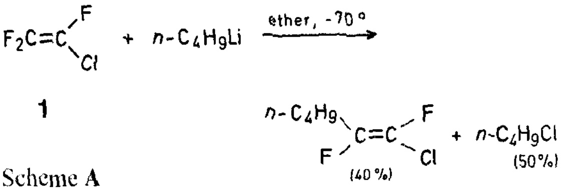
A New Preparation of Trifluorovinyllithium. Applications to the Syntheses of Trifluorovinylalcohols and of α-Fluoro-α-ethylenic Acids and Derivatives

J. F. Normant*, J. P. Foulon*, D. Masure*, R. Sauvêtre*, and J. Villieras**

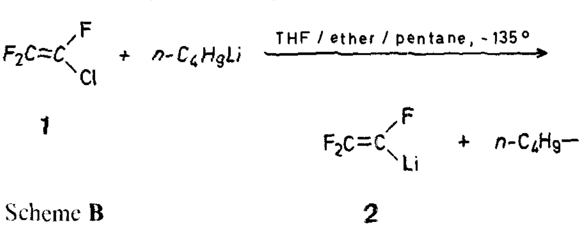
Laboratoire de Chimie des Organoéléments* and de Synthèse Organique**, Université de Paris 6, tour 44, 4 Place Jussieu, 75230 Paris Cedex 05, France

For synthetic purposes, trifluorovinyllithium is superior in many respects to the corresponding Grignard reagent. The former reagent has been prepared from triphenyltrifluorovinyltin[1], bromotrifluoroethylene (73%), and trifluoroethylene (79%)[2,3]. In a study[4] of the nucleophilic substitution reactions of chlorotrifluoroethylene (**1**) with an ethereal solution of N-butyllithium, formation of butyl chloride was observed, indicative of a halogen/metal exchange according to Scheme A.



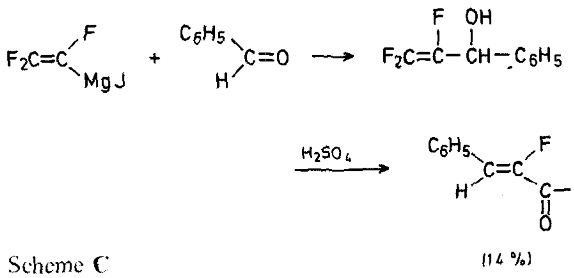
Scheme A

We found that at −135° in a mixture of tetrahydrofuran/ether/pentane (5:3:3), reaction of **1** with n-butyllithium leads to an almost quantitative yield of trifluorovinyllithium (**2**)



Scheme B

The ready access to trifluorovinyllithium according to Scheme **B** allowed us to study the reactions of **2** with various carbonyl compounds. Knunyants et al.[5] have shown that trifluorovinylmagnesium iodide reacts with carbonyl compounds to give alcohols which are difficult to isolate and undergo rapid allylic migration to give acid fluorides on treatment with acid (Scheme C).



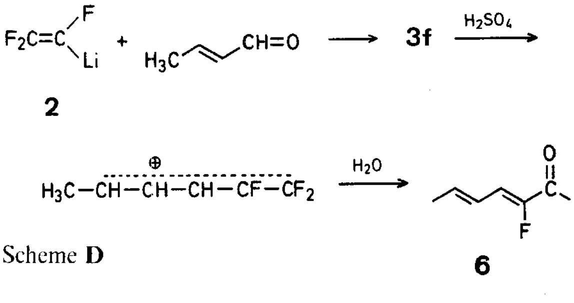
Scheme C

Tarrant, et al.[3] have shown that the yields of substituted α-fluoroacrylic acids are considerably enhenced by use of the lithium derivative **2**. Reactions of **2** with benzaldehyde or cyclohexanone give the corresponding stable alcohols (84 and 53% yield, respectively) which are converted into the α-fluoro-α-ethylenic acids by refluxing in 6*N* hydrochloric acid. However yields are much lower with other studied ketones.

In our investigations of the reactions of **2** with aldehydes and ketones at −135°, the alcohols were obtained in good yields (see Table 1) when they were distilled over sodium hydrogen carbonate.

