

Tetrahedron Letters 42 (2001) 6377-6380

TETRAHEDRON LETTERS

## A direct and useful route to difluoroacylsilanes and difluoroacylstannanes and their potential for the generation of structurally diverse difluoroketones

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Abstract—Allyl trifluoroethyl ethers 2a-2d were prepared; each underwent efficient dehydrofluorination/metallation and trapping to afford a range of difluoroenol silanes and stannanes which rearranged easily and efficiently to the acyl metals. Fluoride-mediated benzylation and allylation of an acylsilane, and Stille coupling of the vinyl- and acyl-stannane were achieved in moderate to good yield. © 2001 Elsevier Science Ltd. All rights reserved.

In 1985, Metcalf, Jarvi and Burkhart published a seminal paper which showed how the [3,3]-Claisen rearrangement could be used to generate a range of  $\alpha, \alpha$ -difluoroketone structures from allyl trifluoroethyl ethers (Scheme 1).<sup>1</sup>

The idea was revisited recently by Taguchi and coworkers<sup>2</sup> as they sought to develop an enantioselective Claisen rearrangement. Both groups used a dehydrofluorination reaction to create the vinyl component of the Claisen system. We noted that the former group



Scheme 1. (a)  $F_3CCH_2ONa$ , THF, reflux, 63%; (b) 3.3 equiv. LDA/TMSCl, THF, -100°C, 88%; (c) CCl<sub>4</sub>, reflux, unknown yield.

had progressed a simple allyl trifluoroethyl ether to a metallated diffuoroenol ether which they were able to quench with water or a silicon electrophile to afford an aldehyde, or more efficiently, an acyl silane after rearrangement. We were unable to find many examples of this chemistry or of reactions of the acylsilane, apart from a single example reported by McCarthy,<sup>3a</sup> while Normant, Sauvêtre and Dubuffet<sup>3b</sup> had isolated a similar acylsilane species from the solvolysis of a difluorinated epoxysilane. We wondered if useful coupling or transfer reactions could be available from the difluoroacyl metals or from the difluorovinyl metal precursors (as none had been reported); we were also aware that acylstannanes possessed useful properties for C-C bond forming reactions,<sup>4</sup> and that the  $\alpha, \alpha$ difluoro species would be novel. Furthermore, the vinyl stannane intermediates would offer the possibility of coupling reactions<sup>5</sup> allowing access to a wide range of aryl difluoroketones. We therefore synthesised a range of allyl trifluoroethyl ethers 2a-2d designed to test the scope of the dehydrofluorination/metallation chemistry (Scheme 2).



Scheme 2. (a) 50% NaOH, Bu<sub>4</sub>NHSO<sub>4</sub>, Bu<sub>4</sub>NI, 1a,1b or 1d; (b) 1,1'-(azodicarbonyl)dipiperidine, Bu<sub>3</sub>P, PhH, 6 h, rt, 1c.

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Different substitution patterns in the allyl system were of interest and we wished to use the chemistry to attach chains to rings. We were able to use phase transfercatalysed allylation of trifluoroethanol very successfully<sup>6</sup> and also the Mitsunobu procedure described by Falck<sup>7</sup> in the case of **2c** for which the halide was less readily available than the alcohol. The former method was also used to prepare **2a** on a 0.1 mol scale in quantitative yield (Table 1).

The dehydrofluorination/metallation (Scheme 3) could be achieved<sup>8</sup> at  $-78^{\circ}$ C with *n*-BuLi (2 equivalents) for the preparation of the vinylsilanes **3a–3d** or -stannanes **4a–4d**, in contrast to the Metcalf report in which it was necessary to use a larger excess of strong base (3.3 equivalents) and trapping conditions (LDA/TMSCI) at lower reaction temperature ( $-100^{\circ}$ C) to prepare the silane shown in Scheme 1 in good yield. This observation indicates that the thermal stability of the simple metallated difluoroenol ether is sufficient at  $-78^{\circ}$ C for rapid trapping to be achieved even in the absence of inductively electron-withdrawing<sup>9</sup> or co-ordinating substituents,<sup>10</sup> or chelation within a part-polyether structure,<sup>11</sup> features we believed necessary to reduce the rate of the antiperiplanar elimination of LiF.

