Pergamon

Tetrahedron Letters 41 (2000) 4463–4466

TETRAHEDRON LETTERS

Observations on the α-fluorination of α-phenylsulfanyl esters using difluoroiodotoluene

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Received 24 March 2000; accepted 10 April 2000

Abstract

α-Phenylsulfanyl esters are fluorinated in the α-position when treated with the hypervalent iodine reagent difluoroiodotoluene. Excess reagent can lead to α-fluoro sulfoxides, which can then undergo thermal *syn* elimination to produce vinyl fluorides. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: halogenation; hypervalent elements; fluorine and compounds.

The α-fluorination of sulfoxides or sulfides through the fluoro-Pummerer reaction is known as an effective strategy for the synthesis of α-fluoro sulfides[1] and a number of reagents have been shown to effect this transformation; notably DAST,[2] xenon difluoride,[3] the combination of tetrabutylammonium dihydrogentrifluoride and 1,3-dibromo-5,5-dimethylhydantoin,[4] N–F reagents[5] and electrochemical oxidation in the presence of triethylamine–HF complexes.[6] The α-fluoro sulfides synthesised in this manner have attracted much attention as enzyme inhibitors,[7] as ^{19}F NMR structural probes in proteins[8] and as synthons for vinyl fluorides.[9]

We have previously demonstrated that hypervalent difluoroiodoarenes have a particular affinity for sulfur-containing functional groups and exploited this in the fluorination of cephalosporins,[10] dithioketals,[11] arylthioglycosides[12] and xanthate esters.[13] As part of our ongoing interest in the use of difluoroiodoarenes as mild and selective fluorinating agents, we therefore elected to investigate the behaviour of a series of α-phenylsulfanyl esters in the fluoro-Pummerer reaction.

From a mechanistic standpoint, we envisaged, as outlined in Scheme 1, that the reaction pathway would involve an initial nucleophilic attack by the sulfur atom at the electrophilic iodine centre to form an iodosulfonium salt **1**. The enhanced acidity of the protons adjacent to the ester carbonyl group would then encourage the liberated fluoride anion to function as a base with resultant formation of the classical Pummerer intermediate **2**. Subsequent trapping of cation **2** with nucleophilic fluoride anion would then yield the product α-fluoro sulfide **3**.

To the best of our knowledge there has been only one isolated report concerning the fluoro-Pummerer reaction of hypervalent difluoroiodoarenes with sulfides.[14] Fuchigami found that ethyl

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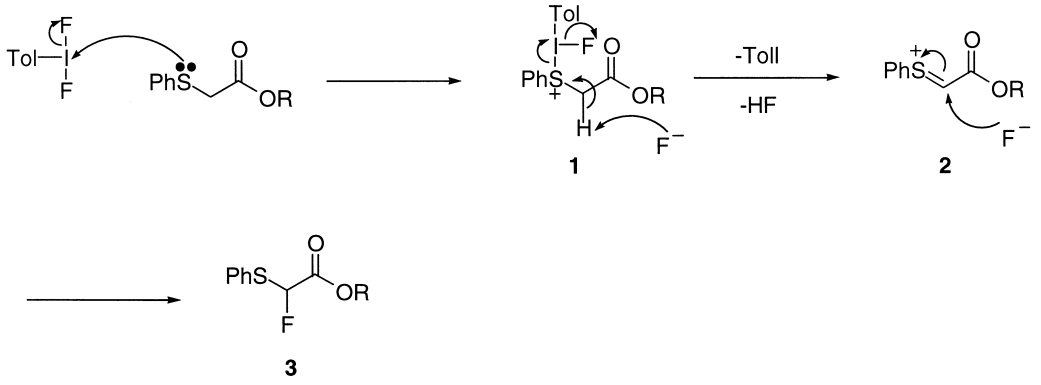
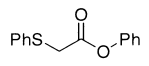
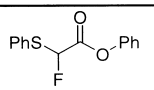
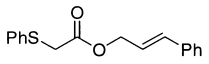
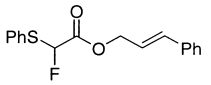
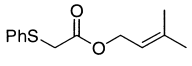
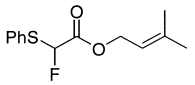
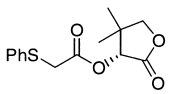
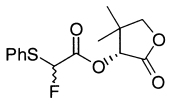
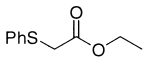
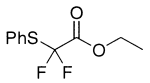
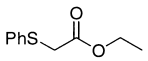
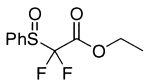
PII: S0040-4039(00)00616-X



Scheme 1.

