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On the Preparation and Unusual Reactivity of a Potential Difluorodienophile

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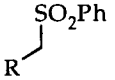
Abstract: Attempts to generate a difluorovinyl sulfone and to react it with cyclopentadiene were hindered by the formation of hydrofluorination products. An α-carbamoyloxy-β,β-difluoroethenyl phenyl sulfone has been prepared in high yield, but reactions with cyclopentadiene have given predominantly mono-fluorinated cycloadducts, *via* reduction of the difluorinated compound *in situ*.

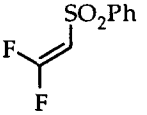
Despite considerable progress in the building block synthesis of selectively fluorinated molecules,[1] few reports describe useful cycloaddition reactions of fluorinated dienophiles, with examples of difluoro species being particularly rare. Wakselman and co-workers[2] have described the [4+2] cycloaddition of methyl-2,2-difluoropropenoate with furan whilst reporting attempts to prepare shikimic acid analogues, though the preparation of the dienophile, the cycloaddition and the manipulation of the cycloadducts were problematic. Two factors have restricted the development of useful Diels-Alder chemistry in the area; firstly difluoroalkenes, lacking a strong activating (electron withdrawing or π-acceptor) group, display low reactivity below elevated temperatures, at which [2+2] reactions, which occur *via* biradical mechanisms, compete effectively.[3,4] Secondly the incorporation of electron withdrawing groups within difluoroalkenyl compounds activates conjugate addition/elimination reactions which lead to loss of fluoride ion, and concomitant hydrofluorination of the potential dienophile. In this communication we describe the synthesis of a difluorinated dienophile and its high (unwanted) reactivity along other pathways.

Vinyl sulfones are competent alkene equivalents[5] with diverse chemistry, yet no β-fluorinated examples are known and the only literature report, of a β-fluorinated vinyl sulfoxide, described a transient and highly electrophilic species.[6] We attempted to prepare a difluorovinyl sulfone from trifluoroethyl tosylate which was converted to sulfide **1a** by a known route[7] and oxidised to the sulfone **2a** with sodium perborate.[8]

1a, R = CF_3
1b, R = CF_2Cl



2a, R = CF_3
2b, R = CF_2Cl



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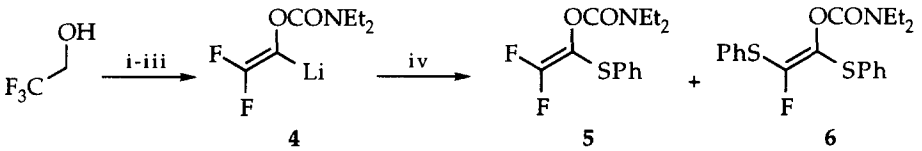
Dehydrofluorination reactions were attempted with a wide range of bases, leading either to the recovery of starting material or the generation of non-fluorinated polymeric products by

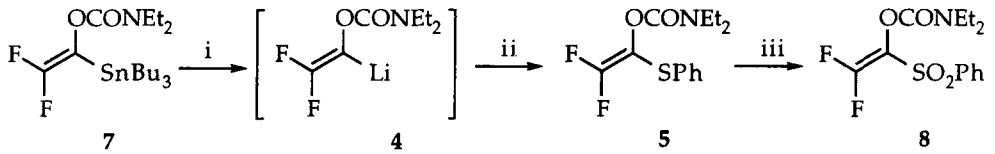
base/nucleophile attack upon the β-difluoroalkene. The difficulties encountered in the problematic dehydrofluorination step[9] prompted the adoption of a dehydrochlorination approach. Chlorodifluoroethyl sulfide **1b** was prepared from chlorodifluoroethanol[10] using the method of Kotsuki[11] and oxidised to sulfone **2b** with sodium perborate.[8] On treatment of **2b** with amine bases, dehydrochlorination occurred readily generating **3** *in situ;* however the formation of the vinyl sulfone was always accompanied by the formation of the hydrofluorination product **2a**. We were unable to characterise **3** fully, nor were we able to trap it *in situ* with cyclopentadiene, but ^{19}F NMR spectra of aliquots of the reaction mixture showed its presence clearly.[12]

Next, we decided to prepare the α-*N*,*N*-diethylcarbamato analogue[13] from metallated enol carbamate **4**.[14] Trapping **4** with diphenyl sulfide led to the formation of **5** (5%) and **6** (81%). The formation of bis-sulfide **6** arises from nucleophilic attack by the phenylthiolate nucleophile on the intermediate difluorovinyl sulfide **5** (**Scheme 1**).



