A Convenient One-pot Synthesis of α-Fluoro-α,β-unsaturated Nitriles From Diethyl Cyanofluoromethanephosphonate

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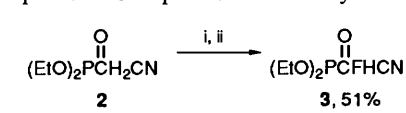
The carbanion of diethyl 1-cyano-1-fluoromethanephosphonate **3**, generated *in situ* from diethyl cyanomethanephosphonate **2** and *N*-fluorobis(trifluoromethanesulfonyl)imide **1**, undergoes the Wittig–Horner reaction with aldehydes and ketones to yield α-fluoro-α,β-unsaturated nitriles **5**.

Fluorine, as a substituent, can significantly affect the properties of molecular systems due to its high electronegativity and small atomic volume. Currently, biologically active molecules containing a vinylic fluorine atom are of special interest,[1] in part, because fluoroolefins are potential mechanism-based enzyme inhibitors [1d,2] and can be used as an isosteric replacement for an amide bond in peptides.[3]

The main synthetic methods for the preparation of vinylic fluorides are the Wittig and Horner–Wadsworth–Emmons reactions. Machleidt and Wessendorf[4] developed a fluorophosphonate reagent from bromofluoroacetate; Burton *et al.*[5] have explored the use of this type of fluoro Wittig reagents. McCarthy *et al.*[6] reported the reaction of fluoro(phenylsulfonyl) methanephosphonate with aldehydes and ketones to give α-fluoro-α,β-unsaturated sulfones. Patrick[7] generated the anion of cyanofluoromethanephosphonate from fluoroacetonitrile and diethyl chlorophosphonate. This anion, however, was reported to have a limited reactivity and to react only with aromatic aldehydes.

Recently, we have found a remarkable electrophilic fluorination reagent, *N*-fluorobis(trifluoromethanesulfonyl)imide **1**,[8] which is easy to handle and effectively fluorinates aromatics,[8a] double bonds[9] and converts enolates into α-fluoro carbonyl compounds.[10] In this communication, we report the synthesis of diethyl cyanofluoromethanephosphonate **3** and its reactions with aldehydes and ketones to produce α-fluoro-α,β-unsaturated nitriles.

Compound **1** reacted with the anion of **2**, generated from **2** and BuLi, in THF at −78 °C for 1 h to form **3** in 51% yield after purification by flash chromatography using CH_2Cl_2–AcEt (1:1) as eluent. Some hydrolysis was found to occur during the purification process. Compound **3** was fully characterized by

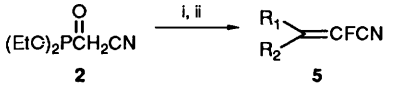


Reagents and conditions: i, BuLi, THF, −78 °C; ii, $(CF_3SO_2)_2NF$ **1**, THF, −78 °C

spectral data.† Its IR spectrum shows a very weak absorption at ν 2244 cm^{-1} and a medium strong peak at ν 1727 cm^{-1}.

Our initial choice was to allow pure **3** to react with aldehydes in the presence of base. The reaction of **3** with BuLi in THF at −78 °C resulted in a deep coloured solution. ^{19}F NMR spectroscopy showed that the CFH group had disappeared, but no signal was found for the anion of **3**. Pyridine-2-carbaldehyde **4b** was then injected into the coloured solution maintained at −78 °C. The mixture was warmed to 22 °C and then heated at reflux for 30 min. Only 5% of the *E*-isomer of **5b** was isolated.

A much better result was obtained when the reaction was carried out without isolation of **3**, by adding a second equivalent of BuLi to the reaction mixture after 30 min, followed immediately by the aldehyde or ketone. This gave the desired fluorocyanoalkenes in moderate yield. In these cases, after the first two steps (Scheme 1), **3** was formed and could be observed



Scheme 1 *Reagents and conditions:* i, BuLi, THF, −78 °C; ii, **1**, THF, −78 °C; iii, BuLi, −78 °C; iv, R′C(O)R² **4**, −78 °C, reflux

by ^{19}F NMR spectroscopy. On addition of the second equimolar amount of BuLi, the previous slightly yellow solution became orange in colour. It appears that the carbanion of **3** was formed because of the disappearance of the CFH group in the ^{19}F NMR spectrum. Carbonyl compounds were added directly to this orange solution, which was allowed to warm to ambient temperature and heated at reflux for 30 min. The results are shown in Table 1. The generality of this one-pot synthesis is demonstrated by reactions with both aromatic and aliphatic aldehydes and ketones. In addition, entry **10** demonstrates the superiority of this procedure over that reported with FCH_2CN,[7] wherein **4j** did not undergo the desired reaction.

