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Studies on the oxidation and fluorination of α-phenylsulfanylacetamides using difluoroiodotoluene

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Abstract

α-Phenylsulfanylacetamides are fluorinated in the α-position when treated with difluoroiodotoluene (DFIT) in a fluoro-Pummerer reaction. For *N*-phenyl amides an intramolecular Friedel–Crafts reaction may compete and produce heterocycles.

Keywords: halogenation; oxidation; fluorine and compounds; hypervalent elements.

In the preceding communication,[1] we have shown that difluoroiodotoluene (DFIT, **1**) is a mild and effective reagent for the α-fluorination of α-phenylsulfanyl acetates and that two sequential fluoro-Pummerer reactions to give α,α-difluorosulfides can be achieved when two equivalents of DFIT are used. We were also intrigued by the finding that, for those substrates such as **2** in which formation of a second Pummerer cation is blocked, DFIT can then function as an oxidant to give sulfoxides **4**, presumably via hydrolysis of an iodosulfonium salt species such as **3** (Scheme 1).

The fact that an α,α-difluoroester **5** was not formed by subsequent nucleophilic displacement of sulfur by fluoride anion in **3** suggested to us that the ester carbonyl group could well be responsible for the relative longevity of iodosulfonium salts such as **3**, especially when the conversion of thioketals to geminal difluorides[2] by DFIT is considered, since this transformation necessarily requires, at some stage, replacement of sulfur by fluorine in an α-fluoro sulfide intermediate. In continuation of this study on the fluoro-Pummerer chemistry of DFIT it was therefore of interest to examine α-phenylsulfanylacetamides as substrates. A range of amides were accordingly prepared, some of which contained suitably placed double bond functionality which could feasibly intercept the Pummerer cation in an intramolecular cyclisation, thus potentially forming fluorinated heterocycles in addition to fluoro-Pummerer products. The results of treating these amides with DFIT are shown below in Table 1 which reveals that the outcome of the reaction is critically dependant on the substituents attached to the nitrogen atom of the amide.[3]

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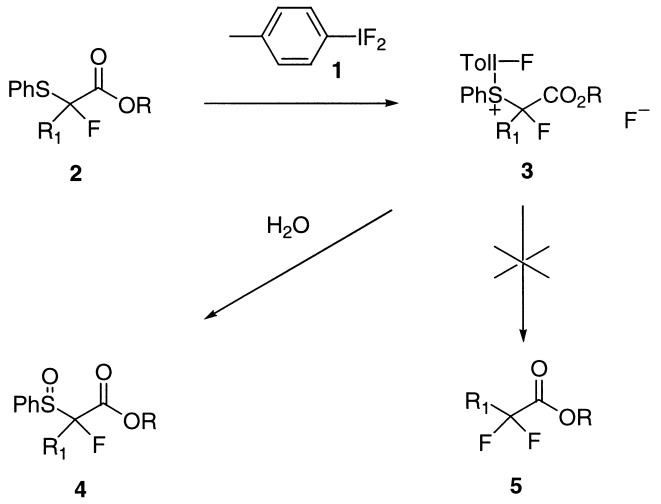
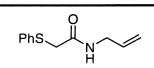
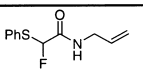
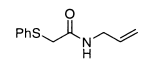
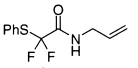
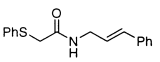
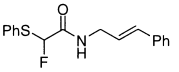
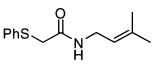
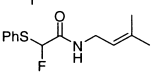
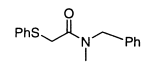
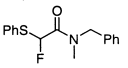
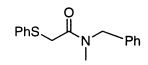
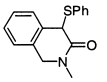
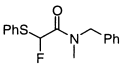
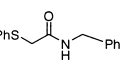
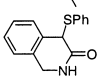
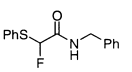
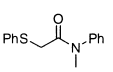
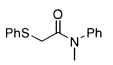
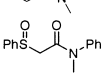
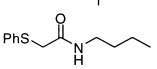
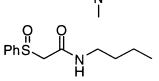
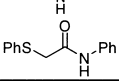
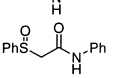


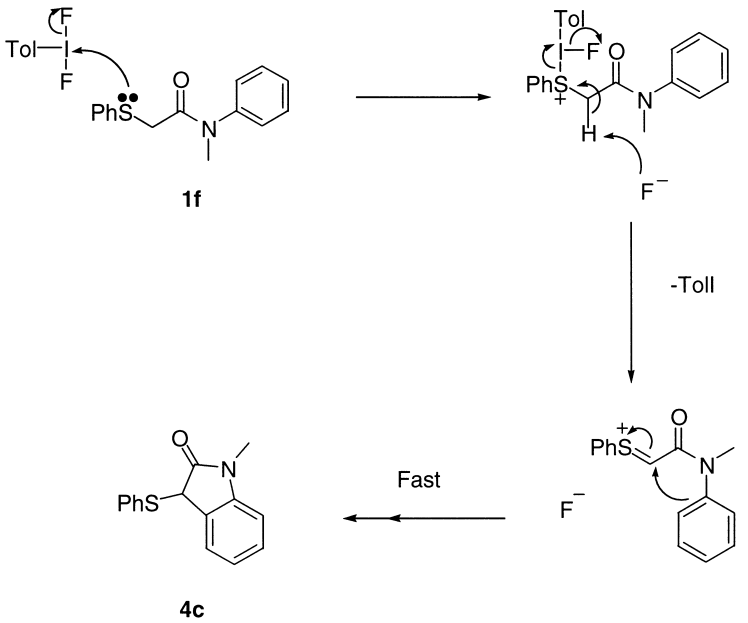
Scheme 1.

