



## Synthesis and Reactivity of a Fluorinated Dienophile

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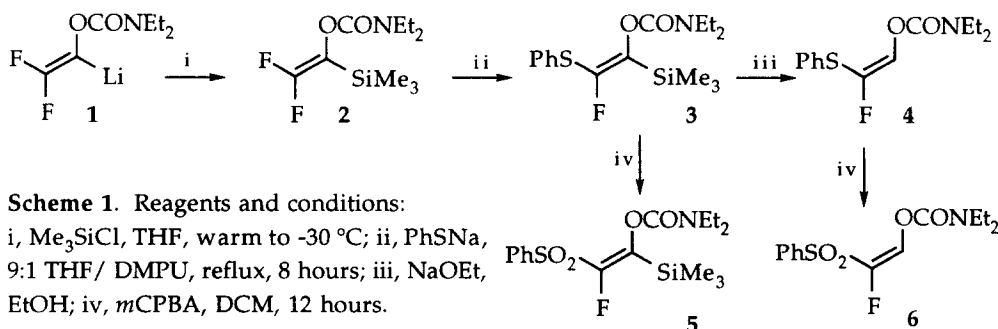
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**Abstract:** 1-(N,N-diethylcarbamoyloxy-2-fluoro-2-(phenylsulfonyl)-ethene has been prepared and reacted with a variety of dienes to give fluorinated [4+2] cycloadducts. In contrast, the desulfonated equivalent 1-(N,N-diethylcarbamoyloxy)-2-fluoro-*E*-ethene reacts with cyclopentadiene alone, to give mixtures of [4+2] and [2+2] cycloadducts. Copyright © 1996 Elsevier Science Ltd

The synthesis of novel, functionalised, mono- or di-fluorinated carbocycles remains a significant synthetic challenge.<sup>1</sup> Diels-Alder reactions may provide a general approach to such compounds but the range of fluorinated dienophiles is narrow.<sup>2</sup> The rarity of reactive fluorinated dienophiles is a consequence of the low [4+2] reactivity of fluoroalkenes lacking a  $\pi$  acceptor group,<sup>3</sup> and the ease with which fluorine atoms  $\beta$ - to electron withdrawing groups can be replaced in substitution reactions.<sup>4,5</sup> It was anticipated that a reactive, but stable, monofluoro dienophile could be prepared by locating the fluorine atom and the activating group on the *same* carbon. Such a compound would not be susceptible to conjugate addition/elimination reactions involving defluorination and would be, potentially, a valuable building block containing a single fluorine atom.<sup>6</sup>


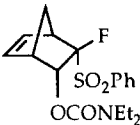

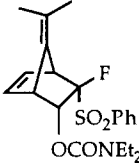

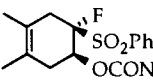

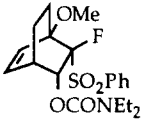

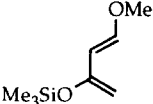
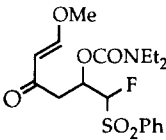
Nucleophiles add to 1,1-difluoroalkenes, yielding either substitution or addition products.<sup>4</sup> A general and versatile approach to a variety of 1,1-difluoroalkenes using metallated difluoroenol derivatives has been described recently.<sup>7</sup> If the substitution of a fluorine atom could be achieved using a sulfur nucleophile, for example, thiophenolate, a monofluorovinyl sulfide would be produced in which the remaining fluorine atom and the phenylthio group would be located on the same carbon. **Scheme 1** shows a synthetic route to the title compound.



The difluorovinyl silane **2** can be made readily from the metallated enol carbamate **1**. The treatment of silane **2** with a solution of sodium thiophenolate at reflux for 8 hours gave the monofluorovinyl silane **3** in high (87%) yield<sup>8</sup> with excellent stereoselectivity (>95%) after flash

column chromatography. Desilylation was achieved quantitatively to give the  $\alpha$ -fluorovinyl sulfide **4**. Sulfides **3** and **4** were oxidised to the sulfones **5** (76%) and **6** (85%) with *m*CPBA. Investigation of the reactivity of **6** revealed it to be a reactive dienophile with a variety of dienes. With cyclopentadiene, best results were achieved when **6** was heated to 100 °C in sealed tubes with neat cyclopentadiene (10 equivalents). The reaction proceeded smoothly to afford cycloadduct **7a** in high yield (82%) as a mixture (1:1) of *endo* / *exo* isomers. Reactions with less reactive dienes required harsher conditions, but yields were still good to moderate (**Table 1**).