<sup>19</sup>F NMR spectra of the crude material in each case revealed relatively clean product mixtures; flash column chromatography on silica gel or alumina delivered pure silane or stannane, respectively (to 98% purity by GC).<sup>8</sup> Rearrangements of **3a–3c** and **4a–4c** occurred smoothly (Table 2) neat or in toluene at 110°C in Ace<sup>®</sup> tubes,<sup>12</sup> whereas **3d** and **4d** rearranged much more slowly, consistent with steric hindrance in the transition states as the bulky trialkylmetal and cyclic array are forced together.

Purification at the vinylmetal stage is not necessary; isolation may even be avoided. For example, crude 4c rearranged to 6c successfully (88% based on starting ether). In one case, the THF reaction solution of 3b was refluxed for 20 h to afford 5b in ca. 50% yield along

Table 1. Synthesis of ethers

Allyl fragment	Trifluoroethyl ether	(%)	Method	
1a	2a	100 <sup>a</sup>	a	
1b	2b	85	a	
1c	2c	100	b	
1d	2d	100	а	

<sup>a</sup> At 5 and 100 mmol scales.

 Table 2. Synthesis of vinyl metals and acyl metals

Ether	Vinyl metal	(%) <sup>a</sup>	Acyl metal	(%) <sup>d</sup>	Time (h)
2a	3a	90 <sup>ь</sup>	5a	100	4
	4a	85	6a	100 <sup>c</sup>	3.5
2b	3b	85	5b	100	10
	4b	77	6b	96	10
2c	3c	78	5c	100	10
	4c	70	6c	88 <sup>e</sup>	8
2d	3d	90	5d	95	120
	4d	80	6d	90	108

<sup>a</sup> At 5 mmol scale.

<sup>b</sup> 66% at 100 mmol scale.

<sup>c</sup> Yield for rearrangement in toluene.

<sup>d</sup> Yield for neat rearrangement.

<sup>e</sup> Yield for purified stannane from unpurified vinylmetal.

with several other (minor) fluorinated products, suggesting that a one-pot preparation of the acylsilanes may be available. However, we have not yet optimised these procedures and recommend at least isolation of the vinylmetal intermediates.

Acylsilane **5a** was transformed into ketone **7** (54%) when treated with TBAF in the presence of benzyl bromide.<sup>13</sup> The reaction with allyl bromide afforded a mixture of ketones **8a** and **8b** (46%, 1:1.2), indicating that double bond migration occurs under the reaction conditions; further applications of this chemistry are under investigation (Scheme 4).

The vinyl stannane seems an obvious substrate for Stille coupling, given our findings that related difluoroenol carbamates can be used successfully.5b The issue of interest here is the possibility of competitive and destructive Pd(II)-catalysed reactions of the allyl ether moiety. Attempting to minimise the possibility of competing rearrangement, we worked at room temperature and though the reaction was slow (72 h for consumption of starting material) we were able to isolate ketones 9 and 11 cleanly and in good yield (60 and 72%. respectively) following exposure (5%) Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub>, 20% CuI, 10% tris(2-furyl)phosphine, DMF, rt then KF work-up)<sup>14</sup> of 4a to iodobenzene or 10, respectively (Scheme 5).

Product 9 was also obtained in 52% yield from iodobenzene and **6a** under the same conditions. Exposure of **4a** to the Stille catalyst/co-catalyst but in the absence of an electrophile consumed the stannane but formed a complex product mixture which contained only a small amount of **6a**, suggesting that there is no



Scheme 3. (a) i, 2.0 *n*-BuLi, THF,  $-78^{\circ}$ C; ii, 1.0 Me<sub>3</sub>SiCl; (b) i, 2.0 *n*-BuLi, THF,  $-78^{\circ}$ C; ii, 1.0 Bu<sub>3</sub>SnCl; (c)  $\Delta$  (110°C, Ace<sup>®</sup> tube).



Scheme 4. TBAF, THF, rt, 12 h and (a) PhCH<sub>2</sub>Br or (b) H<sub>2</sub>C=CHCH<sub>2</sub>Br.



