A Concise Method for the Preparation of Glycosyl Fluorides *via* Displacement Reactions of 1-Arylthioglycosides with 4-Methyl(difluoroiodo)benzene

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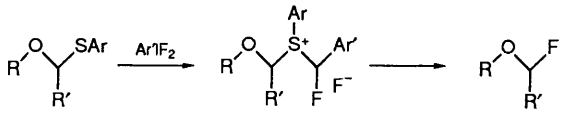
A variety of usefully functionalised 1-fluoroglycosides may be prepared under mild conditions from their corresponding arylthioglycoside derivatives by reaction with 4-methyl(difluoroiodo)benzene.

Extensive studies in recent years have shown that anomeric fluoroglycosides are not only useful biological probes in their own right[1] but also serve as versatile chemical building blocks,[2] especially for controlled glycosidation reactions.[3] A variety of preparative routes to this important class of compounds have accordingly been developed.[4] As a continuation of our interest in the development of iodoarene difluorides as reagents for selective fluorination,[5,6] we reasoned that the demonstrated affinity of a variety of hypervalent iodoarene reagents as electrophiles for divalent sulphur[7]

Table 1

Entry	1-Arylthio-glycoside	1-Fluoro-glycoside	Yield(%)	Ratio α:β
1	**1**	**2**	56	
2	**3**	**5**	65	3:2
3	**4**	**5**	78	3:2
4	**6**	**9**	75	
5	**7**	**8**	33	
6	**10**	**12**	80	3:1
7	**11**			
8	**14**	**15**	55	

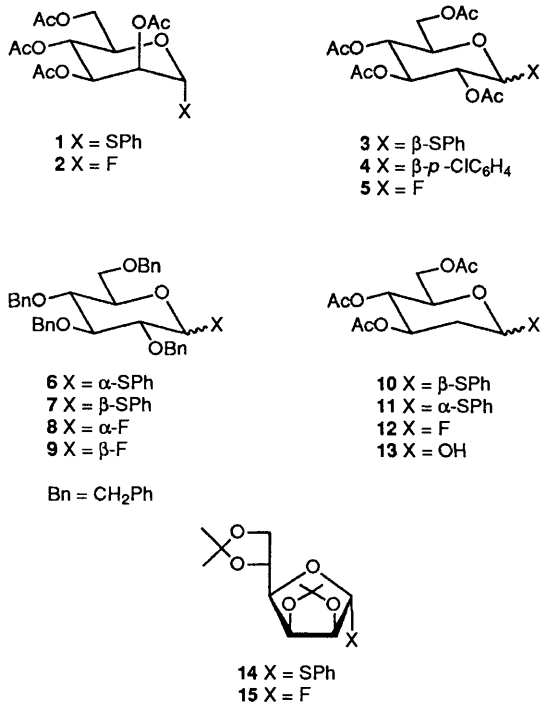


should provide an effective method for fluoride anion displacement from α-(arylthio)ethers, as indicated in Scheme 1. We now report the results of a preliminary study in this area, which confirms this idea, and in which the selection of readily available[8] 1-arylthioglycosides as substrates has led to a useful method for the preparation of glycosyl fluorides.

The yields of fluorinated products and the relative ratios of the α and β anomers produced from a variety of substrates are given in Table 1.

Several stereochemical features in these reactions are worthy of particular comment. Thus, in the first instance, we elected to study the case of the mannose derivative **1** which afforded the axial fluoroglycoside **2** as the exclusive fluorinated product. In this instance, the stereoelectronically favoured direction of axial attack by fluoride on an intermediate oxonium ion would be reinforced by neighbouring group participation from the axial acetate at C-2. Additional support for this rationale came from reactions of the glucose derivatives **3** and **4** which gave an isomeric mixture of fluoroglycosides **5** (α:β; 3:2), as anticipated by a situation in which equatorial acetoxonium ion participation from C-2 leads to preferential shielding of the α face and hence opposes the axial attack mode. We also note that the use of the *p*-chlorophenylthio moiety as an improved leaving group in this reaction leads to a significant increase in the yield (entry 3).

While the above reactions featuring acetoxonium ion participation imply that an S_N1 like mechanism is operating, we have also studied the stereochemical outcome of both the axial **6** (entry 4) and equatorial **7** (entry 5) α-phenylthioglycoside derivatives of tetra-*O*-benzyl-D-glucose where opportunities for participation are negligible. The isolated fluoroglycosides are indicative of clean S_N2 like inversion. The reduced yield in the case of the equatorial thioglycoside **7** (entry 5) may well be a result of competitive debenzylation[9] by the hypervalent iodine reagent since reaction of this substrate does not benefit from anomeric assistance to carbon–sulphur bond cleavage and so proceeds at a slower rate than derivative **6**. A striking contrast was observed in the behaviour of thioglycosides in the 2-deoxy series (entries 6 and 7), where reaction of the equatorial isomer **10** again proceeded predominantly with inversion to give **12** (α:β; 3:1), whereas the axial isomer **11** failed to yield any detectable quantities of fluoroglycosides and only **13** was isolated. Finally, we have also demonstrated (entry 8) that this method may be usefully applied to furanose derivatives. Thus, reaction of **14**, which cannot undergo S_N2 displacement because of its molecular geometry, gave **15** as a single isomer.



Scheme 1

From a practical standpoint, use of the readily prepared,[5] crystalline and organic-soluble reagent 4-methyl(difluoroiodo)benzene provides a simple and experimentally convenient method, without the necessity for the use of molecular fluorine or added excess fluoride anion sources at any stage. Moreover, in terms of carbohydrate chemistry, the reagent tolerates a useful variety of commonly encountered functional groups.

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