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Studies on the additive fluoro-Pummerer reaction of phenylsulfanylated lactams with difluoroiodotoluene

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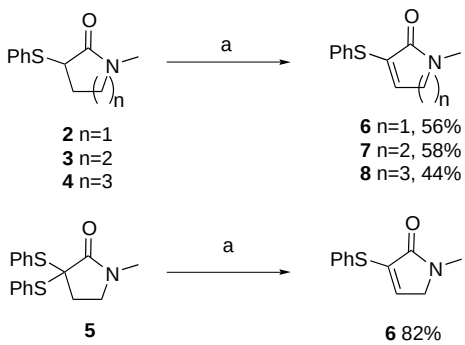
Abstract—Two fluorine atoms are effectively introduced to the 3- and 4-positions of sulfur-containing lactams through the action of the hypervalent iodoarene reagent difluoroiodotoluene (DFIT). The reaction proceeds through the intermediacy of the isolable α,β-unsaturated congener followed by an additive-Pummerer process.

The controlled introduction of fluorine into organic molecules continues to present a challenge to modern synthetic methods.[1] The importance of selectively fluorinated compounds in chemistry and biology is well appreciated[2] and provides a major impetus to the discovery of new fluorinating agents that can operate according to an efficient, safe and mild criteria. We have been interested in the development of fluorinating agents based on the hypervalent iodoarene difluoride structure **1**,[3] such compounds having the advantages of low toxicity, ease of use[4] and scope for re-cycling.[5] We are currently applying these reagents to the synthesis of α-fluoro sulfides through fluoro-Pummerer chemistry.[6] Herein, we describe the fluorination of various sulfur-containing lactams with the tolyl derivative of **1**, difluoroiodotoluene (DFIT).

The prevalence of the pyrrolidinone and piperidinone ring systems in biologically active natural products and drug molecules led us to prepare[7] lactams **2**–**5** with a view to synthesising fluorinated derivatives. We were interested to see if the fluoro-Pummerer reaction would produce simple monofluorides as in our earlier work with acyclic amides, or whether the presence of β-hydrogens in the substrates would lead to alternative products. In the event, treatment of lactams **2**–**5** with 1 equiv. of DFIT in DCM at 0°C led to the unsaturated heterocycles **6**–**8** in moderate to high yields (Scheme 1).

α,β-Unsaturated sulfides frequently occur as side-products in conventional Pummerer reactions. They are often the sole products of Pummerer reactions of α-acyl sulfoxides,[8] this being one of the best ways to prepare this useful functionality.[9] A plausible mechanism is shown in Scheme 2. Initial nucleophilic attack by the divalent sulfur atom in **2** on the electrophilic iodine centre of the reagent gives **9** and liberates fluoride. Deprotonation by basic fluoride anion at the α-position then generates the sulfonium intermediate **10**. Product evolution can then in principle be controlled by fluoride acting either as a nucleophile or as a base. Interestingly, and in contrast to our recent work with γ-lactones and acyclic amides,[6] it is the second pathway that is favoured with a second deprotonation at the β-position producing the unsaturated product **6**. The trapping of the sulfonium species with nucleophilic fluoride followed by elimination of HF would likewise lead to **6**. However, the appropriate monofluoride of **2** has been prepared[10] by anodic fluorination of **2** in $Et_3N{\cdot}3HF$ and no elimination was reported to occur upon product isolation.



Scheme 1. *Reagents and conditions*: (a) 1 equiv. DFIT, DCM, 0°C.

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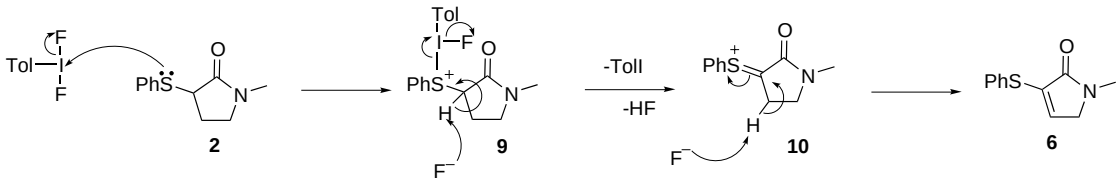
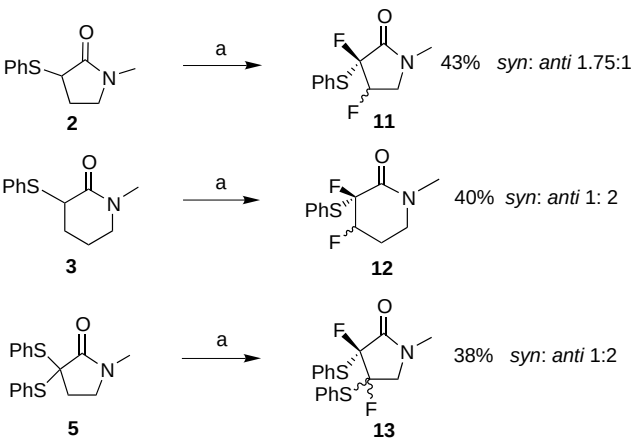


Scheme 2.

