A convenient synthesis of perfluoroalkynamides

Yanchang Shen* and Shu Gao
Shanghai Institute of Organic Chemistry, Academia Sinica, 345 Lingling Lu, Shanghai 200032 (China)

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Abstract

Perfluoroalkynamides have been conveniently prepared by the following reaction sequence. Amidomethylenetriphenylphosphoranes (generated from the corresponding bromides and triethylamine) were acylated by the addition of perfluoroalkanoic anhydrides, followed by deprotonation with triethylamine to give the corresponding perfluoroacyl phosphoranes in 63–87% yield. Pyrolysis of these latter compounds under reduced pressure gave perfluoroalkynamides in 62–95% yields. The title compounds would be expected to be useful intermediates for the synthesis of fluorine-containing biologically active compounds.

Introduction

Methods for the preparation of organofluorine compounds have attracted much interest in recent years, since many of these molecules possess interesting biological activities [1]. One such method is based on the use of building blocks with fluorine substituents. Fluoroalkynes, such as hexafluorobut-2-yne, are good dipolarophiles and dienophiles and valuable building blocks for the synthesis of various trifluoromethylated compounds [2]. In our studies of fluoroalkynes as dipolarophiles for the synthesis of fluorinated heterocyclic compounds, the fluorinated species were also found to be good dipolarophiles [3]. To enable extension of these studies, the preparation of perfluoroalkynamides is of interest. Furthermore, the title compounds could be reduced to perfluoroalkylated *Z*- or *E*-unsaturated amides which would be expected to be useful intermediates in the synthesis of perfluoroalkylated biologically active compounds.

Results and discussion

Thermolysis of 1-acylalkylidenetriphenylphosphoranes is a particularly useful method for the synthesis of acetylenes, especially fluorinated species [4]. However, preparation of alkynamide and perfluoroalkynamide by this methodology has not been reported previously [5]. In the present work, we

*To whom all correspondence should be addressed.

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TABLE 1

Physical constants and yields of compounds **4**

Compound	R^1	R^2	R_F	Melting point (°C)	Yield (%)[a]
4a	C_2H_5	C_2H_5	CF_3	198–200	87
4b	C_2H_5	C_2H_5	n-C_3F_7	172–173	77
4c	H	n-C_4H_9	CF_3	176–177	87
4d	H	n-C_4H_9	C_2F_5	179–181	63
4e		$-(CH_2)_5-$	CF_3	195–197	85
4f		$-(CH_2)_5-$	n-C_3F_7	175–176	80

[a]Isolated yields.

prepared the title compounds successfully using the following reaction sequences:

$$(C_6H_5)_3\overset{+}{P}CH_2C(O)NR^1R^2Br^- \xrightarrow{Et_3N} (C_6H_5)_3P{=}CHC(O)NR^1R^2$$
(1) **(2)**

$$\xrightarrow{(R_FCO)_2O} (C_6H_5)_3\overset{+}{P}-\underset{\displaystyle C(O)R_F}{\overset{\displaystyle C(O)NR^1R^2}{C}}-H \qquad R_FCO_2^- \xrightarrow{Et_3N} (C_6H_5)_3P{=}\underset{\displaystyle C(O)R_F}{\overset{\displaystyle C(O)NR^1R^2}{C}}$$
(3) **(4)**

$$\xrightarrow[-Ph_3PO]{200\text{–}240\ ^\circ C/2\ mmHg} R_FC{\equiv}C{-}C(O)NR^1R^2$$
(5)

Amidomethylenetriphenylphosphoranes **2** generated from the corresponding bromides and triethylamine were acylated by the addition of perfluoroalkanoic anhydrides, followed by deprotonation with triethylamine, to give the corresponding perfluoroacyl phosphoranes in 63–87% yield (Table 1). Compounds **4** were isolated and submitted to vacuum pyrolysis (200–240 °C/2 mmHg) to afford the expected perfluoroalkynamides **5** in 62–95% yield (Table 2). The structures of all products were ascertained via their IR, MS and NMR spectra, and by microanalyses which were satisfactorily consistent with the calculated values.

Experimental

All melting points and boiling points are reported uncorrected. The infrared spectra of solid products were obtained as KCl disks and of liquid products as films using a Shimadzu IR-440 spectrometer. ^{19}F and ^1H NMR spectra were obtained on a Varian EM-360 spectrometer at 60 MHz or an XL-200 spectrometer at 200 MHz using TFA as an external reference and

TABLE 2

Physical constants and yields of compounds **5**

Compound	R^1	R^2	R_F	Boiling point (°C/mmHg)	Yield (%)[a]
5a	C_2H_5	C_2H_5	CF_3	70/10	95
5b	C_2H_5	C_2H_5	n-C_3F_7	75/10	91
5c	H	n-C_4H_9	CF_3	74/2	62
5d	H	n-C_4H_9	C_2F_5	80/2	72
5e	$-(CH)_2)_5-$		CF_3	85/10	93
5f	$-(CH_2)_5-$		n-C_3F_7	98/10	82

[a]Isolated yields.

