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A convenient synthesis of perfluoroalkylated α,β-unsaturated nitriles

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Abstract

A convenient synthesis of perfluoroalkylated α,β-unsaturated nitriles by the consecutive reactions of diethyl (1-cyanoethyl)phosphonate with n-butyllithium, perfluoroalkanoic anhydride and organolithium reagents is described. © 1997 Elsevier Science S.A.

Keywords: n-Butyllithium reagent; Perfluoroalkanoic anhydride reagent; Organolithium reagent; Perfluoroalkylated α,β-unsaturated nitriles

1. Introduction

α,β-Unsaturated nitriles have attracted much interest since such compounds are an important structural feature of a number of naturally occurring compounds which show biological activities [1]. They and their fluoro species are capable of undergoing many synthetic transformations and are utilized as useful intermediates in the synthesis of biologically active compounds [2]. Several synthetic methods including Horner–Wadsworth–Emmons reaction of diethyl (1-fluoro-1-cyano)methylphosphonate with carbonyl compounds have been reported for their preparation [3]. Recently, fluorocarbethoxy substituted phosphonates have been applied to the synthesis of α-fluoro-β-ketoesters [4], α-fluoro-α,β-unsaturated esters [5] and α-fluoro-α,β-unsaturated diesters [6]. To the best of our knowledge, the method for the preparation of title compounds has not appeared in the literature except in our previous paper [7], in which an intramolecular Wittig reaction of perfluoroacylcyano-methylenetriphenylphosphorane via ylide-anion formation and protonation was applied. However, in that method the starting material, perfluoroacylcyanomethylene-triphenylphosphorane, is difficult to prepare and had to be prepared in advance. We now wish to report a convenient synthesis of perfluoroalkylated α,β-unsaturated nitriles by the consecutive reactions of diethyl (1-cyanoethyl)phosphonate, which is commercially available, with n-butyllithium, perfluoroalkanoic anhydrides and organolithium reagents.

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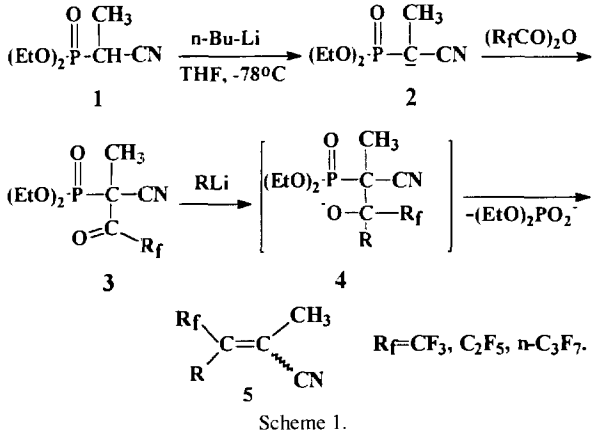

Scheme 1.

2. Results and discussion

The reaction sequence is shown in Scheme 1. Diethyl (1-cyanoethyl)phosphonate **1** was treated with n-butyllithium in THF and the resultant anion **2** was acylated by the addition of perfluoroalkanoic anhydride giving perfluoroacylated phosphonates **3**. Without isolation **3** were attacked by organolithium reagents followed by elimination of phosphonic acid anion affording the desired product **5** in 54–82% yield. The results are summarized in Table 1.

It has been reported [8] that if the trifluoromethyl group is trans with respect to the cyano group, the chemical shifts of the trifluoromethyl group appear upfield, while those cis with respect to the cyano group are shifted slightly downfield. The same is true for a difluoro moiety adjacent to the double bond in the pentafluoroethyl or heptafluoropropyl group. Hence the relative proportions of Z- and E-isomers could be ascertained.

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Table 1
Perfluoroalkylated α,β-unsaturated nitriles prepared

Compound	R	R_f	Yield (%) [a]	E:Z [b]
5a	Ph	CF_3	54	75:25
5b	2-Furyl	CF_3	71	75:25
5c	2-Thienyl	CF_3	74	30:70
5d	n-Bu	CF_3	61	60:40
5e	2-Pyridyl	CF_3	66	57:43 [c]
5f	PhC≡C	CF_3	71	55:45
5g	n-BuC≡C	CF_3	82	43:57
5h	PhC≡C	C_2F_5	53	80:20
5i	2-Thienyl	C_2F_5	56	34:66
5j	n-BuC≡C	C_3F_7	69	55:45

[a] Isolated yields.
[b] The ratios of E- and Z-isomers were estimated on the basis of NMR data.
[c] The ratio of E- and Z-isomer was determined by isolated result.

