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Fragmentation of Carbohydrate Anomeric Alkoxyl Radicals: A New Synthesis of 1,1-Difluoro-1-iodo Alditols

Cosme G. Francisco, Concepción C. González, Nieves R. Paz, and Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206 La Laguna, Tenerife, Spain

esuarez@ipna.csic.es

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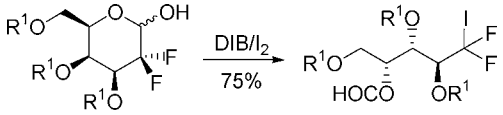
ABSTRACT



R^1 = Protective group; DIB = PhI(OAc)$_2$

The β-fragmentation of 2,2-difluoro-saccharide anomeric alkoxyl radicals, generated under oxidative condition by treatment of the respective alcohols with (diacetoxyiodo)benzene (DIB) and iodine, afforded 1,1-difluoro-1-iodo alditols in high yield. The reactivity of the fluorinated radical generated by rupture of the C–I bond has been preliminarily assessed by reductive deiodination with tributyltin hydride/AIBN and intermolecular allylation using the Keck reaction.

The selective introduction of fluorine into organic molecules and the profound effect this can have on their biological activity has been of great interest to synthetic and medicinal chemists.[1] The *gem*-difluoromethylene group, in particular, is of singular importance, and consequently, a number of methodologies for its synthesis have been published.[2] Knowing the reactivity of fluorinated radicals[3] we became interested in the synthesis of 1,1-difluoro-1-iodo alditols for use as chiral building blocks. These types of compounds could exploit radical methodology in their construction.[4] There are several procedures for the synthesis of difluoroalkyl iodides in the literature. Among those reported are the addition of diiododifluoromethane to olefins[5] and the oxidative decarboxylation of α,α-difluoro carboxylic acids under Hunsdiecker reaction conditions.[6]

In previous papers from this laboratory we have demonstrated the possibility of extending alkoxyl radical fragmentation (ARF) reactions to the preparation of 1,1-dihalo alditols.[7] The glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals were easily generated by reaction of 2-halo-

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(2) For a review, see: Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

(3) Dolbier, W. R. In *Topics in Current Chemistry*; Chambers, R. D., Ed.; Springer-Verlag: Berlin, 1997; Vol. 192, pp 97−163.

(4) Recent reactions of α,α-difluoro radicals: Nagashima, H.; Isono, Y.; Iwamatsu, S.-i. *J. Org. Chem.* **2001**, *66*, 315−319. Itoh, T.; Sakabe, K.; Kudo, K.; Ohara, H.; Takagi, Y.; Kihara, H.; Zaggati, P.; Renou, M. *J. Org. Chem.* **1999**, *64*, 252−265. Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459−3466. Buttle, L. A.; Motherwell, W. B. *Tetrahedron Lett.* **1994**, *35*, 3995−3998. Arnone, A.; Bravo, P.; Cavicchio, G.; Firgerio, M.; Viani, F. *Tetrahedron* **1992**, *48*, 8523−8540. Cavicchio, G.; Marchetti, V.; Arnone, A.; Bravo, P.; Viani, F. *Tetrahedron* **1991**, *47*, 9439−9448.

(5) For recent examples, see: (a) Yang, Z.-Y. *J. Fluorine Chem.* **2000**, *102*, 239−241. (b) Li, A.-R.; Chen, Q.-Y. *Synthesis* **1997**, 333−336. (c) Li, A.-R.; Chen, Q.-Y. *Synthesis* **1997**, 1481−1488.

(6) For recent examples, see: (a) Szlávik, Z.; Tárkányi, G.; Skribanek, Z.; Vass, E.; Rábai, J. *Org. Lett.* **2001**, *3*, 2365−2366. (b) Pedersen, S. D.; Qui, W.; Qui, Z.-M.; Kotov, S. V.; Burton, D. J. *J. Org. Chem.* **1996**, *61*, 8024−8031.

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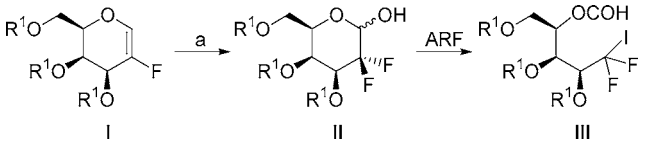
carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine or bromine. Subsequently, alkoxyl radical driven fragmentation of the C1−C2 bond afforded a C2 radical that could be trapped intermolecularly by halogen atoms from the medium. In this way, 1,1-dihalo alditols with one less carbon than the starting carbohydrate were obtained in excellent yields.

