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# Fluorinated succinic acid derivatives from new refrigerants via ozonolysis of haloalkenes

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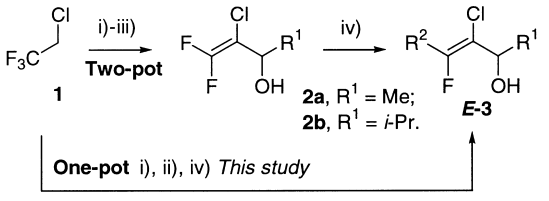
**Abstract**

Fluoro- and di-fluoro allylic alcohols obtained from HFC-134a and HCFC-133a were transformed through [3,3]-sigmatropic rearrangements into 3-fluoro-4-halo-4-alkenoates with variable substitution at the 2- and 3-positions. Ozonolysis of the haloalkenes afforded the corresponding acyl halides which could be trapped with nucleophiles to afford fluorinated succinic acid derivatives in which the two carboxylic acid groups were differentiated. 

Recently, we showed how 1-chloro-2,2,2-trifluoroethane (HCFC-133a) **1** could undergo a high yielding dehydrofluorination/metallation reaction to afford 1-chloro-1-lithio-2,2-difluoroethene from which difluoroallylic alcohols **2** (**2a** and **2b**, for example) could be prepared.[1] In attempting to define the scope and limitations of the chemistry of this potentially important new fluorinated building block, we reacted the difluoroallylic alcohols with a limited range of organolithium reagents and found that they underwent stereoselective displacement of a single fluorine atom to afford **3a**–**d**; *n*-butyllithium, methyllithium and phenyllithium all reacted smoothly (Scheme 1).




| Educt | $R^1$ | $R^2$ | % |
|---|---|---|---|
| **3a** | Me | *n*-Bu | 66 |
| **3b** | Me | Ph | 67 |
| **3c** | *i*-Pr | Me | 61 |
| **3d** | *i*-Pr | *n*-Bu | 56 |

Scheme 1. Preparation of fluoroallylic alcohols. (i) *n*-BuLi, THF, –78°C; (ii) $R^1CHO$; (iii) $H_3O^+$; (iv) $R^2Li$, THF, –78°C to rt, then $H_3O^+$

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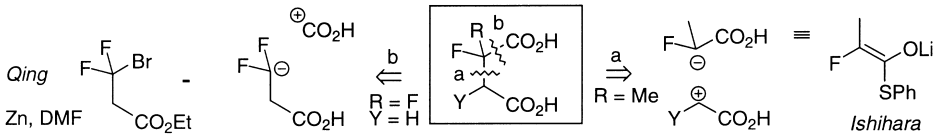
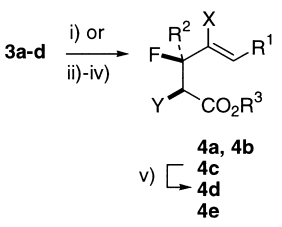
Excellent *E*-stereoselectivities were obtained in a one-pot procedure suggesting that we could use these intermediates to prepare substituted succinate esters (**5**), with a fluorine atom at a *tertiary* centre and with variable substitution at the 3-position, in a stereocontrolled manner using rearrangement methodology.[2] Ozonolysis of the rearrangement educts **4** would afford reactive acyl derivatives from which amides, esters and thioesters could be prepared. Substituted succinic acids have found applications as components in metalloproteinase inhibitors,[3] intermediates en route to (–)-rocellaric acid[4] and mycotoxic fumonisin B fragments.[5] 2,3-Difluoroderivatives (tartaric acid analogues)[6] formed the subject of some recent theoretical interest because of the possibilities of intramolecular hydrogen bond formation involving the fluorine atoms. The proposed route would complement the fluoropropionate aldol chemistry developed recently by Ishihara[7] and correspond to an (alkoxycarbonyl)alkylation of the corresponding enolate (Scheme 2). In the difluoro series (from **2**), our educts would correspond to acylation products of the difluoropropionate ester homoenolate equivalent reagent which Qing and co-workers[8] attempted to synthesise recently (disconnection b).