Scheme 5. (a) PhI or 10 (from 4a only), 5% Pd2dba3·CHCl3, 20% CuI, 10% P(2-furyl)3, DMF, rt, 72 h.



## Scheme 6.

simple catalysis of the rearrangement reaction system under the coupling reaction conditions. The timing of the two events (coupling versus rearrangement) is unknown and we are trying to ascertain their sequence.

These short sequences provide a very general route to fluoroketones of general type **12** from trifluoroethanol. An alternative synthesis could start from an aryl acylsilane and prepare the difluoroenol silyl ether, subjecting the intermediate to allylation, as described by Portella<sup>15</sup> (Scheme 6).

A similar approach can be made using the reductive defluorination chemistry of Uneyama.<sup>16</sup> Various methods have been described for the synthesis of 2,2-difluoropent-4-enoic acid derivatives which could then be elaborated through Weinreb amides and reaction with the Grignard reagents; Gelb's route<sup>17</sup> uses tetra-fluoroethylene which is not particularly convenient, while the Reformatsky–Claisen reaction described by Lang<sup>18</sup> has proved both very difficult to repeat and non-general in our hands. We contend that the method described herein is at least competitive with these more established approaches and represents a direct and reliable route to 2,2-difluoropent-4-enones with variable substitution at C-1, C-3, C-4 and C-5.

## Acknowledgements

We thank the EPSRC and the University of Birmingham for a studentship (M.R.G.) and Ms C. Powell for repeating and scaling the syntheses of **5a–6d**.

## References

- Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron* Lett. 1985, 26, 2861–2684. For a review of rearrangement-based methods, see: Percy, J. M.; Prime, M. E. J. Fluorine Chem. 1999, 100, 147–156.
- Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T. Chem. Commun. 1998, 2441–2442.
- (a) McCarthy, P. A.; Wint, L. T.; Diaz, C. L. Bioorg. Med. Chem. Lett. 1992, 2, 119–122; (b) Dubuffet, T.; Sauvêtre, R.; Normant, J.-F. Bull. Soc. Chim. Fr. 1989, 677–682.
- (a) Shirakawa, E.; Nakao, Y.; Hiyama, T. Chem. Commun. 2001, 263–264; (b) Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. J. Am. Chem. Soc. 2000, 122, 9030–9031.
- (a) For recent couplings of α-metallated enol ethers, see: Yu, W. S.; Jin, Z. D. J. Am. Chem. Soc. 2000, 122, 9840–9841; (b) for couplings to difluoroenol carbamates,

see: DeBoos, G. A.; Fullbrook, J. J.; Owton, W. M.; Percy, J. M.; Thomas, A. C. *Synlett* **2000**, 963–966.

- Schlosser, M.; Strunk, S. Tetrahedron 1989, 45, 2649– 2664.
- Falck, J. R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.* 1994, 35, 5997–6000.
- 8. Dehydrofluorination/metallation/trapping of 2c to 3c: n-Butyllithium (5 mL of a 2 M solution in hexane, 2 equiv.) was added dropwise to a solution of trifluoroethyl allyl ether 2c (1.3 g, 5 mmol) in tetrahydrofuran (15 mL) at -78°C under nitrogen. The mixture was stirred a further 20 minutes at  $-78^{\circ}$ C then chlorotrimethylsilane (0.63 mL) was added in one portion. The mixture was allowed to warm to -40°C over 1 hour, then quenched at -40°C with saturated aqueous ammonium chloride solution (20 mL) and extracted with diethyl ether (3×40 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo to an orange oil which was purified by flash column chromatography on silica gel to afford silane 3c (1.21 g, 78%) as a colourless oil (98% by GC);  $v_{\text{max}}$  (KBr/cm<sup>-1</sup>): 3032, 2959, 2860, 1688 (C=CF<sub>2</sub>), 843; δ<sub>H</sub> (CDCl<sub>3</sub>, 300 MHz) 7.38-7.30 (5H, m), 5.83-5.78 (2H, m), 4.53 (2H, s), 4.24 (2H, d, <sup>3</sup>J<sub>H-H</sub> 4.8 Hz), 4.11 (2H, d, <sup>3</sup>J<sub>H-H</sub> 4.4 Hz), 0.20 (9H, s);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 75 MHz) 160.9 (dd,  ${}^{1}J_{\rm C-F}$  283.16, 283.15 Hz), 138.1, 129.8, 128.7, 128.5, 127.8, 127.7, 117.4  $(dd, {}^{3}J_{C-F}, 7.1, 7.1 Hz), 72.4, 68.6 (dd, {}^{4}J_{C-F}, 2.5, 2.5 Hz),$ 65.7, 1.1;  $\delta_{\rm F}$  (CDCl<sub>3</sub>, 282 MHz) -81.3 (d, <sup>2</sup>J<sub>F-F</sub> 57.9), -104.8 (d,  ${}^{2}J_{F-F}$  57.9); m/z (ES) 335 (100%, M+Na<sup>+</sup>). HRMS calcd for C<sub>16</sub>H<sub>22</sub>F<sub>2</sub>NaO<sub>2</sub>Si: 335.1255. Found: 335.1250.
- Nakai, T.; Tanaka, K.; Ishihawa, N. Chem. Lett. 1976, 1263–1266.