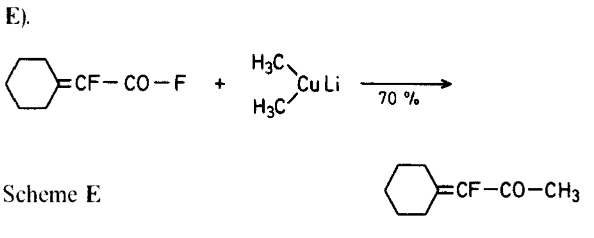
As the allylic migration of the alcohols **3** into the acid fluorides **4** involves a carbocation intermediate, we performed this reaction in concentrated sulfuric acid at −10°. The acid fluorides are formed instantaneously and are readily isolated. Treatment of the acid fluorides with water, alcohols, or amines gives rise to the corresponding α-fluoro-substituted acrylic acids, esters, or amides, respectively (see Table 1).

In the case of 2-buten-1-al, two migrations are possible but only the irreversible formation of α-fluorosorbic fluoride (**6**) is observed (Scheme **D**).



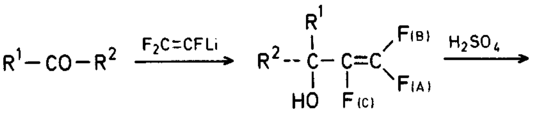
Scheme **D**

Reaction of the α-fluoro-α-ethylenic acid fluoride **4b** ($R^1-R^2 = (CH_2)_5$) with lithium dimethylcuprate represents a new route to α-fluoro-α-ethylenic ketones of the aliphatic series which are difficult to obtain by other methods[6,7] (Scheme **E**).



Scheme **E**

Table 1. Reaction of Carbonyl Compounds with Trifluorovinyllithium (**2**)



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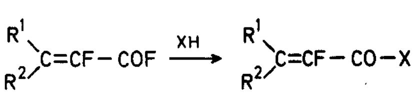
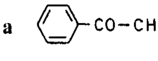
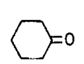
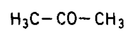
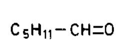


4 5

	Ketone	Yield[a] (%) of 3	Yield[a] (%) of 4	X	Yield (%) of 5
a		88	75	OH	83[b]
				OC_2H_5	85[c]
				$N(C_2H_5)_2$	80[c]
b		88	82	OH	87[b]
				OC_2H_5	71[c]
c	$H_3C-CO-CH_3$	—	—	OH	70[d]
d		83	80	OH	90[b]
				$N(C_2H_5)_2$	70[d]
e	$C_5H_{11}-CH=O$	88	—	OH	85[b]
				$N(C_2H_5)_2$	95[c]
f		—	—	OH	68[d]

[a] Yields based on the starting ketone R^1-CO-R^2.

[b] Yields based on the alcohol **3**.

[c] Yields based on the acid fluoride **4**.

[d] Intermediates were not isolated.

Preparation of Alcohols 3:

A 1*N* solution of butyllithium (63 mmol) in ether cooled at −100° is added in 30 min to a stirred solution of gaseous trifluoroethylene (60 mmol) in a 5:3:3 mixture of tetrahydrofuran/ether/pentane (110 ml) at −135°. Cooling is achieved by circulating nitrogen from a liquid nitrogen container in a plastic tube fitted around the flask and the dropping funnel. The reaction mixture is stirred at −110° for 30 min and a solution of the carbonyl compound (55 mmol) in ether (50 ml) cooled at −100° (−30° for acetophenone) is added at −130° over 5 min. The temperature is allowed to rise to −70° in 30 min, the mixture is hydrolysed by 3*N* sulfuric acid (50 ml), and extracted with ether (2×50 ml). The organic layer is washed with water (100 ml), saturated sodium hydrogen carbonate solution (100 ml), and saturated sodium chloride solution (100 ml). It is then dried over magnesium sulfate, the solvent removed under reduced pressure and the product distilled under vacuum after addition of sodium hydrogen carbonate (1 g). *In the absence of sodium hydrogen carbonate an exothermic isomerisation starting at +50° may lead to an explosion.* The yields of the alcohols are given in Table 1 and characteristic properties in Table 2.