TMS as internal reference. Mass spectra were recorded on a Finnigan GC–MS 4021 mass spectrometer.

*Preparation of trifluoroacetyl(*N,N*-diethyl)amidomethylenetriphenylphosphorane (**4a**)*

(*N,N*-Diethyl)amidomethyltriphenylphosphonium bromide (1.82 g, 4 mmol) in anhydrous THF (20 ml) was cooled in an ice–water bath under nitrogen and treated with triethylamine (0.81 g, 8 mmol) with stirring. After being stirred for 15 min, the mixture was treated with trifluoroacetic anhydride (0.86 g, 4.1 mmol) dropwise and allowed to stir for 1 h. The mixture was poured into water and filtered. The precipitate was purified by recrystallization from methanol to give **4a**: yield, 1.64 g (87%); m.p., 198–200 °C. IR (KCl) cm^{-1}: 1610 (s); 1562 (s). ^1H NMR ($CDCl_3$) δ: 7.78–7.30 (m, 15H); 3.91 (q, 2H, $J=6.4$ Hz); 3.13 (q, 2H, $J=6.4$ Hz); 1.03 (t, 3H, $J=6.4$ Hz); 0.77 (t, 3H, $J=6.4$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −5.47 (s, 3F) ppm. MS *m/e* (rel. int.): 471 (M^+, 27); 402 (17); 399 (64). Analysis: Calcd. for $C_{26}H_{25}F_3NO_2P$: C, 66.21; H, 5.34; N, 2.97%. Found: C, 66.21; H, 5.11; N, 2.90%.

Similar procedures were used to obtain the following products:

Compound **4b**: 77% yield; m.p., 172–173 °C. IR (KCl) cm^{-1}: 1605 (s), 1550 (s). ^1H NMR ($CDCl_3$) δ: 7.83–7.35 (m, 15H); 3.87 (q, 2H, $J=7.2$ Hz); 3.06 (q, 2H, $J=7.2$ Hz); 1.01 (t, 3H, $J=7.2$ Hz); 0.67 (t, 3H, $J=7.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.1 (s, 3F); 37.7 (s, 2F); 48.0 (s, 3F) ppm. MS *m/e* (rel. int.): 571 (M^+, 46); 499 (100); 402 (54). Analysis: Calcd. for $C_{28}H_{25}F_7NO_2P$: C, 58.85; H, 4.41; N, 2.45%. Found: C, 58.88; H, 4.10; N, 2.34%.

Compound **4c**: 87% yield; m.p., 176–177 °C. IR (KCl) cm^{-1}: 1620 (s); 1580 (s). ^1H NMR ($CDCl_3$) δ: 7.84–7.36 (m, 4H); 3.09 (dt, 2H, $J=6.5$, 7.0 Hz); 1.46–1.14 (m, 4H); 0.86 (t, 3H, $J=7.0$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −8.3 (s, 3F) ppm. MS *m/e* (rel. int.): 472 ($M^+ + 1$, 30); 402 (41); 399 (100). Analysis: Calcd. for $C_{26}H_{25}F_3NO_2P$: C, 66.24; H, 5.34; N, 2.97%. Found: C, 66.18; H, 5.10; N, 2.96%.

Compound **4d**: 63% yield; m.p., 179–181 °C. IR (KCl) cm^{-1}: 1620 (s); 1555 (s). ^1H NMR ($CDCl_3$) δ: 7.81–1.40 (m, 16H); 3.08 (dt, 2H, $J=6.5$,

7.1 Hz); 1.48–1.15 (m, 4H); 0.87 (t, 3H, $J = 7.1$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 2.1 (s, 3F); 37.3 (s, 2F) ppm. MS *m/e* (rel. int.): 522 ($M^+ + 1$, 40); 449 (100); 402 (48). Analysis: Calcd. for $C_{27}H_{25}F_5NO_2P$: C, 62.19; H, 4.83; N, 2.68%. Found: C, 62.23; H, 4.61; N, 2.65%.

Compound **4e**: 85% yield; m.p., 195–197 °C. IR (KCl) cm^{-1}: 1590 (s); 1570 (s). ^1H NMR ($CDCl_3$) δ: 7.83–7.42 (m, 15H); 3.77–3.47 (m, 4H); 1.55–1.25 (m, 6H) ppm. ^{19}F NMR ($CDCl_3$) δ: −5.3 (s, 3H) ppm. MS *m/e* (rel. int.): 484 ($M^+ + 1$, 16); 483 (M^+, 16); 399 (100). Analysis: Calcd. for $C_{27}H_{25}F_3NO_2P$: C, 67.07; H, 5.21; N, 2.90%. Found: C, 67.40; H, 5.22; N, 2.77%.

Compound **4f**: 80% yield; m.p., 175–176 °C. IR (KCl) cm^{-1}): 1600 (s); 1550 (s). ^1H NMR ($CDCl_3$) δ: 7.87–7.47 (m, 15H); 3.77–3.47 (m, 2H); 3.35–3.05 (m, 2H); 1.58–1.28 (m, 6H) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.0 (s, 3F); 38.3 (s, 2F); 48.2 (s, 2F) ppm. MS *m/e* (rel. int.): 584 ($M^+ + 1$, 34); 583 (M^+, 74); 499 (100). Analysis: Calcd. for $C_{29}H_{25}F_7NO_2P$: C, 59.69; H, 4.32; N, 2.40%. Found: C, 59.70; H, 3.97; N, 2.28%.

