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LETTERS

HFC-134a as a fluorinated building block: short syntheses of α-fluoroenones

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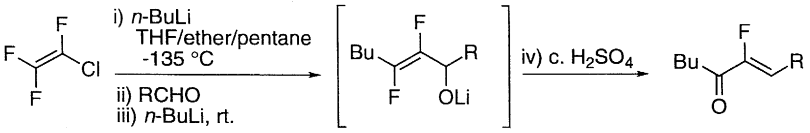
Abstract

1,1,1,2-Tetrafluoroethane (HFC-134a) has been transformed into a range of α-fluoroenones via a direct route. Dehydrofluorination/metallation allowed trifluorovinylsilanes to be prepared; these could be converted in situ, or isolated and treated further, with alkyllithium reagents to give difluorovinylsilanes. Fluoride-catalysed addition to aldehydes followed by acidic work-up allowed the isolation of a range of α-fluoroenones in two- or three-pots.

The development of the chemistry of new CFC replacements is of current interest as the implications of the Montreal Protocol erode the range of available versatile fluorinated starting materials or building blocks. We became interested in the possibility of using HFC-134a in a three component assembly synthesis of α-fluoroenones using readily available aldehydes and organolithium reagents. The title compounds have considerable potential for manipulation through Michael and related reactions and we had failed to reproduce the sequence reported by Normant and co-workers (Scheme 1) that appeared to offer a general route.[1]



Scheme 1.

The route was subverted by an extremely sluggish displacement (in our hands) of fluoride upon treatment of the trifluorovinyl alcohol intermediate with *n*-butyllithium, a reaction that we were unable to drive to completion even after refluxing the solution. We therefore decided to utilise a trialkylsilyl group to facilitate the addition/elimination reaction, and then to use a fluoride-catalysed or -mediated

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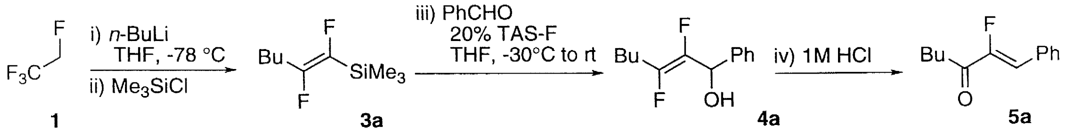
C–C bond forming reaction with an aldehyde to complete the carbon skeleton. Hydrolysis would then complete enone formation.

We therefore took HFC-134a **1** through a dehydrofluorination/metallation sequence[2] and trapped the organolithium reagent with chlorotrimethylsilane. The vinylsilane **2a** underwent further reaction in situ with a second equivalent of *n*-butyllithium to afford the vicinal difluoride **3a** in good yield (82%). Similar compounds have been prepared recently by Burton and co-workers with low(er) temperature (−90°C) halogen–metal exchange of trifluoroalkenyl halides as an initial step.[3] Exposure to catalytic (20 mol%) TAS-F in the presence of benzaldehyde according to the excellent precedent established by Hiyama,[4] followed by mild acid work-up led (via the allylic alcohol **4a**) to the isolation of known enone **5a** in an acceptable 55% yield as a crystalline solid[5] according to Scheme 2.



Scheme 2.

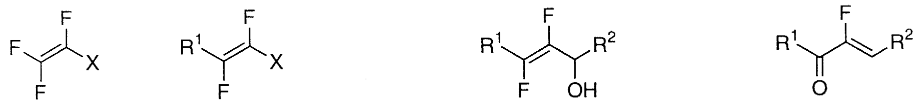
The alkene configuration was assigned on the basis of the large ${}^3J_{H-F}$ coupling constant (36.8 Hz) consistent only with a mutual *trans* arrangement between the nuclei. Similar results were obtained when cinnamaldehyde and furfural were used as electrophiles in the reaction with **3a** and **5b** and **5c** were isolated in comparable yields. The dienone **5b** is a particularly interesting product because of the presence of two electronically very different double bonds. We were also able to trap hexanal, pivalaldehyde and acrolein with **3a** (Fig. 1); however, work up with dilute HCl led to the isolation of the difluoroallylic alcohols **4d–f**, implying that a mechanism with well developed dissociative character is followed during the hydrolysis,[1a] the ease of reaction reflecting acutely the facility of carbenium ion formation. In the case of acrolein, the yield of allylic alcohol product **4f** was particularly poor and crotonaldehyde failed to react at all under these conditions (Table 1).

Table 1
Syntheses of difluoroallylic alcohols **4** and enones **5**

Silane	Aldehyde	Hydrolysis conditions	Alcohol	yield (%)	enone	yield (%)
3a	Benzaldehyde	a	-	-	**5a**	55
3a	Cinnamaldehyde	a	-	-	**5b**	58
3a	Furfural	a	-	-	**5c**	52
3a	Heptanal	a	**4d**	62	-	-
3a	Pivalaldehyde	a	**4e**	48	-	-
3a	Acrolein	a	**4f**	21	-	-
3a	Heptanal	b	-	-	**5d**	74
3a	Pivalaldehyde	b	-	-	**5e**	96
3a	Acrolein	b	-	-	**5f**	0
3a	Acrolein	c	-		**5f**	54
3c	Benzaldehyde	a	**4g**	39[e]	-	-
3c	Benzaldehyde	d	-		**5g**	46
3c	Cinnamaldehyde	d			**5h**	53

Conditions: a, 1M HCl, 0°C. b, 10 eq. H_2SO_4, 5 eq. H_2O, neat, 0°C. c, 1 eq. I_2, Et_2O, reflux. d, 10M HCl, 0°C. e, The trimethylsilyl ether was isolated and co-eluted with PhCHO.