Preparation of Acid Fluorides 4:

The pure alcohol **3** (50 mmol) is added at −10° over a period of 15 min to a stirred solution of 94% sulfuric acid (30 ml) and water (2 ml). Stirring is continued for 10 min at 0°, the mixture is poured on to crushed ice (50 g), and then extracted with ether (100ml). The organic layer is rapidly washed with saturated sodium hydrogen carbonate solution, the solvent removed under reduced pressure, and the residue distilled over dry sodium hydrogen carbonate (1 g) under vacuum. The colourless acid fluoride must be used within 1 h.

Preparation of Acids, Esters, and Amides 5, $X = OH, OR, \text{or } NR_2$**:**
Acids (**5**, X=OH) are prepared by the procedure described previously except that the hydrolysis is carried out by addition of water (30 ml) to the reaction mixture at +20° and stirring for 24 h at +20°. Evaporation of the solvent leaves a white solid.

Esters (**5**, X=OR) are prepared by stirring a mixture of **4** (50 mmol), alcohol (100 mmol), and pyridine (100 mmol) at 20° for 30 min. The reaction mixture is worked up as described for the alcohols.

Table 2. α-Trifluorovinyl Substituted Alcohols **3**

Product	B.p.	n_D^{20}	I.R. (film) ν (cm^{-1})	^{1}H-N.M.R.[a] δ (ppm)	^{19}F-N.M.R. δ (ppm)[b] $F_{(A)}$	$F_{(B)}$	$F_{(C)}$	J (Hz)
3a	40°/0.1 torr	1.4875	1775 ($>$C=C$<$)	1.6(d, 3H), 4.05 (s, 1H), 7.2(m, 5H); $^4J_{HF_{(C)}}$ = 2 Hz	−39.1 (d of d)	−50.7 (d of d)	−122.7 (d of d)	$^3J_{F_BF_C}$ = 112 $^3J_{F_AF_C}$ = 34 $^2J_{F_AF_B}$ = 81
3b	36°/0.05 torr	1.4320	1775 ($>$C=C$<$) (Lit.[3]: 1776)	3.82 (s, 1H),	−39.2 (d of d)	−52.3 (d of d)	−119.0 (d of d)	$^3J_{F_BF_C}$ = 109 $^3J_{F_AF_C}$ = 35 $^2J_{F_AF_B}$ = 83
3d	51°/0.1 torr	1.4865	1785 ($>$C=C$<$)	5.2 (d of m, 1H), $^3J_{HF_C}$ = 28 Hz	−40.2 (d of d)	−57.2 (d of d)	−124.4 (d of d)	$^3J_{F_BF_C}$ = 115 $^3J_{F_AF_C}$ = 31 $^2J_{F_AF_B}$ = 78
3e	37°/0.5 torr	1.3985	1790 ($>$C=C$<$)	4.25 (d of m, 1H), $^3J_{HF_C}$ = 27 Hz	−41.6 (d of d)	−59.6 (d of d)	−127.8 (d of t)	$^3J_{F_BF_C}$ = 112 $^3J_{F_AF_C}$ = 30 $^2J_{F_AF_B}$ = 80

[a] TMS as internal standard, solvent CCl_4.
[b] $C_6H_5CF_3$ as internal standard, neat samples.