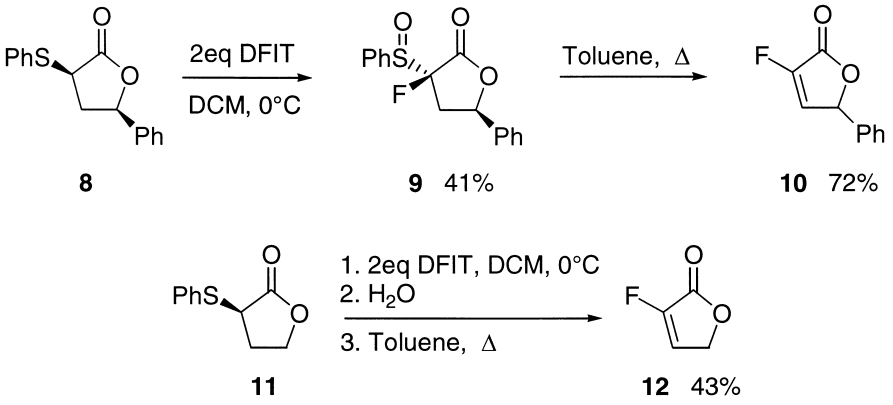
(arylsulfanyl)acetates could be fluorinated using a solution of electrogenerated *p*-methoxyiodobenzene difluoride in the presence of an excess of $Et_3N{\cdot}3HF$. However, reactions were incomplete, necessitating two equivalents of fluorinating agent and the product fluorides were isolated in moderate yields (< 50%). Our results using difluoroiodotoluene (DFIT)[15] in the fluoro-Pummerer reaction of some α-phenylsulfanylacetates are shown in Table 1.[16]

Table 1
Synthesis of α-fluoro sulfides[a]

Entry		Ester		Product	Yield (%)[b]
1	**4a**		**5a**		72
2	**4b**		**5b**		67
3	**4c**		**5c**		64
4	**4d**		**5d**		53[c]
5	**4e**		**6**[d]		80
6	**4e**		**7**[e]		38

a) Method: DFIT (1eq.), DCM, 0°C, stirring overnight.
b) Isolated yields.
c) Isolated as a 1:1 mixture of diastereoisomers (GC and ^{19}F nmr).
d) 2eq. of DFIT.
e) 3eq. of DFIT.

Examination of the results (entries 1–4) shows that the expected α-fluoro sulfides were formed cleanly and in good overall yields upon treatment with only one single equivalent of DFIT in DCM. It was also of interest to note (entries 2 and 3) that capture of the Pummerer intermediate by fluoride anion was faster than cyclisation to give a γ-lactone by π-participation. Most significantly, a second fluorination was also possible with the α,α-difluorosulfide **6** (entry 5) being formed on treatment of the ethyl derivative **4e** with two equivalents of DFIT. Two sequential fluoro-Pummerer reactions have been found to be problematic with the widely-employed fluorinating agent DAST.[2b] The finding that addition of a third equivalent (entry 6) led to the α,α-difluorosulfoxide **7** was also worthy of note and suggested possible applications to the synthesis of vinyl fluorides. Accordingly, we found that treatment of the *syn*-lactone **8** with two equivalents of DFIT gave a 41% yield of the α-fluoro sulfoxide. The fluorine atom was introduced exclusively *syn* to the 5-phenyl substituent[17] and the sulfoxide was formed as a 5:2 mixture of diastereoisomers (Scheme 2). Subsequent thermal elimination of benzenesulfenic acid then furnished the 2-fluoro-2-buten-4-olide **10**. It was later found that isolation of the intermediate α-fluoro sulfoxide was unnecessary. Thus, treatment of **11** with DFIT followed by aqueous work-up and thermolysis of the crude product in refluxing toluene gave the 2-fluoro-2-buten-4-olide **12** directly in 43% yield.



Scheme 2.

Previous syntheses of these fluorinated synthons have required an *E*-selective Wittig–Horner reaction of an aldehyde with a fluorophosphonate followed by hydrolytic ring-closure.[18] Sulfanylation of an appropriate lactone followed by DFIT treatment, hydrolysis and *syn* elimination thus represents a versatile alternative.

In summary, the readily prepared, crystalline and organic-soluble fluorinating agent, difluoroiodotoluene, offers an exceptionally mild method for the α-fluorination of sulfides, without the necessity for any further additions of external fluoride sources or catalysts. Furthermore, the novel sequential fluorination/oxidation character of the reagent offers a potentially general approach to vinyl fluorides.

Acknowledgements

We thank the EPSRC for the award of a studentship to M.F.G.

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16. Typical procedure: A solution of prenyl (phenylsulfanyl)acetate **4c** (1.1 mmol) in DCM (6 mL) was treated with DFIT (1.2mmol) under nitrogen at 0°C in a polypropylene flask. The reaction mixture was stirred for 2 h then quenched with water. The mixture was extracted with DCM, the combined extracts dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (SiO_2) eluting with petroleum ether/diethyl ether 90/10 gave prenyl (2-fluoro-2-phenylsulfanyl)acetate **5c** (178mg, 64%) as a colourless oil. IR (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 1752s (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 1.68 (3H, s), 1.75 (3H, s) 4.58 (2H, d *J* 8 Hz), 5.21–5.25 (1H, m), 6.07 (1H, d $^2J_{HF}$ 52 Hz), 7.33–7.57 (5H, m); ^{19}F NMR (470 MHz, $CDCl_3$): δ –158.6 (d, $^2J_{FH}$ 52 Hz); HRMS (FAB) calcd. for $C_{13}H_{15}FO_2S$: 255.0855. Found: 255.0861.
17. Fluorination of lactone **8** with 1 equiv. of DFIT gave 3-*syn*-fluoro-4,5-dihydro-3-phenylsulfanyl-5-phenyl-2(3*H*)-furanone in 62% yield. The stereochemistry was established by X-ray crystallography and will be discussed in the full paper.
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