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Chelated [3,3]-Rearrangements of Difluoroallylic Alcohols.

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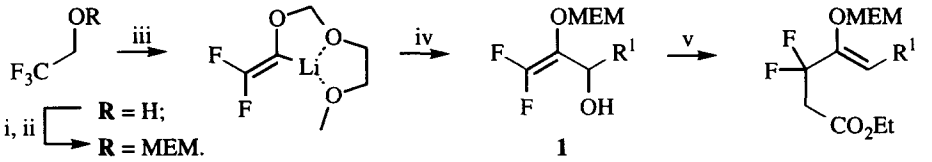
Abstract:Whereas the lithium enolates of acetate and propionate esters of difluoroallylic alcohols fragment rapidly, even at -78 °C, methoxy- and benzyloxy-acetates form chelated enolates which undergo smooth [3,3]-rearrangement as their silyl ketene acetals. The latent ketone function can be revealed under mild conditions (MeOH, $SOCl_2$) to afford very highly functionalised CF_2 compounds.

The synthesis of highly-functionalised molecules containing a limited number of fluorine atoms remains a significant challenge to synthetic organic chemists.[1] A well-tried approach involves the transformation of suitable functional groups by fluorinating agents. For example, a difluoromethylene (CF_2) group can be introduced by the transformation of a ketonic carbonyl group directly using DAST (diethylaminosulfur trifluoride). We have explored building block approaches[2] to CF_2 compounds based upon trifluoroethanol; the preparation of a metallated difluoroenol acetal and its interception with carbonyl electrophiles[3] (**Scheme 1**) sets the stage for a number of sigmatropic transformations including [2,3]-Wittig,[4] [2,3] heteroatomic[5] and [3,3]-Claisen[6] rearrangements. These sequences allow the location of a CF_2 centre within different arrays of functional groups from a very readily available precursor.

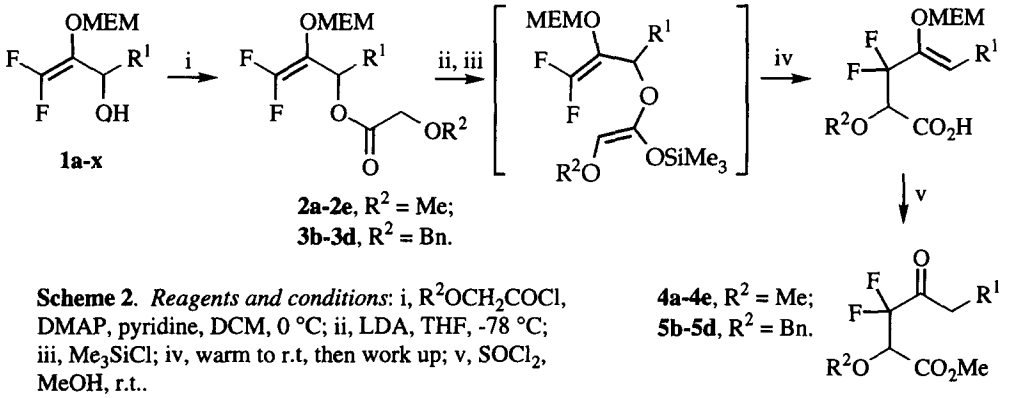


Scheme 1. *Reagents and conditions*: i, NaH, THF, 0 °C; ii, MEM-Cl; iii, LDA, THF, -78 °C; iv, R^1CHO; v, $MeC(OEt)_3$, propionic acid, Δ, 0.75-18 hours.

However, we were unable to use Ireland silyl ketene acetal procedures because the enolates of propionate (and even *iso*butyrate) esters appeared to be particularly labile, fragmenting even under trapping conditions (that is, when generated at -78 °C in the presence of silicon electrophiles). We attributed this lability to the combined inductive electron withdrawing effects of the two fluorine atoms and the -OMEM group, which raised the nucleofugacity of the allylic alkoxide anion facilitating the α-elimination pathway to ketene.[7] However, when we prepared esters containing an alkoxy substituent, so that a chelated enolate could be formed, rearrangement proceeded smoothly[8] affording products with a most attractive level of functionality.[9]

Esters **2a-e** and **3b-d** were prepared from the freshly-distilled acid chlorides and difluoroallylic alcohols using standard conditions. Exposure to freshly-prepared LDA at -78 °C in THF, followed by treatment with

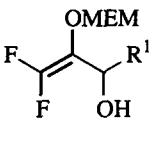
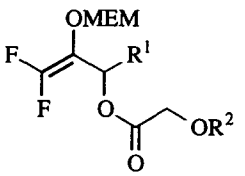
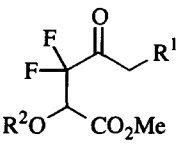
chlorotrimethyl silane afforded a range of acids after warming to room temperature and acidic work-up (**Scheme 2**).



