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Preparation of glycosyl fluorides from phenyl 1-seleno- and phenyl 1-telluroglycosides

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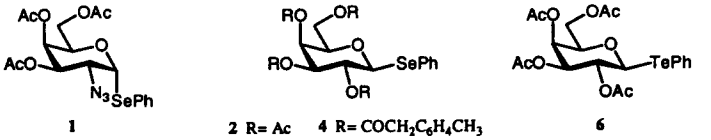
Abstract

Treatment of readily available phenyl 1-selenoglycosides and phenyl 1-telluroglycosides with DAST in the presence of halonium ion activators yields the corresponding glycosyl fluoride in high yield. The stereoselectivity of the conversion is affected by C-2 substituents, stereochemistry of starting glycoside and reaction solvent.

Keywords: glycosides; selenium; selenium compounds; neighbouring group effects; solvents; solvent effects.

Glycosyl fluorides have many applications in both chemical and biomedical research. Their main importance arises from their donor-potential in enzymatic and chemical glycoside synthesis.[1] However, glycosyl fluorides have also found use as molecular probes for NMR investigations into carbohydrate transport and metabolism[2] and as mechanistic probes in enzymatic studies.[3] We herewith report the high yielding chemical synthesis of glycosyl fluorides from a variety of corresponding phenyl selenoglycosides[4] (**1–5**) as well as the synthesis of a glycosyl fluoride from phenyl telluroglycoside **6** (Fig. 1).[5] We additionally report how the stereoselectivity of these conversions is affected by C-2 substituent, stereochemistry of starting glycoside and reaction solvent.

The conversion of phenyl selenoglycosides into glycosyl fluorides has recently been reported using 4-methyl(difluoroiodo)benzene.[6] However, this process yielded the corresponding fluoride in only mod-



1 **2** R= Ac **3** R= Bz **4** R= $COCH_2C_6H_4CH_3$ **5** R= Bn **6**

Figure 1.

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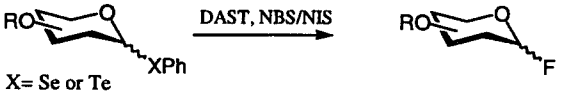
erate yield (40–47%) and was deemed to be unsuitable for selenoglycosides containing electron rich groups[7] such as the azido function in **1**. In order to improve the viability of synthesising glycosyl fluorides from selenoglycosides it was decided to follow the method of Nicolaou et al. for the synthesis of glycosyl fluorides from thioglycosides.[8] The phenyl seleno substituent behaves largely like thioglycosides[9] with respect to stability towards protecting group manipulations and lability towards electrophilic reagents. However selenium is more nucleophilic, larger and more polarisable than sulfur and the carbon–selenium bond is weaker and less polar than the carbon–sulfur bond.[10] Consequently, many of the reactions originally developed for thioglycosides can be readily and more conveniently applied to their selenium counterparts. Treatment of phenyl 1-selenoglycoside **1–5** or phenyl 1-telluroglycoside **6** with DAST in the presence of either NBS or NIS in CH_2Cl_2, MeCN, or Et_2O yielded anomeric mixtures of the corresponding glycosyl fluorides in high yield (Scheme 1 and Table 1).[11]



Scheme 1.

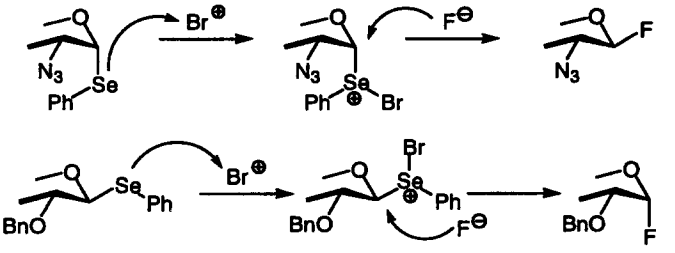
As can be seen from Table 1, the stereochemical outcome of the reaction is influenced by the nature of the C-2 substituent (participating or non-participating), the stereochemistry of the starting glycoside and the reaction solvent. In CH_2Cl_2 the conversions proceeded in satisfactory yield (73–83%). However, the formation of the fluorides occurred, in the majority of cases with little stereocontrol. The exceptions to this were entries 1 and 5, in which the C-2 substituent was non-participating (azido for entry 1 and benzyl for entry 2). These conversions proceeded with inversion of configuration; indicative of an S_N2-type of mechanism (Scheme 2).

When the C-2 substituent of the β-linked selenoglycoside was changed from non-participating to participating (acetyl, benzoyl, toluoyl) a change in the stereochemical outcome of the reaction was noticed (Table 1, entries 2–4 and 6). In these instances the proportion of the β-linked product was considerably higher than could be explained by an S_N2-type mechanism. It is believed that when a participating group is adjacent to the anomeric centre the reaction proceeds by an S_N1-type mechanism (Scheme 3).