**Table 1**

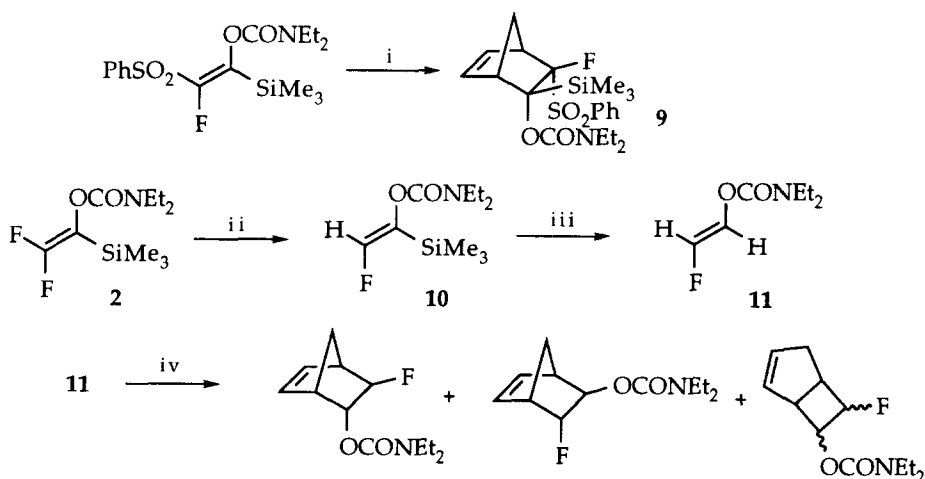
Diene	Conditions	Product	Yield %	<i>endo</i> / <i>exo</i>
	100 °C, 8 hours		82	1:1
	100 °C, 72 hours		53	1:1
	150 °C, 72 hours		66	-
	150 °C, 72 hours		40	1:1
	150 °C, 72 hours	No Reaction	-	-
	100 °C, 8 hours <sup>a</sup>		57	-

<sup>a</sup> 2eq of diene in toluene

The limiting case of dienophile reactivity was reached with furan, which showed no reaction with **6** after extended reaction times and temperatures.<sup>9</sup> Additionally, attempts to react **6** with Danishefsky's diene gave the conjugate addition product **8** instead of the expected [4+2] cycloadduct.

While **6** is an effective dienophile, it is much less reactive than phenylvinyl sulfone which reacted with cyclopentadiene at room temperature to afford 3.6:1 *endo/exo* mixture of cycloadducts.<sup>10</sup> The lower reactivity of **6** may be due to the extra steric demands that the (*N,N*-diethyl)carbamato group is imposing on the reaction and we are attempting to discover the reason for the low reactivity using semi-empirical computational methods. The fluorovinyl silane **5** was a much less reactive dienophile and only reacted with cyclopentadiene (**Scheme 2**) to afford cycloadduct **9** as a 5:1 mixture of *endo* and *exo* isomers.<sup>11</sup>

A satisfying aspect of these results was the total absence of [2+2] products from the reaction mixtures.<sup>12</sup> In order to determine if this was solely the effect of the sulfonyl group, the desulfonated dienophile **11** was prepared from silane **2** by selective reduction to **10** (72%) and desilylation to **11** (87%).<sup>13</sup>



**Scheme 2.** Reagents and conditions: i, 10.0  $\text{C}_5\text{H}_6$ , 150  $^\circ\text{C}$ , 72 hours; ii,  $\text{LiEt}_3\text{BH}$ , THF; iii, TBAF, THF; iv, 10.0  $\text{C}_5\text{H}_6$ , 150  $^\circ\text{C}$ , 72 hours.

Under the reaction conditions used for **6**, monofluoroenol carbamate **11** did not react with cyclopentadiene. In fact, for complete consumption of **11**, it was necessary to heat the mixture to 150  $^\circ\text{C}$  with cyclopentadiene for 72 hours. Careful inspection of the product mixture revealed that it contained a mixture of two [4+2] cycloadducts and two [2+2] cycloadducts in approximately equal proportions. Such a high proportion of [2+2] cycloadduct is surprising for a compound that lacks a terminal  $\text{CF}_2$  group.

The need for forcing reaction conditions and the presence of the [2+2] cycloadducts in the reaction of **11** with cyclopentadiene highlight the activating effect exerted by the phenyl sulfonyl group which makes **6** a potentially useful synthetic building block. Work to elaborate the cycloadducts and remove the phenyl sulfonyl and carbamato groups is in progress and will be reported in full in due course.

## Acknowledgements

We wish to thank the EPSRC and Zeneca Agrochemicals for a CASE Studentship to KS.