With these results in mind, we turned our attention to the synthesis of 1,1-difluoro-1-iodo alditols (**III**) following the methodology outlined in Scheme 1. The difluorohydrin (**II**)

Scheme 1. Synthesis and β-Fragmentation of 2,2-Difluoro-saccharides[a]

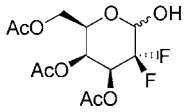
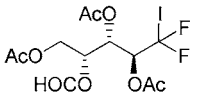
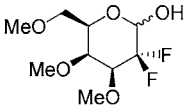
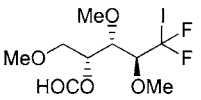
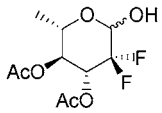
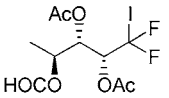
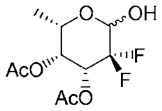
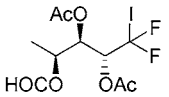
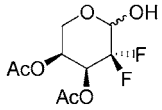
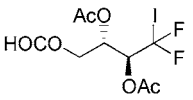


[a] Reagents and conditions: (a) F-TEDA-BF_4 (Selectfluor) (1.5 equiv), CH_3NO_2/H_2O (4:1, 10 mL), rt, 14 h and then refluxed 30 min. R^1 = protective group. ARF = alkoxyl radical fragmentation reaction.

was prepared from readily accessible 2-deoxy-2-fluoro-hex-1-enitol (**I**) by its reaction with F-TEDA-BF_4 (Selectfluor) in the presence of water.[8] 2-Deoxy-2-fluoro-hex-1-enitol derivatives (**I**) were, in turn, synthesized from the corresponding 2-deoxy-hex-1-enitols (glycals) by reaction with Selectfluor using magnesium bromide as nucleophile.[8b] Elimination of the resulting anomeric bromide obtained with TEA in CH_3CN afforded the required vinyl fluoride.[9] The ARF reaction of the difluorohydrin was expected to give the difluoroiodo compounds (**III**).

To explore the generality and scope of this methodology, experiments were carried out using a variety of 2-deoxy-2,2-difluoro hexopyranoses (entries 1−4) and pentopyranoses (entry 5) as described in Table 1. These difluorohydrins are

Table 1. Synthesis of 1,1-Difluoro-1-iodo-alditols[a]

entry	substrate	product	yield (%)[b]
1	 **1**	 **6**	75
2	 **2**	 **7**	57[c]
3	 **3**	 **8**	76
4	 **4**	 **9**	82
5	 **5**	 **10**	77

[a] All reactions were performed in dry CH_2Cl_2 (50 mL/mmol) under irradiation with two 80-W tungsten-filament lamps at rt for 1 h, containing 1.5 mmol (diacetoxyiodo)benzene (DIB) and 1 mmol I_2 per mmol of substrate. [b] Isolated yield. [c] Crude difluorohydrin **2** was used.

relatively unknown compounds, and to our knowledge, the only examples obtained hitherto described have been derivatives of D-glucose[8d−g] and L-rhamnose.[8h] The required 2-deoxy-2-fluoro-hex-1-enitol derivatives were obtained by applying the above-mentioned methodology to D-galactal (entries 1 and 2), L-rhamnal (entry 3), L-fucal (entry 4), and L-arabinal (entry 5) in 45−50% yield (two steps).

The ARF reactions were performed under the conditions stated, with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 at room temperature and irradiation with two 80-W tungsten filament lamps to give difluoroiodine compounds **6**−**10**. The reaction proceeded smoothly with complete consumption of the starting material and without isomerization of the adjacent stereogenic center. Fragmentation yields were 75−82%, except in the case of entry 2 where we used a crude difluorohydrin. The structures of compounds **6**−**10** were confirmed by ^1H and ^{13}C NMR spectroscopy including DEPT, COSY, HMQC, and HMBC experiments. These difluoroiodo alditols were quite stable and could be purified via chromatography over silica gel and handled without special precautions apart from avoiding overexposure to light or heat.

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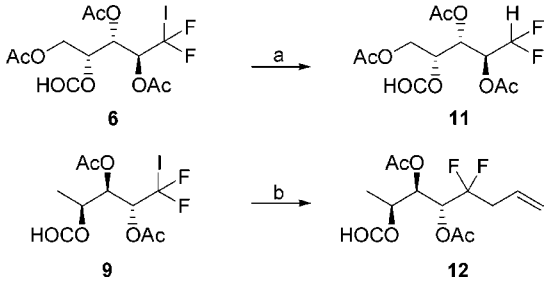
The synthetic usefulness of these compounds as chiral synthons has been preliminarily assessed, and the results are summarized in Scheme 2. We were particularly interested

Scheme 2. Radical Reactions of 1,1-Difluoro-1-iodo-alditols[a]



[a] Reagents and conditions: (a) tri-*n*-butyltin hydride (5 mmol), AIBN (0.4 mmol), PhH (30 mL), reflux, 0.5 h, 87%; (b) allyltri-*n*-butyltin (5 mmol), AIBN (0.4 mmol), PhH (30 mL), reflux, 1 h, 90%.

in the reactivity of the fluorinated radical generated by rupture of the C−I bond. The reductive deiodination of compound **6** with tributyltin hydride/AIBN led to 1,3,4-tri-*O*-acetyl-5-deoxy-5,5-difluoro-2-*O*-formyl-D-arabinitol (**11**) in excellent yield.

Radical intermolecular allylation was also possible following the Keck and Yates protocol.[10] Reaction of compound **9** with allyltributylstannane in the presence of AIBN gave the expected 3,4-di-*O*-acetyl-1,5,6,7,8-pentadeoxy-5,5-difluoro-2-*O*-formyl-L-*arabino*-oct-7-enitol (**12**) in 90% yield.

In summary, we believe that the methodology reported will be of interest for the facile preparation of *gem*-difluorinated chiral building blocks, which may themselves prove of value for incorporation into important complex target molecules. The further development of these studies is the subject of ongoing investigations in our laboratory.

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Supporting Information Available: Experimental procedure and characterization for all pure compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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