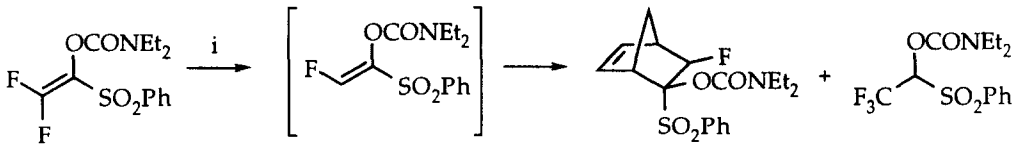
Scheme 1. Reagents and conditions: i, NaH, THF, 0 °C; ii, Et_2NCOCl; iii, 2.0 LDA, THF, -78 °C, inverse addition; iv, PhSSPh,warm to -30 °C.

However, treatment of **4**, generated by tin-lithium exchange from stannane **7**[14] with the phenylthio benzenesulfonate reagent developed by Trost[15] afforded sulfide **5** in good (82%) reproducible yield after flash column chromatography. Oxidation with dimethyldioxirane afforded sulfone **8** in good yield.[16] In this case, full characterisation of the sulfone was possible[17] indicating that the carbamato group at the α-position is indeed acting to stabilise the compound (**Scheme 2**).



Scheme 2. Reagents and conditions: i, *n*-BuLi, THF, -78 °C; ii, $PhSO_2SPh$, warm to -30 °C ; iii, DMDO, acetone, 0 °C.

With the β,β-difluorovinyl sulfone in hand, we attempted a cycloaddition reaction with the paradigmal diene, cyclopentadiene (10 equivalents, refluxing xylene) (**Scheme 3**). To our great suprise, we isolated a good (67%) yield of monofluoro-cycloadduct **10**.[18] We believe that dienophile **9** is formed *in situ* by hydride reduction of **8**, with cyclopentadiene acting as the hydride donor.[19] Similar results were obtained using perfluorodecalin as the reaction solvent. Reactions with furan gave the hydrofluorination product **11** alone.



8 9 10 11

Scheme 3. Reagents and conditions: i, 10.0 C_5H_6, Xylene or $C_{10}F_{16}$, Reflux, 4 hours.

These results indicate the extremely high reactivity of strongly activated difluoroalkenes towards opportunistic nucleophiles and the problems inherent in the design of reactive difluorinated dienophiles.

Acknowledgements

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9. Dehydrofluorination reactions often involve a high degree of $E1_cB$ character to initiate cleavage of the strong C-F bond, requiring the use of strong bases. Dehydrochlorination (and other dehydrohalogenations) are usually considerably easier to achieve. For examples, see Percy, J.M. in *Comprehensive Organic Functional Group Transformations*, ed. by Katritzky, A.R.; Meth-Cohn, O.; Ress, C.W. Pergamon, **1995**, *1*, Chapter 1.13, 570-574.
10. The alcohol was prepared by $LiAlH_4$ reduction of methyl chlorodifluoroacetate.
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12. In a typical procedure, (0.1g, 0.48 mmol) of sulfone **2b** was dissolved in dry $CDCl_3$ (5ml) and cooled to 0 °C. Triethylamine (0.048 ml, 0.48 mmol, or one equivalent of an other amine base) was added slowly to the solution. After 20 minutes, an aliquot was withdrawn and analysed by ^{19}F NMR spectroscopy. Signals consistent with the presence of a difluorovinylic compound **3** were observed [δ_F(90 MHz; $CDCl_3$) -63.2 (*d*, $^2J_{F\text{-}F}$ 12.2), -68.6 (*d*, $^2J_{F\text{-}F}$ 12.2)]. Removal of the solvent *in vacuo* from the crude reaction mixture gave trifluoroethyl sulfone **2a** alone.