The high yield of **6** starting from the bis-phenylsulfanylated compound **5** is presumably a consequence of the substantially easier generation of sulfonium intermediate **10** through thioketal cleavage with DFIT.[11]

Treatment of lactams **2** and **3** with 2 equiv. of DFIT produced fluorinated material. The pyrrolidinone **2** and piperidinone **3** were both fluorinated in the α- and β-positions to produce the diastereomeric difluorides **11** and **12** (Scheme 3).

The *syn* and *anti* diastereomers were separable by column chromatography and a single crystal could be grown for both *syn* **11** and *anti* **12**, thus unambiguously characterising the difluoride products by X-ray crystallography.[12,13] Introduction of the fluoride nucleophile to the seemingly unactivated β-position is readily understood in terms of an initial Pummerer reaction to generate the α,β-unsaturated derivative as in Scheme 1, followed by a so-called additive-Pummerer reaction.[14] In the additive-Pummerer reaction, two molecules of the nucleophile add across the double bond of an α,β-unsaturated sulfoxide to generate the saturated α,β-difunctionalised sulfide. Scheme 4 shows an additive-Pummerer mechanism for the DFIT-activated sulfide **2**.



Scheme 3. *Reagents and conditions*: (a) 2 equiv. DFIT, DCM, 0°C.

Thus, the first equivalent of DFIT generates **6** as previously discussed, whilst the second equivalent activates the β-position to addition of fluoride, forming the β-fluoro sulfonium species **14**, which is then quenched with a second fluoride nucleophile to provide the difluoride **11**. The modest stereoselectivity is a consequence of the small size of the initially introduced fluorine atom in the 4-position having little influence on the steric approach control of the second fluoride nucleophile.

Fluorination of the bis-phenylsulfanylated compound **5** with DFIT produced difluoride **13** as a diastereomeric mixture, the structure being determined by X-ray diffraction of a single crystal of anti-**13** grown from the product mixture (Fig. 1). Clearly, in this instance, the

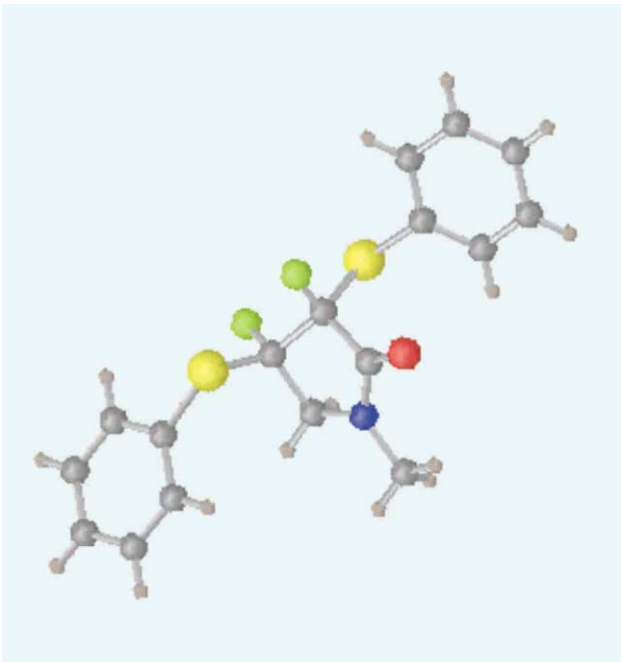
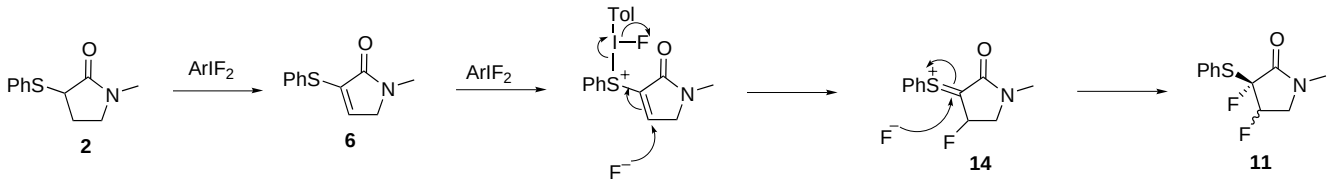


Figure 1. X-Ray structure of difluoride **13**.



Scheme 4.

strongly nucleophilic thiophenoxide generated upon thioketal cleavage of **5** with DFIT will add to **6** upon DFIT activation in preference to fluoride. Basic fluoride then regenerates the α,β-unsaturation, presumably as a consequence of the now increased acidity of the β-proton, and an additive-Pummerer reaction furnishes the difluoride. Again the product evolution is dictated by fluoride acting as a base rather than a nucleophile when both pathways are possible.