## REFERENCES AND NOTES

- For recent examples, see Buttle, L.A.; Motherwell, W.B. *Tetrahedron Lett.*, **1994**, *35*, 3995-3998; Shibuya, A.; Kurishita, M.; Ago, C.; Taguchi, T. *Tetrahedron*, **1996**, *52*, 271-278; Arnone, A.; Bravo, P.; Frigiero, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *Tetrahedron*, **1994**, *50*, 12361-12374; Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem.*, **1995**, *60*, 2320-2321.
- Leroy, J.; Molines, H.; Wakselman, C. *J. Org. Chem.*, **1987**, *52*, 290-292.
- DeCock, C.; Piettre, S.; Lahousse, F.; Janousek, Z.; Merenyi, R.; Viehe, H.G. *Tetrahedron*, **1985**, *41*, 4183-4193; Bartlett, P.D.; *Quart. Rev.*, **1970**, *24*, 473-497.
- Ichikawa, J.; Kobayashi, M.; Yokota, N.; Minami, T. *Tetrahedron*, **1994**, *50*, 11637-11646.
- See Crowley, P.J.; Percy, J.M.; Stansfield, K. *Tetrahedron Lett.*, **1996**, previous paper in this issue.
- Percy, J.M. *Contemporary Organic Synthesis*, **1995**, *4*, 251-268.
- Howarth, J.A.; Owton, W.M.; Percy, J.M.; Rock, M. *Tetrahedron*, **1995**, *51*, 10289-10302.
- In a typical procedure, a solution of sodium thiophenolate was made by the careful addition of thiophenol (2.0 g, 9.1 mmol) to sodium hydride (0.38 g, of a 60 % dispersion in oil which had been washed with dry toluene) in THF (30 ml). The thick white suspension became homogeneous upon addition of DMPU (4 ml). Silane **2** (5.0 g, 9.0 mmol) was added and the reaction was refluxed for eight hours. The cool reaction mixture was poured into water (100 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic extracts were washed with brine (100 ml) and dried (MgSO<sub>4</sub>) before filtration and concentration *in vacuo*. Purification by column chromatography (20% ethyl acetate in hexane, *R<sub>f</sub>* = 0.68) afforded silane **3** as single isomer (2.49 g, 87 %). (Found: C, 56.20; H, 7.11; N, 4.02. Calc. for C<sub>16</sub>H<sub>24</sub>O<sub>2</sub>NFSSi: C, 56.27; H, 7.08; N, 4.10 %);  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>) 7.45-7.10 (5H, *m*, *Ph*), 3.40 (2H, *q*,  $^3J_{\text{H-H}}$  7.0, N(CH<sub>2</sub>CH<sub>3</sub>)), 3.20 (2H, *q*,  $^3J_{\text{H-H}}$  7.0, N(CH<sub>2</sub>CH<sub>3</sub>)), 1.20 (6H, *t*,  $^3J_{\text{H-H}}$  7.0, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 0.12 (9H, *s*, Si(CH<sub>3</sub>)<sub>3</sub>);  $\delta_{\text{F}}$  (90 MHz; CDCl<sub>3</sub>) -108.9 (*s*);  $\delta_{\text{C}}$  (75 MHz; CDCl<sub>3</sub>) 159.2 (C-3), 150.6 (C-1 *d*,  $^1J_{\text{C-F}}$  289.4), 132.1 (C-7), 128.9 (C-8), 126.2 (C-2 *d*,  $^2J_{\text{C-F}}$  38.6), 124.8 (C-9), 121.8 (C-10), 40.3, 40.2 (C-4), 14.2, 13.4, (C-5), 1.1 (C-6); *m/z* (CI) 342 (80%, [M+H]), 349 (100 [M+NH<sub>4</sub>]<sup>+</sup>) 100 (50 [CONEt<sub>2</sub>]<sup>+</sup>). Oxidations were performed using 4 equivalents of *m*CPBA. Cycloaddition reactions were performed in Ace Tubes (#8648B) using the diene as the reaction solvent.
- In the attempted reaction with furan, **6** was recovered unchanged with no sign of isomerisation.
- Carr, R.V.C.; Williams, R.V.; Paquette, L.A. *J. Org. Chem.*, **1983**, *48*, 4976-4986.
- Presumably formation of the product with the trimethylsilyl group in the *endo* position involves highly unfavourable steric repulsions with the diene.
- Percy, J.M.; Rock, M.H. *Tetrahedron Lett.*, **1992**, *33*, 6177-6180.
- Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.*, **1993**, *34*, 415-418.