Table 3. Acid Fluorides **4**

Product	B.p.	n_D^{20}	I.R. (film) ν (cm^{-1})	^{1}H-N.M.R.[a] δ (ppm)	^{19}F-N.M.R.[b] δ (ppm)
4a[c]	46°/0.1 torr	—	1810 ($>$C=O)	(*E*): 2.09 (d, 3H, $^4J_{HF}$ = 5 Hz); (*Z*): 2.36 (d, 3H, $^4J_{HF}$ = 4 Hz); (*E*+*Z*): 7.2 (s, 5H);	(*E*): −66.6 (d of m, 1F), +89.3 (d, —CO—F), $^3J_{FF}$ = 27 Hz. (*Z*): −62.0 (d of m, 1F), +88.4 (d, —CO—F), $^3J_{FF}$ = 24 Hz.
4b	41°/2 torr	1.4485	1810 ($>$C=O)	1.64 (m, 6H), 2.38 (m, 2H), 2.66 (m, 2H)	−70.7 (d, 1F), +88.9 (d, —CO—F), $^3J_{FF}$ = 27 Hz
(*Z*)-**4d**	65°/0.1 torr (Lit.[5]: 83–85°/10)	—	1810 ($>$C=O)	6.80 (d, 1H, $^3J_{HF}$ = 33 Hz)	−63.6 (d of d, 1F), +87.6 (d, —CO—F), $^3J_{FF}$ = 22 Hz
(*Z*)-**4e**	54°/13 torr	1.4115	1830 ($>$C=O)	6.16 (d of t, 1H, $^3J_{HF}$ = 31 Hz)	−68.5 (d of d, 1F), +73.8 (d, —CO—F), $^3J_{FF}$ = 20 Hz

[a] TMS as internal standard, solvent CCl_4.
[b] $C_6H_5CF_3$ as external standard, neat samples.
[c] (*Z*):(*E*) ratio: 7:3.

Table 4. Physical Properties of Acids, Esters, and Amides **5**

Product No.	X	M.p. (Lit. m.p.)	B.p./torr	n_D^{20}	Elemental Analysis				
5a	OH	129° (129–130°)[2]	—	—	$C_{10}H_9FO_2$ (180.18)	calc. found	C 66.83 66.13	H 5.0 5.11	
5b	OH	110° (109–110°)[3]	—	—	$C_8H_{11}FO_2$ (158.17)	calc. found	C 60.38 59.78	H 6.96 7.23	
5c	OH	64–65° (64–66°)[2]	—	—	$C_5H_7FO_2$ (118.11)	calc. found	C 50.85 50.92	H 5.93 6.07	
5d	OH	158° (156°)[9]	—	—	$C_9H_7FO_2$ (166.15)	calc. found	C 65.06 65.33	H 4.22 4.48	
5e	OH	34°	80°/0.1	—	$C_8H_{13}FO_2$ (160.19)	calc. found	C 60.00 60.27	H 8.12 8.01	
5f	OH	140°	—	—	$C_6H_7FO_2$ (130.11)	calc. found	C 55.39 54.96	H 5.38 5.76	
5a	OC_2H_5	—	69–78°/0.1	—	$C_{12}H_{13}FO_2$ (208.23)	calc. found	C 69.23 69.46	H 6.25 6.47	
5b	OC_2H_5	—	77°/1	1.4697	$C_{10}H_{15}FO_2$ (186.22)	calc. found	C 64.59 64.44	H 8.06 8.15	
5a	$N(C_2H_5)_2$	—	105°/0.1	—	$C_{14}H_{18}FNO$ (231.26)				
5d	$N(C_2H_5)_2$	41°	150°/0.05	—	$C_{13}H_{16}FNO$ (221.27)	calc. found	C 70.59 70.94	H 7.24 7.06	N 6.33 6.46
5e	$N(C_2H_5)_2$	—	82°/0.1	1.4575	$C_{12}H_{22}FNO$ (215.31)	calc. found	C 66.97 66.94	H 10.23 10.10	N 6.51 6.57

