro **17** were detected under either photochemical or thermal conditions (entries 4 and 5), only decomposition products being obtained (vide infra). The structures of compounds **13**–**15** were confirmed by ^1H NMR and ^{13}C NMR spectroscopy including DEPT, COSY, HMQC, and HMBC experiments. Special attention was devoted to the isotope pattern of the molecular ion in the MS spectra, that in all cases matched those calculated. Compounds **13**–**15** can be purified by column chromatography and stored in a refrigerator (−20 °C) in the dark for a short period of time but decomposed rapidly under irradiation with ambient light.[12]

The products obtained during the ARF of **11** and **12** deserve a brief comment (Scheme 2). The 1,1,1-tribromo alditol **18** and the interesting orthoester **19** were isolated, from the ARF of **11**, as the two principal compounds. A minor amount of 2,3,5-tri-*O*-acetyl-4-*O*-formyl-D-arabinonic acid (**22**) was also isolated and identified as its methyl ester.[13] Orthoester **19** was obtained as a single stereoisomer and its structure determined by X-ray crystallographic analysis.[14]

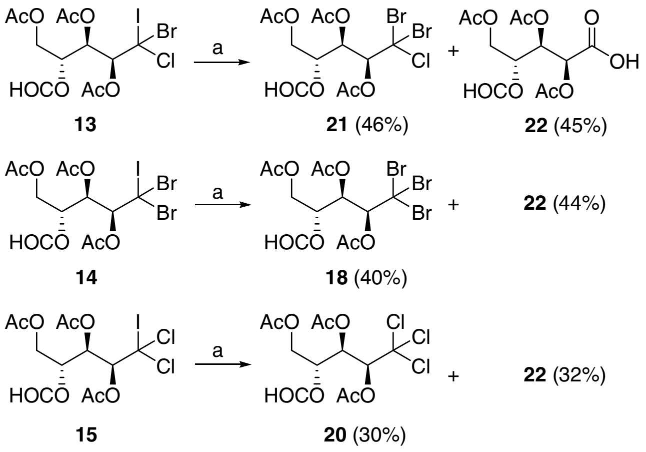
The formation of **18** could be rationalized by proposing that the expected diiodobromo **16** is indeed initially formed, but under the reaction conditions rapidly undergoes an intermolecular iodo–bromo exchange reaction.[15] The orthoester **19** is formed very probably from the debrominated molecules, presumably through a transient intermediate acyl halide which undergoes a neighboring group participation reaction by the C-2 acetyl group.[16] The oxocarbenium ion thus formed is subse-



Scheme 2. Reagent and conditions: (a) (diacetoxyiodo)benzene (DIB) (1.5 mmol), I_2 (1 mmol), hν, reflux temperature, 1 h, 2,3,5-tri-*O*-acetyl-4-*O*-formyl-D-arabinonic acid (**22**) isolated and identified as its methyl ester was also obtained (5% from **11** and 33% from **12**).

quently trapped by an acetate anion coming from the (diacetoxyiodo)benzene. Similar results were observed for the ARF of iodochlorohydrin **12** although not a totally unexpected lower yield of trichloroalditol **20** was obtained (Scheme 2).

The effect of light on the stability of trihalocompounds **13**–**15** was also studied and the results are illustrated in Scheme 3.[17] A solution of the trihalocompound in $CDCl_3$ was added to an NMR tube and irradiated with visible light (2 × 80 W tungsten-filament lamps), complete consumption of starting material being observed after 1 h (monitored by ^1H NMR). Compounds **13** and **14** were totally transformed respectively into **21** and **18** through an iodo–bromo exchange reaction. In both cases the debrominated compound was arabinonic acid derivative **22**[13] and the ratio between brominated and debrominated products was 1:1. An iodo–chloro exchange reaction was observed during the photolysis of dichloroiodo **15** and the ratio of chlorinated to dechlorinated compounds was also 1:1. It is worth noting that compounds **13**–**15** seem to be more stable under the visible light irradiation of the ARF reaction conditions than under similar irradiation in the pure state. Although a small percentage (8%) of photolytic decomposition product **18** is obtained during the ARF of dibromohydrin **9** (Table 1, entry 2), compounds **13** and **15** survived the irradiation of the ARF conditions without any detectable decomposition.



Scheme 3. Reagent and conditions: (a) $CDCl_3$, hν (2 × 80 W tungsten-filament lamps), 20–25 °C, 1 h.

The results obtained in the photoexperiments outlined in Scheme 3 strongly suggest that the photostability of the mixed trihalo molecules decreases with increasing steric bulkiness of the halogen atoms. Thus, the relative stability order is $\mathrm{R{-}CCl_2I}$ (**15**) > $\mathrm{R{-}CBrClI}$ (**13**) > $\mathrm{R{-}CBr_2I}$ (**14**) > $\mathrm{R{-}CClI_2}$ (**17**) > $\mathrm{R{-}CBrI_2}$ (**16**). The first three were prepared and fully characterized using this protocol but the last two diiodo compounds were found to decompose in situ via a halogen exchange reaction to give, respectively, the more stable 1,1,1-trichloro **20** and 1,1,1-tribromo **18**.

Acknowledgements

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Supplementary data

Experimental procedure and characterization data for compounds **7**–**15**, **18**–**21** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.118.

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