According to the sequence rules, in **5c** and **5i** (sulfur-containing compounds), when perfluoroalkyl group is cis with respect to the cyano group, the stereoisomer is assigned as the E-isomer; while in the other case they are assigned as the Z-isomer. For example:

E-isomer **Z-isomer**

The effects of base, solvent and reaction temperature on the reaction have been investigated. The results are listed in Table 2 with **5g** as the example.

From Table 2, we can see that no change was observed in the stereoselectivity as the temperature was increased; bases play an important role in the yields and stereoselectivity of the reaction, and n-BuLi was the best base; various solvents other than DMF gave reasonable yields, although n-Buli in DMF gives no reaction.

This one-pot synthesis of perfluoroalkylated α,β-unsaturated nitriles is convenient and offers a wide scope, since R may be an alkyl, aryl, alkynyl or heterocyclic group.

Table 2
The effects of base, solvent and temperature on the yields and stereoselectivity of **5g**

Entry	Base	Solvent	Temp. (°C)	Yield (%) [a]	E:Z [b]
1	BuLi	THF	−78	82	43:57
2	NaH	THF	−78	47	66:34
3	LDA [c]	THF	−78	0	
4	BuLi	THF	−30	77	43:57
5	BuLi	THF	0	56	44:56
6	BuLi	Et_2O	−78	70	27:73
7	BuLi	CH_2Cl_2	−78	63	45:55
8	BuLi	DMF	−78	0	

[a] Isolated yields.
[b] The ratios of Z- to E-isomers were estimated on the basis of NMR spectra.
[c] Lithium diisopropylamide.

The reaction provides a new method for the convenient synthesis of the title compounds which should be useful for further elaboration in the synthesis of biologically active compounds.

3. Experimental details

All boiling points are uncorrected. The IR spectra of products were obtained as films on a Digilab FTS-20E spectrometer. ^{19}F-NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer with TFA as external standard, positive for upfield shifts. ^{1}H-NMR spectra were carried out on a Bruker AM-300 (300 MHz) instrument with TMS as reference; $CDCl_3$ was used as solvent, Coupling constants J are in Hz. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer. HRMS data were obtained on a Finnigan-Mat 8430 high-resolution mass spectrometer.

Diethyl (1-cyanoethyl)phosphonate **1** was prepared according to the method reported in the literature [9].

3.1. General procedure for the preparation of perfluoroalkylated α-methyl-α,β-unsaturated nitriles (5)

Treatment of diethyl (1-cyanoethyl)phosphonates **1** (3 mmol) with butyllithium (3 mmol) at −78°C in absolute THF (15 ml) gave the phosphoryl-stabilized carbanion **2** which was stirred at −78°C for 0.5 h under nitrogen. Perfluoroalkanoic anhydride (3 mmol) was added to it in one portion. Stirring was continued at −78°C for 1 h after which organolithium reagent (3 mmol) was added dropwise to the mixture which was stirred and allowed to warm to room temperature over 4 h. The reaction mixture was poured into water (30 ml) and the water layer was extracted with diethyl ether (3×15 ml). The combined organic layer was washed with brine (3×10 ml) and water (3×10 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by column chromatography eluting with petroleum ether (60–90°C)–ethyl acetate (99:1) to give the product **5**.

3.2. 4,4,4-Trifluoro-3-phenyl-2-methyl-but-2-enenitrile (5a)

Ratio E:Z = 75:25; b.p. 82°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{11}H_8F_3N$ (211.19): C, 62.56; H, 3.82; N, 6.63%. Found: C, 62.67; H, 3.78; N, 6.55%. MS m/z (rel. int): 211 (M^+, 100), 210 (39), 184 (25), 142 (39), 115 (85). IR (film): 2220, 1640, 1340, 1240, 1130. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.52–7.42 (m, 3H), 7.36–7.28 (m, 0.25×2H, Z), 7.20–7.12 (m, 0.75×2H, E), 2.30 (q, 0.25×3H, J=2.4, Z), 1.93 (q, 0.75×3H, J=2.0, E). ^{19}F-NMR ($CDCl_3$) δ (ppm): −19.2 (s, 0.25×3F, Z), −15.8 (s, 0.75×3F, E).