Table 5. Spectral Data for the Acids, Esters, and Amides **5**

Product No.	X	I.R. (film or KBr) ν (cm – 1)	^{1}H-N.M.R. (CCl$_4$) δ (ppm) vs. TMS	^{19}F-N.M.R (neat) δ (ppm) vs. $C_6H_5CF_3$
5a	OH	1700 ($>C{=}O$) 1630 ($>C{=}C<$)	(E) 40%: 2.08 (d, 3H, $^4J_{HF}=5$ Hz) (Z) 60%: 2.36 (d, 3H, $^4J_{HF}=4$ Hz) ($E+Z$): 7.08 (s, 5H), 11.56 (s, 1H).	(E): −62.6 (m) (Z): −60.5 (m)
5b	OH	1695 ($>C{=}O$)	1.22 (m, 6H), 1.86 (m, 2H), 2.36 (m, 2H), 6.22 (s, 1H).	−66.7 (s)
5c	OH	1700 ($>C{=}O$)	1.88 (d, 3H), 2.12 (d, 3H), $^4J_{HF}(cis)=5$ Hz, $^4J_{HF}(trans)=3.7$ Hz.	−63.6 (m)
(Z)-**5d**	OH	1700 ($>C{=}O$)	6.48 (d, 1H, $^3J_{HF}=35$ Hz)	−61.5 (d)
(Z)-**5e**	OH	1710 ($>C{=}O$)	6.14 (d of t, 1H, $^3J_{HF}=32$ Hz), 12.45 (s, 1H)	−68.5 (d)
(2Z),(4E)-**5f**	OH	1695 ($>C{=}O$)	190 (d of d, 3H, $^3J_{H_3C-H}\approx 1.5$ Hz, $^4J_{H_3C-H}=5$ Hz), 6.0–7.0 (m, 3H), 10.26 (s, 1H)	−67.2 (d) $^3J_{HF}=30$ Hz
5a	OC_2H_5	1720 ($>C{=}O$)	(E) 35%: 0.90 (t, 3H), 2.02 (d, 3H), 3.84 (q, 2H), $^4J_{HF}=5$ Hz (Z) 65%: 1.26 (t, 3H), 2.34 (d, 3H), 4.14 (q, 2H), $^4J_{HF}=4$ Hz ($E+Z$): 7.16 (s, 5H)	(E): −62.5 (m) (Z): −60.2 (m)
5b	OC_2H_5	1725 ($>C{=}O$)	1.28 (t, 3H), 1.60 (m, 6H), 2.30 (m, 2H), 2.70 (m, 2H), 4.14 (q, 2H).	−67.7 (s)
5a	$N(C_2H_5)_2$	1630 ($>C{=}O$)	(E) 40%: 0.94 (m, 3H), 1.95 (d, 3H), $^4J_{HF}=5$ Hz (Z) 60%: 1.14 (t, 3H), 1.99 (d, 3H), $^4J_{HF}=4$ Hz ($E+Z$): 3.2 (m, 4H), 7.12 (s, 5H)	(E): −53.4 (m) (Z): −49.7 (m)
5d	$N(C_2H_5)_2$	1630 ($>C{=}O$)	1.18 (t, 6H), 3.30 (m, 4H), 6.40 (d, 1H), 7.12–7.38 (m, 5H)	−52.5 (d) $^3J_{HF}=38$ Hz
5e	$N(C_2H_5)_2$	1630 ($>C{=}O$)	5.48 (d of t, 1H), $^3J_{HF}=36$ Hz	−57.6 (d)

Amides (**5**, $X=NR_2$) are prepared by adding over a period of 10 min the acid fluoride (**4**, 50 mmol) to a solution of an amine (125 mmol) in ether (100 ml) at +20°. The mixture is worked up as described for alcohols.

Preparation of 1-Cyclohexylidene-1-fluoro-2-oxopropane:

A solution of **4b** (50 mmol) in ether (30 ml) is added at −80° to a stirred ethereal[10] solution of lithium dimethylcuprate[8] (65 mmol). A yellow precipitate of methylcopper is formed immediately. Stirring is maintained for 30 min. The reaction mixture is then hydrolysed with 3N sulfuric acid (50 ml) and filtered on hyflosel. After dilution with pentane (100 ml) the organic layer is successively washed with water, saturated sodium hydrogen carbonate solution, 3N sodium thiosulfate solution, and twice with water. It is then dried over magnesium sulfate and distilled under reduced pressure to give the product: yield: 70%; b.p. 78°/12 torr; $n_D^{20}=1.4735$.

$C_9H_{13}FO$	calc.	C 69.23	H 8.33
(157.09)	found	69.33	8.47

I.R. (film) $\nu_{max}=1700$ cm^{-1} ($C{=}O$).

^{1}H-N.M.R. (CCl$_4$) $\delta=1.6$ (m, 6H), 2.28 (m, 2H), 2.72 (m, 2H), 2.18 ppm (d, 3H).

^{19}F-N.M.R. (neat) $\delta=-52.8$ ppm (s).

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