Table 1
Treatment of α-phenylsulfanylacetamides with DFIT

Entry		Amide	Method[a]		Product	Yield (%)[b]
1	**1a**		A	**2a**		71
2	**1a**		C	**3**		61
3	**1b**		A	**2b**		55
4	**1c**		A	**2c**		25
5	**1d**		B	**2d**		68
6	**1d**		A	**4a**	 + **2d** 	**4a** 47 **2d** 25
7	**1e**		A	**4b**	 + **2e** 	**4b** 11 **2e** 35
8	**1f**		A	**4c**		59
9	**1f**		B	**5a**		86
10	**1g**		C	**5b**		86
11	**1h**		B	**5c**		78

a) Method: A. DFIT (1eq.), DCM, reflux overnight; B. DFIT (1eq.), DCM, 0°C, overnight; C. DFIT (2eq.), DCM, 0°C, overnight.
b) Isolated yields.

As in the case of esters, α-fluorination of the amides in entries 1–5 takes place in good overall yield, and the use of a second equivalent of DFIT (entry 2) leads to a simple one-pot method for α,α-difluorination. Substrate **1a** was also selected to demonstrate the stability of DFIT under storage, a six month old batch of the reagent producing fluoride **2a** in 61% yield as compared with the 71% yield with freshly prepared reagent. Although no competing cyclisation reactions were observed at 0°C, presumably as a consequence of the preferred transoid conformation of the amide linkage, it was of interest to note that reactions performed at higher temperature (entries 6, 7 and 8) did lead to competitive formation of heterocyclic products which can formally be derived by π-participation from the aromatic ring, as illustrated in Scheme 2 for the exclusive formation of the oxindole derivative **4c** from **1f**. The absence of any acyclic fluorinated product in this reaction, relative to the mixtures obtained in the cases of the benzylamine derivatives **1d** and **1e** (entries 5 and 6) can be attributed to the faster rate of 5-*exo*-*trig* ring closure.[4]



Scheme 2.

To some extent, these reactions mirror the results of Tamura and Ishibashi,[5] who have reported that tertiary α-phenylsulfinyl acetamides are much better substrates for Pummerer induced cyclisations than their secondary amide congeners. The isolated yields of heterocycles are moderate and poorer than those yields recorded by Tamura[6] for similar cyclisaitons of α-phenylsulfanyl acetamides mediated by iodobenzene(bistrifluoroacetate). However, potential exists for the incorporation of a further carbon–fluorine bond forming step in the lactam products using the difluoride and work is in progress in this area. Finally, to our surprise, the last three entries 9–11 demonstrate once again that DFIT can function as a convenient reagent for the oxidation of the phenylsulfanyl group to the sulfoxide. At this stage, it is apparent that in all of the substrates **1a**–**1h** studied, formation of the initial iodosulfonium salt can occur at 0°C. However, the evolution or otherwise of this intermediate, either to give α-fluoro sulfides, sulfoxides or cyclised products is strongly influenced by the substituents around the nitrogen atom of the amide group. This stands

in stark contrast to the reactions of the α-phenylsulfanyl esters described in the preceding paper where α-fluorination was always observed to precede oxidation of sulfide to sulfoxide. Clearly, a simple extrapolation from ester to amide cannot be made. Furthermore, although it is tempting at first sight to speculate that neighbouring group participation from the amide carbonyl group could lead to displacement of a second fluoride anion from the initially formed iodosulfonium salt and that such a process would be more facile for amides than for esters, the diversity in product evolution for various amides cannot be simply explained.

In summary, the foregoing results have indicated that DFIT is a mild and readily controlled reagent for the fluoro-Pummerer reaction of α-phenylsulfanyl esters and acetamides. The reagent is easily prepared through the *trans*-halogenation of dichloroiodotoluene with aqueous hydrofluoric acid and mercuric oxide in DCM, and isolated as an off-white crystalline solid.[7] The chief by-product of reaction, iodotoluene, is readily separated from all but the most non-polar products, and can be easily recycled.

Acknowledgements

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References

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3. Typical procedure: A solution of *N*-benzyl-(phenylsulfanyl)acetamide **1e** (1 equiv.) in DCM was treated with DFIT (1.1 equiv.) under nitrogen and refluxed for 1 h. The reaction mixture was quenched with water and extracted with DCM. Drying of the combined extracts over $MgSO_4$ and concentration in vacuo gave an oil that was chromatographed (SiO_2) eluting with petroleum ether/diethyl ether 80/20 to afford 3-oxo-4-phenylsulfanyl-1,2,3,4-tetrahydroisoquinoline **4b** (45mg, 11%) as a colourless oil. IR (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3248m (NH), 1644s (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (2H, d J 6 Hz), 4.94 (1H, s), 6.72 (1H, br), 6.83–7.61 (9H, m); HRMS (FAB) calcd. for $C_{15}H_{13}NOS$ (MH^+): 256.0800. Found: 256.0796; and *N*–benzyl-(2-fluoro-2-phenylsulfanyl)-acetamide **2e** (152 mg, 35%) as colourless crystals; m.p. 65°C (DCM/PE 30–40); IR (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 3391s (NH), 1669s (C=O), 1516m (amide II), ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18–4.32 (2H, m), 6.02 (1H, d $^2J_{HF}$ 52Hz), 6.35 (1H, br), 6.90–7.55 (10H, m); ^{19}F NMR (282 MHz, $CDCl_3$): δ –156.8 (dd J 53, 3 Hz). Anal. calcd for $C_{15}H_{14}FNOS$: C, 65.43; H, 5.12; N, 5.09; S, 11.65%. Found: C, 65.35; H, 5.00; N, 4.98; S, 11.89%.
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