Scheme 2. Possible disconnections for fluorinated succinic acid derivatives

We therefore performed Johnson–Claisen[9a] and chelated ester enolate Claisen rearrangements[9b] of the alcohols (Scheme 3); the former all occurred smoothly, as did the latter except when alkoxyacetates of alcohol **3c** were exposed to strong base (LDA). The rearrangement occurred with the expected stereoselectivity[2] but in low yield; de's for all substrates were ca. 90%.

In this case, we believe that allylic metallation competes with ester enolate formation and that fragmentation with diene formation follows. The addition of an extra alkyl group at this position (as in **3d** for example) slows down the unwanted metallation sufficiently for the enolate to be formed as the major pathway and rearrangement succeeds.



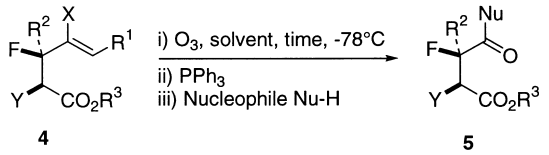

| Substrate | $R^1$ | X | $R^2$ | Y | $R^3$ | Yield (%) |
|---|---|---|---|---|---|---|
| **4a** | Me | Cl | *n*-Bu | H | Et | 70 |
| **4b** | *i*-Pr | Cl | Me | H | H | 64 |
| **4c** | *i*-Pr | Cl | *n*-Bu | OBn | H | 68 |
| **4d** | *i*-Pr | Cl | *n*-Bu | OBn | Me | 39[a] |
| **4e** | Me | F | *n*-Bu | H | Et | 71 |

[a]For three steps

Scheme 3. (i) Triethyl orthoacetate, propionic acid, 140°C, 16 hours; (ii) $BnOCH_2COCl$, pyridine, DMAP, DCM, rt; (iii) LDA, THF, –78°C then $Me_3SiCl$; (iv) $NH_4Cl$; (v) MeOH, EDC, DMAP, $CH_2Cl_2$

We were able to find few examples of vinyl chloride, and no examples of vinyl fluoride, ozonolyses in the literature.[10] However, when we exposed the rearrangement educts to ozone,[11] we found that cleavage occurred readily in some cases and very slowly in others (Scheme 4, Table 1). When the

reaction was performed in an alcohol solvent, we recovered the clean succinate esters in good yield. Alternatively, we could run the ozonolysis in dichloromethane, work-up with triphenylphosphine and isolate the acid chloride. An attempt to use polymer-supported phosphine was completely unsuccessful with phosphine oxide being released from the resin.




4 5

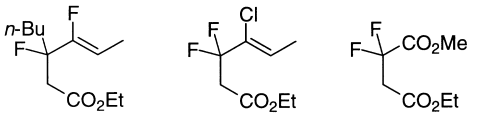
Scheme 4.

Table 1
Representative ozonolysis experiments

| Substrate | Solvent | Time (hrs) | Nu-H | Product | Yield (%) |
|---|---|---|---|---|---|
| **4a** | MeOH | 2.75 | MeOH | **5a** | 78 |
| **4a** | $CH_2Cl_2$ | 3.25 | $Et_2NH$ | **5b** | 73 |
| **4a** | $CH_2Cl_2$ | 3.25 | $Bn_2NH$ | **5c** | 69 |
| **4a** | $CH_2Cl_2$ | 3.00 | EtSH[a] | **5d** | 81 |
| **4a** | $CH_2Cl_2$ | 3.25 | Gly-OEt | **5e** | 54 |
| **4a** | $CH_2Cl_2$ | 3.25 | MeONHMe | **5f** | 47 |
| **4b** | $CH_2Cl_2$ | 3.00 | *i*-PrOH | **5g** | 68 |
| **4c** | $CH_2Cl_2$ | 12.00[b,c] | (-)[d] | (-) | (-) |
| **4d** | MeOH | 12.00[b,c] | MeOH | **5h** | 43 |
| **6** | MeOH/$CH_2Cl_2$ | 3.25 | MeOH | **5a** | 74 |
| **7** | MeOH | 4.75 | MeOH | **8** | 27 |

All reactions were run at 10 mM in substrate at -78°C and followed by TLC. Upon consumption of starting material, the solution was purged with $N_2$, then solid $Ph_3P$ was added. There were no changes in NMR spectra suggestive of epimerisation of the stereogenic centre next to the ester group.
[a]A solution of the sodium salt in THF was cannulated into the ozonolysis mixture after reduction.
[b]No change occurred by TLC after 5 hours; extended exposure failed to result in complete consumption of substrate.
[c]The same behaviour was observed in MeOH or $CH_2Cl_2$.
[d]Neither anhydride nor methyl ester could be identified.