Though an effective catalyst here, TAS-F is expensive so we sought an alternative. Soluble fluoride ion sources are of some interest and a number of non-hygroscopic species have been described recently including the Gingras reagent ($Ph_3SnF_2 \cdot NBu_4$)[6] and De Shong's silicate (TBAT, $Ph_3SiF_2 \cdot NBu_4$);[7] we explored the effectiveness of these and TBAF, KF, TBADHTF ($Bu_4N \cdot H_2F_3$) and CsF as promoters of



2a, X = $SiMe_3$;
2b, X = $SiMe_2Ph$;
2c, X = $SiEt_3$.

3a, R^1 = *n*-Bu, X = $SiMe_3$;
3c, R^1 = Me, X = $SiEt_3$.

4a, R^1 = *n*-Bu, R^2 = Ph;
4b, R^1 = *n*-Bu, R^2 = CH=CHPh;
4c, R^1 = *n*-Bu, R^2 = 2-furyl;
4d, R^1 = *n*-Bu, R^2 = *n*-C_6H_{13};
4e, R^1 = *n*-Bu, R^2 = *t*-Bu;
4f, R^1 = *n*-Bu, R^2 = $CH=CH_2$;
4g, R^1 = Me, R^2 = Ph;
4h, R^1 = Me, R^2 = CH=CHPh.

5a, R^1 = *n*-Bu, R^2 = Ph;
5b, R^1 = *n*-Bu, R^2 = CH=CHPh;
5c, R^1 = *n*-Bu, R^2 = 2-furyl;
5d, R^1 = *n*-Bu, R^2 = *n*-C_6H_{13};
5e, R^1 = *n*-Bu, R^2 = *t*-Bu;
5f, R^1 = *n*-Bu, R^2 = $CH=CH_2$;
5g, R^1 = Me, R^2 = Ph;
5h, R^1 = Me, R^2 = CH=CHPh.

Fig. 1.

C–C bond formation in the reaction of **3a** and PhCHO. Only TBAF afforded any product at all despite an exhaustive survey of reaction stoichiometries, a full equivalent being required to achieve a 28% yield of enone **5a** after acid work-up. This observation suggests strongly that the alternative fluoride sources were not able to form the reactive silicate intermediate effectively.

The less reactive difluoroallylic alcohols could be hydrolysed upon treatment with carefully controlled amounts of concentrated sulfuric acid and water and **5d** and **5e** were obtained in good yield by this method. Again, the acrolein adduct **4f** was recalcitrant and only the method of Normant (iodine in diethyl ether at reflux)[8] allowed progression to the dienone **5f**. Montmorillonite K-10, an effective catalyst for the hydrolysis of related systems[9] was quite ineffective for this reaction.

Next, we attempted to use methyllithium as the organometallic nucleophile; due to difficulties in isolating the adduct with chlorotrimethylsilane due to volatility, we prepared the dimethylphenyl silane **2b** attempting to preserve the high level of reactivity in silic-*ate* formation. Treatment of **2b** with methyllithium under a range of conditions afforded only products of attack at silicon and none of the difluorocompound. However, the triethylsilane **3c** could be synthesised readily in an unoptimised 75% yield and TAS-F-catalysed addition to benzaldehyde and cinnamaldehyde was successful. Treatment of the crude products with 10 M HCl afforded the enone **5g** and dienone **5h** in 46% and 53% yield, respectively. The requirement for stronger acid conditions reflects the lower degree of substitution on reducing the length of the sidechain. The success of the sequence with the less reactive methyllithium suggests that generality of the substituent attached to the acyl carbon could be achievable, though access to difluorovinylsilanes via one-pot reactions of the trifluorosilane were unsuccessful with this nucleophile. The use of metallated alkoxymethanes will form the subject of future study. Related compounds have been synthesised by Schlosser,[10] McCarthy,[11] Yamanaka and co-workers,[12] Haufe,[13] and Funabiki.[9]

However, the procedure described herein offers a direct (at best two-, and at worst, three-pot) access to the target enones from a particularly readily available and inexpensive starting material HFC-134a. This sequence is strongly competitive with all the alternatives because of its directness and ready availability of starting material. Optimisation of the individual reaction steps is in progress.

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5. Preparation of **3a**. *n*-Butyllithium (20.0 ml of a 1.8 M solution in hexane, 36 mmol) was added dropwise to a stirred solution of HFC-134a (600 ml, 25 mmol) in THF (30 ml) at −78°C. After 1 h, trimethylsilyl chloride (2.3 ml, 18 mmol) was added dropwise, then 1 h later, *n*-butyllithium (11.0 ml of a 1.8 M solution in hexane, 20 mmol) was added dropwise. The reaction was stirred at −78°C for 1 h and then warmed to −30°C, then quenched after 30 min with saturated aqueous ammonium chloride. Extractive work-up and concentration then filtration though an alumina column (Brockmann, activity 1) eluting with pentane afforded silane **3a** (2.82 g, 81%) as a colourless oil. Preparation of **5a**. TASF (0.43 g, 1.4 mmol) was added gradually to a stirred solution of silane **3a** (1.3 g, 7.0 mmol) and benzaldehyde (0.82 ml, 7.7 mmol) in THF (14 ml) at −30°C under argon over 24 h. Dilute HCl (15 ml of a 1 M solution, 2.1 equiv.) was added and the mixture was stirred for 15 min before extractive work-up. Column chromatography (R_f 0.26, 10ether, 90% petroleum ether) and recrystallisation from diethyl ether/hexane afforded **5a** (0.74 g, 51%) as white needles, mp 52–53°C.
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