Scheme 2. *Reagents and conditions*: i, R^2OCH_2COCl, DMAP, pyridine, DCM, 0 °C; ii, LDA, THF, -78 °C; iii, Me_3SiCl; iv, warm to r.t, then work up; v, $SOCl_2$, MeOH, r.t..

The crude products were converted directly to the corresponding γ-ketoesters **4a-e** and **5b-d** (**Table 1**) in methanol that contained thionyl chloride, following a recent method.[10,11] Presumably, the enol acetal is cleaved by HCl generated *in situ*. Attempts to repeat the reaction in propan-2-ol were unsuccessful suggesting that a reasonably nucleophilic alcohol is required. The rearrangement appears to be quite general in secondary alcohol. Both methoxy- and benzyloxy-esters rearranged smoothly, a pleasing result because of the potential for unmasking the C-2 hydroxyl group in the latter case.

Table 1. Allylic esters and Ketoesters

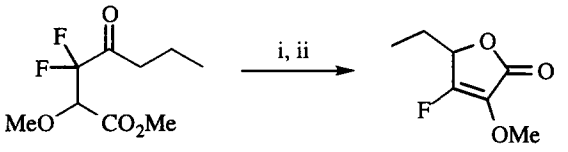
Alcohol	Ester	Yield(%)	Ketoester	Yield(%)[b]
				
1a; R^1 = H;	**2a**; R^2 = Me;	62	**4a**;[a]	60
1b; R^1 = Et;	**2b**; R^2 = Me;	85	**4b**;	67
1c; R^1 = *i*-Pr;	**2c**; R^2 = Me;	70	**4c**;	59
1d; R^1 = *t*-Bu;	**2d**; R^2 = Me;	65	**4d**;	48
1e; R^1 = Ph;	**2e**; R^2 = Me;	52	**4e**;	45
1b; R^1 = Et;	**3b**; R^2 = Bn;	70	**5b**;	60
1c; R^1 = *i*-Pr;	**3c**; R^2 = Bn;	65	**5c**;	55
1d; R^1 = *t*-Bu;	**3d**; R^2 = Bn;	67	**5d**.	54

[a]Dimethyl ketal was also isolated.

[b]Isolated yield based upon allylic ester precursor.

The fluorine atoms are located β-to a carbonyl group, a location which cannot be achieved directly using the well-known Reformatsky chemistry,[12] or aldol reactions with difluoroenolates[13] or their synthetic equivalents.[14] The products contain three differentiated oxygen functions in addition to the CF_2 centre and are therefore attractive intermediates for the synthesis of highly-oxygenated difluorocompounds. In the case of the least sterically hindered ketone product **4a**, we were unable to separate the product completely from the dimethyl ketal; the formation and relatively high stability of this product is entirely consistent with the effect of the CF_2 centre on the reactivity of the adjacent ketonic carbonyl group.

Chemoselective reduction was achieved upon treatment of **2b** with sodium borohydride in methanol; however, to our surprise, substituted butenolide **6** was isolated directly from the crude reaction mixture upon work-up (**Scheme 3**). Previously, we showed that β,β-difluoroesters were reasonably stable, retaining both fluorine atoms at 140 °C, so the dehydrofluorination reaction is interesting and we are looking to establish its timing.[15]



4b **6**

Scheme 3. *Reagents and conditions*: i, $NaBH_4$, MeOH, 0 °C; ii, H_3O^+.

Acknowledgement

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7. Examination of crystal structures of ester enolates showed that the α-elimination was incipient in the ground state, suggesting that these intermediates will be close to the limit of stability in solution; see Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. *J. Am. Chem. Soc.* **1985**, *107*, 5403-5409.
8. See Norley, M.; Kocienski, P.; Faller, A. *Synlett* **1996**, 900-902 for a recent example. Also Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323-4326 for earlier applications and Oh, T.; Wrobel, Z.; Devine, P. N. *Synlett* **1992**, 81-83 for a non-anionic version.
9. The yields are as yet unoptimised; ^{19}F NMR spectra of crude acids and ketoesters were essentially clean indicating that improvements in isolation methods should result in still higher isolated yields.