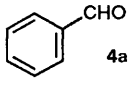
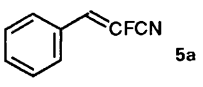
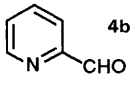
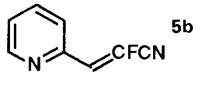
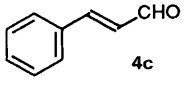
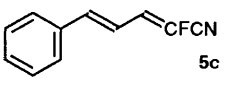
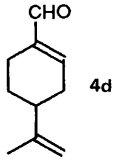
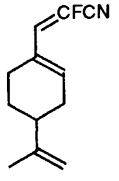
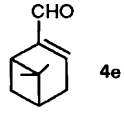
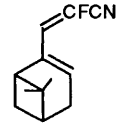
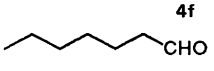
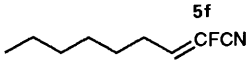
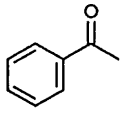
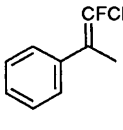
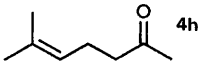
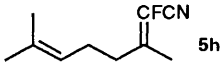
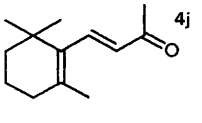
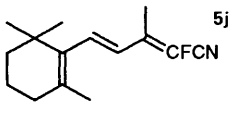
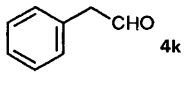
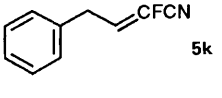
In summary, a one-pot, Wittig–Horner reaction utilizing the *in situ* generated reagent **3** with various aldehydes and ketones produces a general and convenient method to α-fluoro-α,β-unsaturated nitriles **5**.

Experimental

Synthesis of **5e** *from* **4e**.—A typical example is illustrated by the synthesis of α-fluoro-β-[6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl]acrylonitrile **5e**: BuLi in hexane (2.5 mol dm^{-3}; 0.65 cm^3, 1,7 mmol) was added dropwise *via* a syringe to a solution of diethyl cyanomethanephosphonate **3** (0.27 g, 1.5 mmol) in dry THF (4 cm^3) at −78 °C with stirring, forming some white solid. A solution of *N*-fluorobis(trifluoromethanesulfonyl)imide **1** (0.60 g, 2.0 mmol) in THF (2 cm^3) was then added dropwise within 2 min. The resulting slightly yellow solution was stirred at −78 °C for 1 h, and a further portion of BuLi (0.65 cm^3) was added dropwise *via* syringe. The mixture was stirred at −78 °C for 30 min and (1*R*)-(−)-myrtenal (0.30 g, 2.0 mmol) was added in one portion *via* a syringe. After 10 min the resultant mixture was warmed to 22 °C during a period of 2 h and then heated at

† Patrick (ref. 7) did not isolate **3**. A patent (ref. 11) claimed to have purified **3** but no spectral data were given; *m/z* (int., assign.) (Cl, CH_4) 140 (30.0, M − $2C_2H_4$ + 1), 168 (31.0, M − C_2H_4 + 1) and 196 (100, M + 1); ν(film, KCl)/cm^{-1}; 2977s, 2911s, 2244vw, 1727m, 1471m, 1439m, 1389s, 1366s, 1273vs, 1191s, 1159vs, 1095vs, 1013vs, 980vs, 803s, 779m, 705m and 550s; δ_F($CDCl_3$; 188.13 MHz; from $CFCl_3$) −213.10 (dd, J_{PF} 70.4, J_{HF} 45.8); δ_H($CDCl_3$; 200.31 MHz; from TMS) 1.42 (6 H, t, *J* 7.1, CH_3), 4.29–4.45 (4 H, m, OCH_2) and 5.46 (1 H, dd, J_{HF} 45.9, J_{HP} 12.8, CFH); δ_C($CDCl_3$; 75.47 MHz) 16.08 (d, *J* 4.6, CH_3), 65.26 (t, *J* 6.9, OCH_2), 74.14 (dd, J_{FC} 194.1, J_{PC} 171.9, CFH) and 111.93 (d, *J* 26.4, CN).