Treatment of the crude acid chloride/phosphine oxide mixture with an alcohol, amine or thiolate nucleophile allowed isolation of the succinates; only a solution of *t*-BuOH containing DMAP and pyridine proved ineffective. Ethyl glycinate (which had been converted to the free amine by pre-treatment with triethylamine) intercepted the acid chloride in moderate yield, a reaction with considerable scope for optimisation given the sophistication of modern methods of peptide synthesis. Of particular interest are Weinreb amide **5f** and thioethylester **5d** because of their potential for use in parallel synthesis of ketones following treatment with Grignard reagents,[12] or organozinc reagents[13] in the presence of Pd(0) catalysts, respectively. The corresponding vinyl fluoride educt **6** obtained from HFC-134a also underwent cleavage to afford the less reactive acid fluorides after similar reaction times.[14] Ozonolysis of the difluoro species **7** was also successful; a slightly longer exposure to ozone was required but complete conversion to ester **8** was achieved, although the isolated purified yield was modest (27%).



6 7 8

Surprisingly, we were unable to push the oxidations of **4c** and **4d** to completion; the reactions appeared to stop after ca. 5 hours and no further disappearance of starting material occurred even after 12 hours. Free acid groups are known to be compatible with ozone[15] though ozonide cleavage by phosphine is slow when the carboxyl group is present which may account for our failure to isolate any identifiable products from the ozonolysis of **4c**. Nevertheless, an acceptable yield of ester product was obtained from **4d** upon work-up.

In conclusion, this method allows the synthesis of differentially protected monofluorinated succinic acid derivatives in which the level of substitution and type of functionality contained can be varied. Both HCFC-133a and (though less conveniently) HFC-134a can be used as starting materials for this interesting class of products, extending the range of fluorinated targets which can be reached via building block methods[16] significantly.

## Acknowledgements

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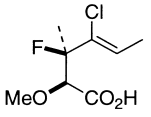

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11. Typical procedure: Ozone was bubbled through a solution of **4a** (0.1003 g, 0.4 mmol) in methanol (40 ml) at –78°C. The reaction was followed by TLC; disappearance of starting material coincided with the appearance of the characteristic blue colour. After purging with nitrogen, triphenylphosphine (0.183 g, 0.8 mmol) was added; the mixture was allowed to stir at –78°C for 15 min then warmed to rt. Concentration in vacuo, then column chromatography, afforded **5a** (0.073 g, 71%) as a pale yellow oil; $\nu_{max}$ (film)/cm$^{-1}$ 1769 ($CO_2Me$), 1742 ($CO_2Et$); $\delta_H$ (300 MHz, $CDCl_3$) 4.12 (2H, q, $J=7$ Hz), 3.81 (3H, s), 3.03 (1H, dd, $J=34.4$, 16.4 Hz), 2.81 (1H, dd, $J=16.4$, 9.7 Hz), 1.98–1.71 (2H, m), 1.50–1.24 (4H, m), 1.22 (3H, t, $J=7$ Hz), 0.87 (3H, t, $J=7$ Hz); $\delta_C$ (75 MHz, $CDCl_3$) 171.3 (d, $^2J_{C-F}=25.4$ Hz), 168.6 (d, $^3J_{C-F}=1.7$ Hz), 94.7 (d, $^1J_{C-F}=191.6$ Hz), 61.1, 52.6, 42.2 (d, $^2J_{C-F}=23.7$ Hz), 37.3 (d, $^2J_{C-F}=22.0$ Hz), 25.0, 22.5, 14.1, 13.8; $\delta_F$ (282 MHz, $CDCl_3$) –164.1 (dddd, $J=34.4$, 26.2, 17.8, 9.7 Hz); [HRMS (ES, M[Na]$^+$); found: 257.1155; $C_{11}H_{19}FO_4Na$ requires: 257.1165]; $m/z$ (ES) 257 (100%, M[Na]$^+$). The reaction was run at such high dilution purely to retain solvent throughout.
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