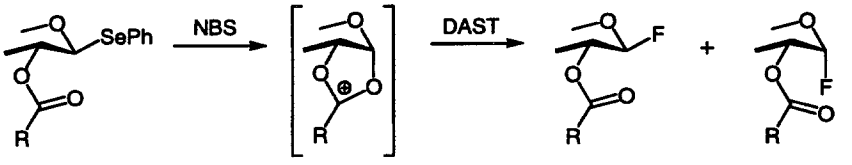
Table 1

Entry	Starting Material[a]	Solvent	Yield (%)	α:β[b]
1	**1**	CH_2Cl_2	77	03:97
2	**2**	CH_2Cl_2	81	39:61
3	**3**	CH_2Cl_2	82	51:49
4	**4**	CH_2Cl_2	77	39:61
5	**5**	CH_2Cl_2	82	91:09
6	**6**	CH_2Cl_2	76	22:78
7	**1**	MeCN	76	00:100
8	**2**	MeCN	79	01:99
9	**3**	MeCN	76	01:99
10	**4**	MeCN	81	00:100
11	**5**	MeCN	77	26:74
12	**6**	MeCN	79	02:98
13	**1**	Et_2O	69	33:67
14	**2**	Et_2O	71	37:63
15	**3**	Et_2O	69	11:89
16	**4**	Et_2O	75	04:96
17	**5**	Et_2O	79	67:33
18	**6**	Et_2O	81	27:73

a: as shown in Figure 1; **b**: anomeric ratio derived from integratioin of ^{19}F NMR spectra.

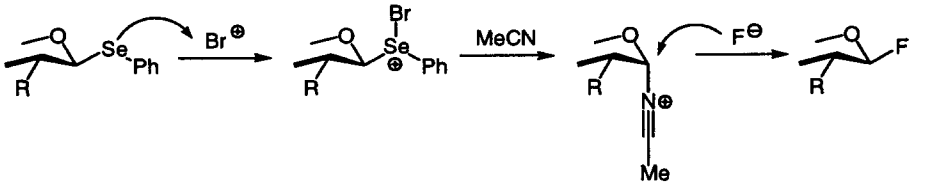


Scheme 2.



Scheme 3.

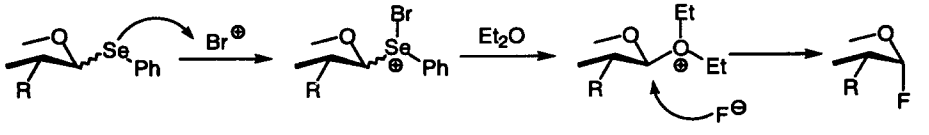
In MeCN the proportion of β-fluoride formed in each conversion was considerably higher than that obtained from when the reactions were carried out in CH_2Cl_2 (Table 1, entries 7–12). This is particularly the case when selenoglycoside **5** was used as the starting material. When the reaction was carried out in CH_2Cl_2 the proportion of β-fluoride formed was 9% with the reaction proceeding via an S_N2-like mechanism. Changing the reaction solvent to MeCN resulted in a considerable increase in the proportion of β-fluoride formed. This is believed to be a consequence of the 'nitrile effect'[12] in which substitution occurs through an α-orientated nitrilium intermediate (Scheme 4).[13]



Scheme 4.

By forming the nitrilium intermediate, attack of the fluoride anion preferentially takes place on the β-face of the carbohydrate. However, since 26% of the fluorinated product is α, it is believed that the S_N2-like substitution of the SePh moiety for the fluoride anion also occurs. The mechanism shown in Scheme 4 is also supported by the results obtained for the conversions of glycosides **1–4** and **6** in which the proportion of β-fluoride formed was greater than the corresponding conversion carried out in CH_2Cl_2.

Similarly to the increase in β-fluoride formed for reaction in MeCN, it was believed that using Et_2O as reaction solvent would increase the proportion of α-fluoride through the intermediary formation of an exoanomerically stabilised β-orientated exocyclic oxonium ion (Scheme 5).[14]



Scheme 5.

However, the anticipated increase in α-linked product failed to materialise (Table 1, entries 13–18). The reasons for this are unknown, but it could be that the formation of the exocyclic oxonium ion

was unfavoured in the reaction conditions used. It is known that the diethyl ether-assisted formation of α-glycosides is dependent upon reaction temperature with colder temperatures favouring exocyclic oxonium formation. It is possible that the temperature used in this investigation (0°C) was too high for such assistance.

These results reveal that the stereoselectivity of the conversion of seleno- and telluroglycosides into glycosyl fluorides is affected by C-2 substituent (participating or non-participating), reaction solvent and the stereochemistry of the starting glycoside. When CH_2Cl_2 is the reaction solvent and the C-2 substituent is participating, mixed anomers are produced. However, by selecting acetonitrile as reaction solvent, the proportion of β-fluoride increases. Conversely, when the C-2 substituent is non-participating, the fluoride resulting from inversion of configuration is the major anomer when CH_2Cl_2 is used as reaction solvent. Again, selecting acetonitrile as reaction solvent increases the proportion of β-fluoride. Consequently, by careful selection of the reaction conditions (C-2 substituent, solvent, stereochemistry of selenoglycoside) the stereoselectivity of the conversion can be controlled.

Acknowledgements

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11. Typical procedure: Starting seleno- or telluroglycoside (1 mmol) was dissolved in reaction solvent (5 ml) and stirred at 0°C for five minutes under argon. DAST (2 mmol, 264 μl) was added and the solution was stirred for 30–60 minutes until all starting material had been consumed (TLC). The reaction mixture was diluted with $CHCl_3$ (10 ml) and was washed with H_2O (2×10 ml), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified on a short silica gel column to yield the corresponding glycosyl fluorides.
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