Table 1 Synthesis of α-fluoro-α,β-unsaturated nitriles

Entry	Starting material	Product	Yield[a] (%)	$Z:E$[b]	$\delta_F(J_{HF}/Hz)$[d] Z-	E-
1	 **4a**	 **5a**	54	1:2	−121.92 (24.3)	−122.62 (16.0)
2	 **4b**	 **5b**	53	2:3	−117.16 (34.3)	−118.62 (15.3)
3	 **4c**	 **5c**	38	2:3	−126.68 (30.6)	−127.73 (9.7)
4	 **4d**	 **5d**	42	1:2	−127.01 (36.3)	−127.58 (18.6)
5	 **4e**	 **5e**	54	1:2	−126.45 (35.4)	−128.27 (18.5)
6	**4f** 	**5f** 	30	7:3[c]	−125.80 (32.2)	−123.94 (13.9)
7	 **4g**	 **5g**	58	1:1	−124.41 (3.5)	−127.71 (3.7)
8	 **4h**	 **5h**	40	1:1	−129.99 (m)	−130.77 (3.3)
9	 **4j**	 **5j**	46	1:2	−132.14 (2.9)	−132.90 (3.6)
10	 **4k**	 **5k**	50	3:2	125.35 (29.9)	122.88 (13.6)

[a] Isolated yield after purification by flash chromatography and based on diethyl cyanomethanephosphonate. [b] Determined by ^{19}F NMR spectroscopy. [c] Isolated ratio was 1:1 in crude product, but some of the *E*-isomer was lost during the purification. [d] Measured at 188.31 MHz and positive downfield from $CFCl_3$.

reflux for 30 min. A mixture of *Z*- and *E*-**5e** (120 mg) and pure *Z*-**5e** (30 mg) were isolated after extraction (CH_2Cl_2) and washing (6 mol dm^3 HCl, H_2O, NaCl solution) followed by a flash chromatography using light petroleum–CH_2Cl_2 (2:1) as eluent; *m/z* (Cl, CH_4) 190 (41.6, M^+) and 191 (100, M + 1); *ν*(film, KCl)/cm^{-1} 2216 (CN), 1632 and 1588 (C=C); *Z*-**5e**: $\delta_F(CDCl_3$; 188.31 MHz; from $CFCl_3$) −126.45 (d, *J* 35.4);* $\delta_H(CDCl_3$; 200.13 MHz; from TMS) 0.83 (3 H, s, CH_3), 1.18 (1 H, d, *J* 9.1, CH), 1.32 (3 H, s, CH_3), 2.10–2.13 (1 H, m), 2.41–2.52 (3 H, m), 2.68 (1 H, dt, *J* 5.6, 1.8, CH), 5.95 (1 H, dd, *J* 35.5, 0.77, C*H*=CF) and 6.06–6.09 (1 H, m, CH=); $\delta_C(CDCl_3$; 75.47 MHz) 21.00, 26.00, 31.21, 32.88, 37.72, 39.90, 44.11 (d, *J* 5.7), 113.74 (d, *J* 46.0, CN), 124.29 (d, *J* 5.6, *C*H=CF), 128.82 (d, *J* 252.1, CF=), 134.87 (d, *J* 8.4, CH=) and 141.10 (d, *J* 7.0, C=).

E-**5e**: δ_F −128.27 (d, *J* 18.5); δ_H 0.85 (3 H, s, CH_3), 1.19 (1 H, d, *J* 9.1, CH), 1.35 (3 H, s, CH_3), 2.11–2.19 (1 H, m), 2.43–2.55 (3 H, m), 2.84 (1 H, td, *J* 5.6, 1.5, CH), 6.01–6.05 (1 H, m, CH=) and

* *J* values are given in Hz throughout.

6.58 (1 H, dd, *J* 18.0, 0.99, C*H*=CF); δ_C 20.98, 25.74, 31.25, 32.75, 37.91, 40.08, 42.47, 112.67 (d, *J* 46.6, CN), 127.00 (d, *J* 23.7, *C*H=CF), 129.31 (d, *J* 234.2, CF=), 133.77 (d, *J* 8.9, CH=) and 138.65 (d, *J* 3.5, C=).

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