3.3. 4,4,4-Trifluoro-3-(2-furyl)-2-methyl-but-2-enenitrile (**5b**)

Ratio E:Z = 75:25; b.p. 50°C, 1 mm Hg^{-1}. Analysis: Calc for $C_9H_6F_3NO$ (201.15): C, 53.74; H, 3.01; N, 6.96%. Found: C, 53.72; H, 2.98; N, 7.00%. MS *m/z* (rel. int): 202 (71), 201 (M^+, 100), 172 (12), 152 (14), 132 (35), 104 (15). IR (film): 2220, 1620, 1340, 1260, 1140. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.65–7.58 (m, 1H), 6.88–6.78 (m, 1H), 6.60–6.52 (m, 1H), 2.39 (q, 0.75 × 3H, J = 1.5, E), 2.33 (q, 0.25 × 3H, J = 2.9, Z). ^{19}F-NMR ($CDCl_3$) δ (ppm): −21.4 (s, 0.25 × 3F, Z), −19.3 (s, 0.75 × 3F, E).

3.4. 4,4,4-Trifluoro-3-(2-thienyl)-2-methyl-but-2-enenitrile (**5c**)

Ratio E:Z = 30:70; b.p. 66°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_9H_6F_3NS$ (217.21): C, 49.77; H, 2.78; N, 6.45%. Found: C, 49.72; H, 2.69; N, 6.55%. MS *m/z* (rel. int): 217 (M^+, 55), 189 (100), 149 (53), 148 (36), 133 (44), 121 (22). IR (film): 2220, 1660, 1320, 1160, 720. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.62–7.54 (m, 1H), 7.35–7.10 (m, 2H), 2.34 (q, 0.30 × 3H, J = 2.7, E), 2.17 (q, 0.70 × 3H, J = 1.9, Z). ^{19}F-NMR($CDCl_3$) δ (ppm): −18.2 (s, 0.30 × 3F, E), −15.3 (s, 0.70 × 3F, Z).

3.5. 3-Trifluoromethyl-2-methyl-hept-2-enentrile (**5d**)

Ratio E:Z = 60:40; b.p. 70°C, 10 mm Hg^{-1}. HRMS Calc. for $C_9H_{12}F_3N$: 191.0922. Found, 191.0918. MS *m/z* (rel. int): 192 (M^+ + 1, 10), 149 (100), 136 (17), 122 (23), 56 (17), 43 (69). IR (film): 2960, 2220, 1640, 1330, 1260, 1130. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.54 (t, 0.40 × 2H, J = 7.6, Z), 2.32 (t, 0.60 × 2H, J = 7.4, E), 2.15–2.05 (m, 3H), 1.60–1.20 (m, 4H), 0.94 (t, 3H, J = 7.0). ^{19}F-NMR ($CDCl_3$) δ (ppm): −17.2 (s, 0.40 × 3F, Z), −14.1 (s, 0.60 × 3F, E).

3.6. 4,4,4-Trifluoro-3-(2-pyridyl)-but-2-enenitrile (**5e**)

Ratio E:Z = 57:43. E-isomer: b.p. 92°C, 1 mm Hg^{-1}. HRMS Calc. for $C_{10}H_7F_3N_2$: 212.0561. Found, 212.0591. MS *m/z* (rel. int): 213 (93), 212 (M^+, 63), 211 (51), 191 (100), 186 (38), 142 (18), 116 (6), 78 (6). IR (film): 2230, 1640, 1590, 1470, 1330, 1140 .^{1}H-NMR ($CDCl_3$) δ (ppm): 8.74–8.68 (m, 1H), 7.86–7.80 (m, 1H), 7.46–7.30 (m, 2H), 1.99 (q, 3H, J = 1.9). ^{19}F-NMR ($CDCl_3$) δ (ppm): −16.5 (s, 3F).

Z-isomer: oil. HRMS Calc. for $C_{10}H_7F_3N_2$: 212.0561. Found, 212.0558. MS *m/z* (rel. int): 212 (M^+, 74), 211 (60), 191 (100), 185 (33), 142 (26), 116 (14), 78 (30). IR (film): 2220, 1660, 1340, 1240, 1140. ^{1}H-NMR ($CDCl_3$) δ (ppm): 8.74–8.68 (m, 1H), 7.86–7.78 (m, 1H), 7.48–7.35 (m, 2H), 2.35 (q, 3H, J = 2.6). ^{19}F-NMR ($CDCl_3$) δ (ppm): −19.7 (s,3F).

3.7. 5-Phenyl-3-trifluoromethyl-2-methyl-pent-2-en-4-ynenitrile (**5f**)

Ratio E:Z = 55:45; b.p. 92°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{13}H_8F_3N$ (235.21): C, 66.37; H, 3.43; N, 5.96%. Found: C, 66.26; H, 3.43 N, 5.94%. MS *m/z* (rel. int): 235 (M^+, 100), 215 (16), 166 (67), 140 (29), 139 (24), 115 (10). IR (film): 2220, 1600, 1360, 1260, 1140, 760, 690. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.65–7.55 (m, 2H), 7.55–7.46 (m, 3H), 2.38 (q, 0.55 × 3H, J = 1.8, E), 2.24 (q, 0.45 × 3H, J = 2.3, Z). ^{19}F-NMR ($CDCl_3$) δ (ppm): −17.4 (s, 0.45 × 3F, Z), −15.2 (s, 0.55 × 3F, E).