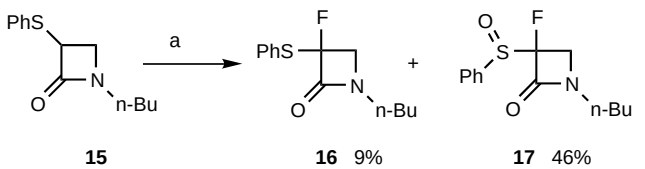
The mechanism shown in Scheme 4 dictates the consumption of 3 equiv. of DFIT in the formation of **13** and, accordingly, an improved yield of 46% was obtained with this stoichiometry.

Treatment of unsaturated sulfides **6** and **7** with 1 equiv. of DFIT directly gave the difluorides in comparable to lower yields than those obtained through the tandem process. This surprising result may be related to the generation of 2 equiv. of HF in the first Pummerer reaction having a catalytic effect on the second Additive process. However, attempts at promoting the direct fluorination of **6** and **7** with DFIT using py·9HF or $Et_3N{\cdot}3HF$ were not generally successful, although in one case the yield of **11** from the sulfide **2** was improved to 59% through the addition of 25 mol% of $Et_3N{\cdot}3HF$ to the reaction.[15]

β-Lactams are especially important substrates for fluorination owing to the unique biological activity of penicillins and cephalosporins.[16] Azetidinone **15** is monofluorinated in the α-position in 92% yield by anodic fluorination in a $Et_3N{\cdot}3HF$ electrolyte.[17] When treated with DFIT fluoro-sulfoxide **17** was isolated in 46% yield as a mixture of sulfoxide diastereomers, along with a small amount of the known[17] fluoro-sulfide **16** (Scheme 5).

Characterisation of **17** was secured by oxidation to the sulfone, whereby the two signals in the ^{19}F NMR of the starting material collapsed to one in the product. The additive-Pummerer reaction is not observed in this case, presumably due to the prohibitively large ring-strain associated with formation of a double bond in the four-membered azetidinone ring. We have previously observed fluoro-Pummerer reaction followed by sulfide oxidation in our studies on α-phenylsulfanylated lactones, and applied the transformation to the synthesis of vinyl fluorides,[6a] and the scope and mechanism of these transformations are currently under study.[18]

In conclusion, we have developed a new method for dehydrogenative α,β-difluorination of certain α-phenylsulfanylated lactams that utilises a new tandem Pummerer-mediated unsaturation protocol followed by additive-Pummerer reaction using the hypervalent iodine reagent difluoroiodotoluene. The causative factors which influence the evolution of the Pummerer intermediates in both cyclic and acyclic esters, amides and related systems are currently under examination.



15 **16** 9% **17** 46%

Scheme 5. *Reagents and conditions*: (a) 2 equiv. DFIT, DCM, 0°C.

Acknowledgements

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11. The conversion of simple thioketals to *gem*-difluoro compounds with iodoarene difluorides is known. See: Motherwell, W. B.; Wilkinson, J. A. *Synlett* **1991**, 191.
12. Data for the X-ray structure of **13** have been deposited. The X-ray structures of **11** and **12** will be discussed in detail in a full paper.
13. Data for *syn*-**11**: mp 91.5–93°C (DCM/PE); R_f 0.30 (SiO_2, ether); IR (thin film/cm^{-1}): $\tilde{\nu}_{max}$ 2927w (CH), 1717s (C=O), 1436m, 1307m, 1149m, 1053s, 756m, 694s; ^1H NMR (400 MHz, $CDCl_3$): δ 2.96 (3H, s, CH_3), 3.49 (1H, ddd $^3J_{HF}$ 22 Hz, $^2J_{HH}$ 12 Hz, $^3J_{HH}$ 1 Hz, 5-H), 3.80 (1H, ddd $^3J_{HF}$ 32 Hz, $^2J_{HH}$ 12 Hz, $^3J_{HH}$ 3 Hz, 5-H), 4.85 (1H, dd $^2J_{HF}$ 53 Hz, $^3J_{HH}$ 3 Hz, 4-H), 7.28–7.62 (5H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.2 (CH_3), 51.9 (d $^2J_{CF}$ 24 Hz, 5-C), 87.3 (dd $^1J_{CF}$ 199 Hz, $^2J_{CF}$ 19 Hz, 4-C), 99.6 (dd $^1J_{CF}$ 238 Hz, $^2J_{CF}$ 17 Hz, 3-C), 127.2

(C_{ipso}), 129.5, 130.2, 135.3, 164.6 (d $^2J_{CF}$ 27 Hz, C=O); ^{19}F NMR (564 MHz, $CDCl_3$): δ −190.6 to −190.8 (m, 4-F), −155.9 (d J_{FF} 17 Hz, 3-F); MS (FAB): m/z 244 (MH^+, 100%); Anal. calcd for $C_{11}H_{11}F_2NOS$: C, 54.31; H, 4.56; N, 5.76; S, 13.18. Found: C, 54.17; H, 4.30; N, 5.70; S, 13.37%.

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18. Preliminary results show that coordinating heteroatoms are required in the substrate for DFIT to perform this transformation. Simple dialkyl sulfides, for example, are not oxidised by the reagent. See: Greaney, M. F. *Ph.D. Dissertation*; University of London: UK, 2000.