13. Shi has claimed that an oxygen substituent (an alkoxy group) at the α-position stabilises β,β-difluoroalkenoates considerably; Shi, G.Q.; Cao, Z. *J. Chem. Soc., Chem. Commun*, **1995**, 1969-1970.
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17. Satisfactory analyses was obtained for sulfone **8** and cycloadduct **10**. Purification by flash column chromatography (20% ethylacetate in hexane, R_f = 0.24) afforded **9** as a clear oil (0.41 g, 84 %): δ_H(300 MHz; $CDCl_3$) 8.00-7.90 (2H, *m, Ph*), 7.70-7.50 (3H, *m, Ph*), 3.36 (2H, *q*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)$), 3.25 (2H, *q*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)$) 1.25 (3H, *t* $^3J_{H-H}$ 7.0, $N(CH_2CH_3)$), 1.05 (3H, *t*, $^3J_{H-H}$ 7.0, $N(CH_2CH_3)$); δ_F(90 MHz; $CDCl_3$) -80.5 (1F, *d*, $^2J_{F-F}$ 12.1), -88.4 (1F, *d*, $^2J_{F-F}$ 12.1); δ_C(75 MHz; $CDCl_3$) 159.1 (C-1, *dd*, $^1J_{C-F}$ 308.3, 308.4), 150.9 (C-3), 139.1 (C-6), 134.9 (C-7), 129.2 (C-8), 128.6 (C-9), 116.1 (C-2, *dd*, $^2J_{C-F}$ 39.6, 37.2), 43.2 (C-4), 42.4 (C-4), 13.9 (C-5), 13.0 (C-5); *m/z* (CI) 337 (80, $M+NH_4^+$), 320 (100% $[M+H]^+$), 100 (65, $[CONEt_2]^+$); HRMS calc. for $C_{13}H_{15}NO_4F_2S$: 319.10331; found: 319.10373.
18. Cycloadduct **10** was prepared by dissolving sulfone **8** (0.20 g, 0.62 mmol) in distilled xylene (10 ml). Freshly cracked cyclopentadiene (0.40 g, 6.2 mmol) was added and the mixture was refluxed for 4 hours. During this time, a straw yellow colour developed slowly. After cooling, the xylene was removed *in vacuo* and the brown residue purified by column chromatography (20% ethyl acetate in hexane, R_f = 0.15). Cycloadduct **10** was isolated as the major isomer (>90%) as a clear oil (0.15 g, 67 %): δ_H(300 MHz; $CDCl_3$) 8.00-7.95 (2H, *m, Ph*), 7.70-7.60 (1H, *m, Ph*), 7.58-7.49 (1H, *m, Ph*), 6.25-6.15 (2H, *m*, CHCHCHCH), 4.20-4.15 (1H, *m*, CHF) 3.34-3.26 (1H, *m*, $CHC(SO_2Ph)$), 3.22-2.95 (4H, *m*, $N(CH_2CH_3)_2$), 2.88-2.75 (1H, *m*, CHCHF), 1.75-1.64 (2H, *m*, $CHCH_2CH$) 1.10 (6H, *m* , $N(CH_2CH_3)_2$); δ_F(90 MHz; $CDCl_3$) -100.4 (*d* $^2J_{H-F}$ 54.6); δ_C(75 MHz; $CDCl_3$); 150.8 (C-8), 138.1 (C-7, $^2J_{C-F}$ 37.2), 137.3 (C-2) 134.5 (C-11), 134.2 (C-1), 134.1 (C-12), 130.4, (C-13), 129.8 (C-14), 112.8 (C-6, *d*, $^1J_{C-F}$ 230.7), 49.5 (C-3, $^2J_{C-F}$ 12.2), 48.4 (C-5), 44.9 (C-4), 41.8, 41.0 (C-9), 13.8, 13.3 (C-10); *m/z* (CI) 385 (40% $[M+H]^+$, 100), 100, $[CONEt_2]^+$). The relative stereochemistry of the cycloadduct was elucidated by an nOe experiment; irradiation of the multiplet at 4.20-4.15 resulted in positive nOe's in the two proton vinylic multiplet, and the *ortho*-protons in the phenylsulfonyl group, consistent with a *cis* arrangement between the fluorine atom and the carbamoyloxy group, and an *endo* orientation for the phenylsulfonyl group.
19. Cyclopentadiene itself can only release hydride with the formation (formally) of an anti aromatic (4π electron) cation.

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