Preparation of N,N-*diethyl-trifluoro-2-butynamide (**5a**)*

The phosphorane **4a** (1.4 g, 2 mmol) was pyrolyzed under nitrogen at reduced pressure (200–240 °C/2 mmHg). The pyrolysate collected in traps cooled with Dry Ice/ethanol was redistilled to give **5a**: yield, 0.55 g (95%); b.p., 70 °C/10 mmHg. IR (film) cm^{-1}: 2253 (w); 1652 (s). ^1H NMR ($CDCl_3$) δ: 3.56 (q, 2H, $J = 7.2$ Hz); 3.45 (q, 2H, $J = 7.2$ Hz); 1.27 (t, 3H, $J = 7.2$ Hz); 1.17 (t, 3H, $J = 7.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −26.3 (s, 3F) ppm. MS *m/e* (rel. int.): 193 (M^+, 43); 178 (100); 124 (20). Analysis: Calcd. for $C_8H_{10}F_3NO$: C, 49.74; H, 5.22; N, 7.25%. Found: C, 49.99; H, 5.37; N, 7.28%.

Similar procedures were used to obtain the following products:

Compound **5b**: 91% yield; b.p., 75 °C/10 mmHg. IR (film) cm^{-1}: 2250 (w); 1655 (s). ^1H NMR ($CDCl_3$) δ: 3.52 (q, 2H, $J = 6.3$ Hz); 3.44 (q, 2H, $J = 6.3$ Hz); 1.23 (t, 3H, $J = 6.3$ Hz); 1.15 (t, 3H, $J = 6.3$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 3.2 (s, 3F); 23.7 (s, 2F); 49.7 (s, 2F) ppm. MS *m/e* (rel int.): 295 ($M^+ + 2$, 100); 293 (M^+, 42). Analysis: Calcd. for $C_{10}H_{10}F_7NO$: C, 40.96; H, 3.44; N, 4.78%. Found: C, 40.83; H, 3.36; N, 4.80%.

Compound **5c**: 62% yield; b.p., 74 °C/2mmHg. IR (film) cm^{-1}: 2290 (m); 1660 (s). ^1H NMR ($CDCl_3$) δ: 6.14 (br, 1H); 3.35 (dt, 2H, $J = 6.7$, 7.0 Hz); 1.69–1.20 (m, 4H); 0.94 (t, 3H, $J = 7.0$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: −26.1 (s, 3F) ppm. MS *m/e* (rel. int.): 194 ($M^+ + 1$, 47); 121 (100). Analysis: Calcd. for $C_8H_{10}F_3NO$: C, 49.74; H, 5.22; N, 7.25%. Found: C, 49.41; H, 4.98; N, 7.27%.

Compound **5d**: 72% yield; b.p., 80 °C/2 mmHg. IR (film) cm^{-1}: 2250 (w); 1655 (s). ^1H NMR ($CDCl_3$) δ: 6.08 (br, 1H); 3.32 (dt, 2H, $J = 6.7$, 6.8 Hz); 1.69–1.20 (m, 4H); 0.92 (t, 3H, $J = 6.8$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 8.3 (s, 3F); 26.7 (s, 2F) ppm. MS *m/e* (rel. int.): 244 ($M^+ + 1$, 89); 171 (49). Analysis: Calcd. for $C_9H_{10}F_5NO$: C, 44.45; H, 4.14; N, 5.76%. Found: C, 44.22; H, 4.25; N, 5.79%.

Compound **5e**: 93% yield; b.p., 85 °C/10 mmHg. IR (film) cm^{-1}: 2250 (w); 1160 (s). ^1H NMR ($CDCl_3$) δ: 3.74–3.26 (m, 4H); 1.78–1.50 (m, 6H) ppm. ^{19}F NMR ($CDCl_3$) δ: −26.3 (s, 3F) ppm. MS *m/e* (rel. int.): 206 ($M^+ + 1$, 100); 205 (M^+, 80); 136 (61). Analysis: Calcd. for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83%. Found: C, 52.72; H, 5.11; N, 6.83%.

Compound **5f**: 82% yield: b.p., 98 °C/10 mmHg. IR (film) cm^{-1}: 2250 (w); 1660 (s). ^1H NMR ($CDCl_3$) δ: 3.74–3.26 (m, 4H); 1.77–1.50 (m, 6H) ppm. ^{19}F NMR ($CDCl_3$) δ: 2.9 (s, 3F); 23.3 (s, 2F); 49.6 (s, 2F) ppm. MS *m/e* (rel. int.): 306 ($M^+ + 1$, 82); 305 (M^+, 74); 186 (100). Analysis: Calcd. for $C_{11}H_{10}F_7NO$: C, 43.29; H, 3.30; N, 4.59%. Found: C, 43.17; H, 3.30; N, 4.59%.

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