- (a) Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* 1993, 34, 415; (b) Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* 1993, 34, 411–414; (c) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* 1995, 51, 10289–10302.
- Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* 1995, *51*, 9201–9216.
- 12. Rearrangement of **3c** and data for **5c**: Neat silane **3c** was heated in an Ace<sup>®</sup> tube at 110°C to afford **5c** which was purified by Kugelrohr distillation bp 125°C/0.1 mmHg (96% by GC);  $v_{max}$  (KBr/cm<sup>-1</sup>): 3033, 2960, 2870, 1673, 847;  $\delta_{\rm H}$  (CDCl<sub>3</sub>, 300 MHz) 7.35–7.27 (5H, m), 5.82–5.69 (1H, m), 5.31 (1H, d, <sup>3</sup>J<sub>H-H</sub> 7.35 Hz), 5.28 (1H, d, <sup>3</sup>J<sub>H-H</sub> 16.9 Hz), 4.42 (2H, s), 3.70–3.45 (2H, m), 3.36–3.21 (1H, m), 0.21 (9H, s);  $\delta_{\rm C}$  (CDCl<sub>3</sub>, 75 MHz) 137.6, 130.0 (t, <sup>3</sup>J<sub>C-F</sub> 4.2 Hz), 128.4, 127.8, 127.7, 121.3, 118.7 (dd, <sup>1</sup>J<sub>C-F</sub> 252.4, 252.9 Hz), 72.9, 68.6 (dd, <sup>2</sup>J<sub>C-F</sub> 3.96, 3.95 Hz), 65.9, 15.3; the C=O carbon was too weak to assign properly;  $\delta_{\rm F}$  (CDCl<sub>3</sub>, 282 MHz) –106.3 (1F, dd, <sup>2</sup>J<sub>F-F</sub> 275.0, <sup>3</sup>J<sub>F-H</sub> 9.9 Hz), -115.6 (1F, dd, <sup>2</sup>J<sub>F-F</sub> 275.0, <sup>3</sup>J<sub>F-H</sub> 20.0 Hz); *m*/*z* (ES) 335 (100%, M+Na<sup>+</sup>). HRMS calcd for C<sub>16</sub>H<sub>22</sub>F<sub>2</sub>NaO<sub>2</sub>Si: 335.1255. Found: 335.1245.
- Schinzer, D.; Heathcock, C. H. Tetrahedron Lett. 1981, 22, 1881–1884.
- Farina, V.; Baker, S. R.; Benigni, D. A.; Sapino, C. Tetrahedron Lett. 1988, 29, 5739–5742.
- 15. Lefebvre, O.; Brigaud, T.; Portella, C. *Tetrahedron* **1999**, *55*, 7233–7242.
- Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. Chem. Commun. 1999, 1323–1324.
- Yuan, W.; Berman, R. J.; Gelb, M. H. J. Am. Chem. Soc. 1987, 109, 8071–8081.
- Greuter, H.; Lang, R. W.; Romann, A. J. Tetrahedron Lett. 1988, 29, 3291–3294.