10. Hosangadi, B. D.; Dave, R. H. *Tetrahedron Lett.* **1996,** *37*, 6375-6378.

11. A typical sequence follows:

Esterification: Pyridine (0.71 ml, 8.8 mmol), followed by methoxyacetyl chloride (0.8 ml, 8.8 mmol), was added to a stirred solution of **1b** (2 g, 8.8 mmol) in DCM (25 ml) containing DMAP (0.04 g, 0.35 mmol). The mixture was stirred at room temperature and followed by TLC. After 18 hours, all of the starting material had been converted to a new product (R_f = 0.32; the change R_f in is *small*). Aqueous work-up and concentration *in vacuo* afforded a yellow oil. Kugelrohr distillation afforded ester **2b** (2.23 g, 85 %) as a colourless oil, b.p. 80°C/0.05 mmHg; δ_F (282MHz, $CDCl_3$) -97.00 (1F, *d*, $^2J_{F\text{-}F}$ 55.3), -105.39 (1F, *d*, $^2J_{F\text{-}F}$ 55.3).

Rearrangement: Methoxyacetate ester **2b** (0.60 g, 2 mmol) was added to a stirred solution of LDA (2 mmol) in THF (25 ml) at -78 °C. Approximately five minutes after the addition of the ester was complete, chlorotrimethylsilane (0.3 ml, 2.2 mmol) was added to the yellow solution in one portion and the reaction mixture was allowed to warm to room temperature with stirring over one hour. Dilute HCl (5 ml, 1 M) was added to the pale yellow coloured solution (to hydrolyse the TMS ester) and the mixture was stirred for a further 15 minutes before extractive work-up and concentration *in vacuo* to give the crude carboxylic acid as a yellow oil. δ_F (282MHz, $CDCl_3$) -106.9 (1F, one half of an AB quartet, $^2J_{F\text{-}F}$ 258.1, $^3J_{H\text{-}F}$ 8.9), -110.3 (1F, one half of an AB quartet, $^2J_{F\text{-}F}$ 258.1, $^3J_{H\text{-}F}$ 11.4).

Enol Acetal Methanolysis: Thionyl chloride (0.16 ml, 2.14 mmol) was added slowly to a cool (0 °C) solution of the crude acid (0.58 g, 1.95 mmol) in methanol (25 ml). The reaction mixture was then allowed to stir overnight. The methanol was removed *in vacuo* and water (25 ml) was added. Extractive work-up and concentration *in vacuo* afforded a yellow oil. Column chromatography (R_f = 0.32, 10 % ethyl acetate/hexane) afforded ketoester **4b** (0.29 g, 67 %); (Found: C, 48.21; H, 6.29. Calc. for $C_9H_{14}F_2O_4$: C, 48.27; H, 6.17 %); δ_H (300 MHz, $CDCl_3$) 4.30 (1H, *dd*, $^3J_{H\text{-}F}$ 9.93, 10.29) 3.80 (3H, *s*,, 3.50 (3H, *s*), 2.65 (2H, *t*, $^3J_{H\text{-}H}$ 6.98), 1.70 - 1.50 (2H, *m*), 0.9 (3H, *t*, $^3J_{H\text{-}H}$ 7.34); δ_F (282 MHz, $CDCl_3$) -113.6 (1F, *dd*, one half of an AB quartet, $^2J_{F\text{-}F}$ 270, $^3J_{H\text{-}F}$ 10.2), -118.7 (1F, *dd*, one half of an AB quartet, $^2J_{F\text{-}F}$ 270.0, $^3J_{H\text{-}F}$ 13.8); δ_C (75 MHz, $CDCl_3$) 198 (*t*, $^2J_{C\text{-}F}$ 26.56), 166.7, 113.8 (*t*, $^1J_{C\text{-}F}$ 260.0), 79.1 (*t* , $^2J_{C\text{-}F}$ 24.87), 60.0, 52.7, 39.3, 15.8, 13.2; *m/z* 242 (100% $[M + NH_4]^+$).

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15. We expected that the $E1_cB$ elimination of fluorine atom would be suppressed by the presence of a π-donor substituent group at the acidic position, so it is possible that the dehydrofluorination is acid-catalysed.

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