Observations on the Reaction of Xanthate Esters with 4-Methyl(difluoroiodo)benzene: a New Method for the Conversion of Alcohols to Alkyl Fluorides

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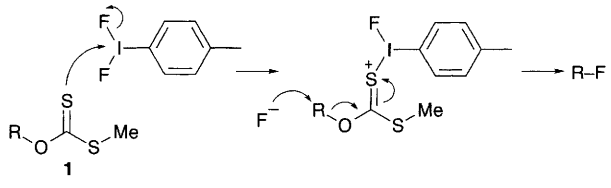
Treatment of a range of *S*-methyldithiocarbonates (xanthates) with 4-methyl(difluoroiodo)benzene gives the corresponding alkyl fluorides.

The selective replacement of a hydroxy group by a fluorine atom has often proved to be an effective stratagem within the pharmaceutical industry for the generation of biologically active molecules.[1] At the present time, this transformation can be achieved either directly, through selection of diethylaminosulfur trifluoride[2] (DAST), or indirectly, *via* the displacement of a leaving group such as triflate with a variety of fluoride anion sources of varying degrees of nucleophilicity and basicity.[3] The hydrolytic sensitivity of the reagents and intermediates employed may, however, cause problems, particularly on larger scale operation.

We have shown, as part of our studies on the reactivity of hypervalent (dofluoroiodo)arenes,[4,5] that the electrophilic iodine centre of 4-methyl(difluoroiodo)benzene and related congeners has a particular affinity for the sulfide linkage in cephalosporin,[6] dithioketals[7] and anomeric arylthioglycoside derivatives,[8] and that this may be used for the controlled formation of a carbon–fluorine bond.

We therefore reasoned (Scheme 1) that the selection of an easily prepared xanthate ester[9] **1** of an alcohol could lead, *via* activation of the thiocarbonyl group by the hypervalent iodoarene reagent, to the *in situ* generation of a leaving group capable of displacement by the concomitantly liberated fluoride anion. The thiocarbonyl–carbonyl interconversion involved in this sequence provides an additional thermodynamic driving force for the reaction, and further support for this hypothesis may be found in an elegant study by Barton and coworkers[10] describing the behaviour of a series of thiocarbonyl ester derivatives with various electrophiles.

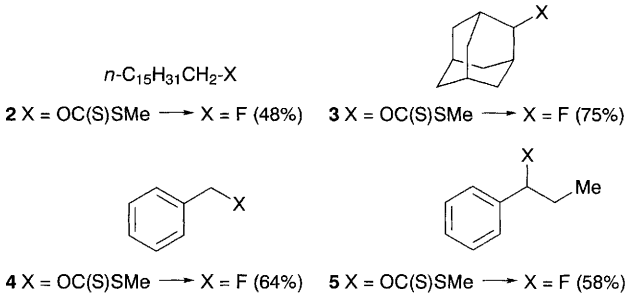


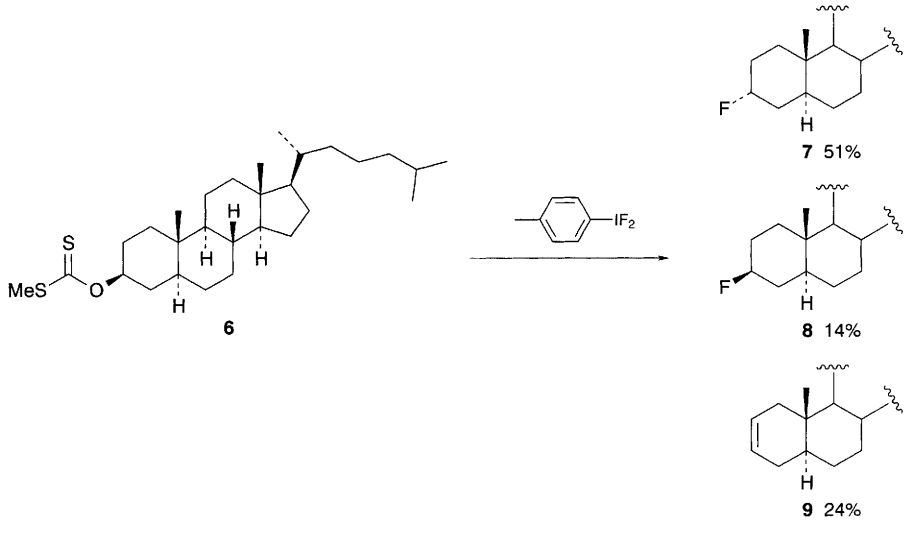
Scheme 1

Although optimum reaction conditions remain to be established, the results for a series of simple primary, secondary and benzylic substrates are summarised under the formulae **2**–**5** which confirm the overall feasibility of this process.

We have also examined some of the stereochemical features of this transformation. Thus, reaction of the equatorial derivative, 3β,5α-cholestanyl xanthate **6** (Scheme 2) gave both 3α-fluoro-5α-cholestane **7** (51%) and 3β-fluoro-5α-cholestane **8** (14%), together with the elimination product 5α-cholest-2-ene **9** (24%). By way of comparison, the reaction of DAST with the corresponding alcohol[11] also suffers from competitive alkene formation (32%), and, although less successful in terms of overall formation of the carbon–fluoride bond (43%), is reported to occur with clean stereochemical inversion.

By way of contrast, reaction of the menthol derivative **10** proceeded with retention of configuation to give **11** (51%), as evidenced by NMR studies which indicated preservation of the *trans* diaxial coupling constants [$J(H^1, F)$ 49.9, $J(H^1, H^6eq)$ 4.6, $J(H^1, H^6ax)$ 10.6, $J(H^1, H^2ax)$ 10.6 Hz]. The reaction of menthol itself with DAST was described in the original publication of Middleton,[2a] although curiously, no stereochemical assignment was made. We have therefore repeated this reaction and find that **11** is also produced in 50% yield. Clearly, in the ultimate fluoride anion displacement step, using either DAST or the xanthate–(difluoroiodo)arene combination, the stereochemical





Scheme 2

outcome can be influenced by substrate structure. In the case of menthol, it is possible that the neighbouring isopropyl group is sufficient to tilt the balance away from the S_N2 mechanism towards an S_Ni pathway.

Finally, we have also examined the case of cholesteryl xanthate **12** which again mirrors the behaviour of DAST[2] with the parent alcohol in yielding the 3β-fluoro derivative **13** in 95% yield, presumably as a result of classical homoallylic participation.

From a practical standpoint, reactions of the readily prepared crystalline and organic-soluble reagent 4-methyl-(difluoroiodo)benzene were simply carried out in ordinary laboratory glassware by dropwise addition of the xanthate ester to a stirred solution of a single molar equivalent of the (difluoroiodo)arene at 0 °C using dichloromethane as solvent under an inert atmosphere. The present sequence therefore offers promise as a very mild and convenient two-step method for the conversion of alcohols to fluorides.

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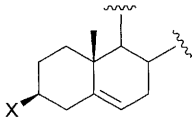
10 X = OC(S)SMe
11 X = F



12 X = OC(S)SMe
13 X = F

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