3.8. 3-Trifluoromethyl-2-methyl-non-2-en-4-ynenitrile (**5g**)

Ratio E:Z = 43:57; b.p. 76°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{11}H_{12}F_3N$ (215.22): C, 61.39; H, 5.62; N, 6.51%. Found: C, 61.50; H, 5.50; N, 6.60%. MS *m/z* (rel. int): 215 (M^+, 14), 214 (46), 200 (100), 173 (35), 146 (45), 131 (30), 119 (12), 43 (42). IR (film): 2980, 2230, 2220, 1600, 1350, 1240, 1140. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.56–2.48 (m, 2H), 2.24 (q, 0.43 × 3H, J = 1.8, E), 2.18 (q, 0.57 × 3H, J = 2.4, Z), 1.58–1.55 (m, 2H), 1.55–1.42 (m, 2H), 0.94 (t, 3H, J = 7.2). ^{19}F-NMR ($CDCl_3$) δ (ppm): −17.6 (s, 0.57 × 3F, Z), −14.8 (s, 0.43 × 3F, E).

3.9. 5,5,5,4,4-Pentafluoro-3-phenylacetyl-2-methyl-pent-2-enentrile (**5h**)

Ratio E:Z = 80:20; b.p. 94°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{14}H_8F_5N$ (285.22): C, 58.96; H, 2.83; N, 4.91%. Found: C, 58.87; H, 2.69; N, 4.98%. MS *m/z* (rel. int): 285 (M^+, 100), 216 (60), 189 (16), 166 (53), 140 (24), 115 (11). IR (film): 2220, 1600, 1330, 1220, 1190, 760, 690. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.60–7.28 (m, 5H), 2.42 (t, 0.80 × 3H, J = 1.8, E), 2.27 (t, 0.20 × 3H, J = 2.8, Z). ^{19}F-NMR ($CDCl_3$) δ (ppm): 6.0(s, 3F), 33.0 (s, 0.20 × 2F, Z), 34.3 (s, 0.80 × 2F, E).

3.10. 5,5,5,4,4-Pentafluoro-3-(2-thienyl)-2-methyl-pent-2-enenitrile (**5i**)

Ratio E:Z = 34:66; b.p. 64°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{10}H_6F_5NS$ (267.22): C, 44.94; H, 2.26; N, 5.24%. Found: C, 44.82; H, 2.13; N, 5.41%. MS *m/z* (rel. int): 267 (M^+, 100), 240 (33), 198 (18), 171 (27), 148 (51), 121 (36). IR (film^1): 2220, 1640, 1340, 1240, 1150. ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.58–7.50 (m, 1H), 7.22–7.00 (m, 2H), 2.32 (t, 0.34 × 3H, J = 2.6, E), 2.14 (t, 0.66 × 3H, J = 2.2, Z). ^{19}F-NMR ($CDCl_3$): 4.4 (s, 0.66 × 3F, Z), 4.6 (s, 0.34 × 3F, E), 32.0 (s, 0.34 × 2F, E), 33.2 (s, 0.66 × 2F, Z).

3.11. 3-Heptafluoropropyl-2-methyl-non-2-en-4-ynenitrile (**5j**)

Ratio E:Z = 55:45; b.p. 68°C, 1 mm Hg^{-1}. Analysis: Calc. for $C_{13}H_{12}F_7N$ (315.23): C, 49.53; H, 3.84; N, 4.44%.

Found: C, 49.64; H, 3.65; N, 4.54%. MS m/z (rel. int): 316 ($M^+ + 1$, 100), 300 (38), 287 (10), 247 (7), 196 (44), 181 (12), 146 (27), 131 (9). IR (film): 2960, 2230, 2220, 1600, 1350, 1240, 1140. ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.52–2.42 (m, 2H), 2.29 (t, 0.55×3H, $J=1.9$, E), 2.17 (t, 0.45×3H, $J=2.8$, Z), 1.64–1.52 (m, 2H), 1.52–1.48 (m, 2H), 0.91 (t, 3H, $J=7.1$). ^{19}F-NMR ($CDCl_3$) δ (ppm): 2.6 (t, 3F, $J=10$), 30.0 (q, 0.45×2F, J = 10, Z), 31.2 (q, 0.55×2F, $J=10$, E), 47.9 (s, 0.55×2F, E), 48.4 (s, 0.45×2F, Z).

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