A new one-pot synthesis of trifluoromethyl-2-enyl and 2,4-enynyl amides

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Abstract

A new one-pot synthesis of trifluoromethyl-2-enyl and 2,4-enynyl amides in 72–90% yield via ylide-anion formation and protonation is described.

Introduction

The synthesis of functionalized molecules containing trifluoromethyl groups is attracting much interest since such molecules can be employed to the synthesis of the fluorinated analogues of biologically active molecules.

Unsaturated amides belong to an important class of compounds which occur widely in a number of natural products and which have been reported as possessing biological activity [1]. They are also useful intermediates for the synthesis of various complex compounds [2] capable of undergoing many organic transformations [3]. However, the methods for the preparation of trifluoromethyl analogues are still limited [4]. Thus, the development of an effective method for their preparation would be valuable.

Results and discussion

We have recently established a novel intramolecular Wittig reaction via ylide-anion formation and protonation and applied this to the synthesis of perfluoroalkylated α,β-unsaturated carbonyl compounds [5] and nitriles [6]. As a result of our continuing investigations aimed at exploiting the synthetic utility of this reaction in organic synthesis, we now report a new one-pot synthesis of trifluoromethyl-2-enyl and 2,4-enynyl amides in 72–90% yield via ylide-anion formation and protonation.

The reaction sequence is as follows:

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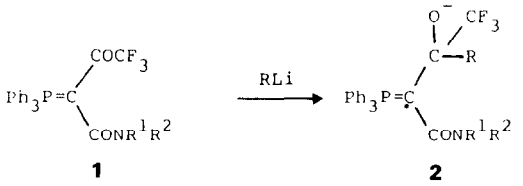
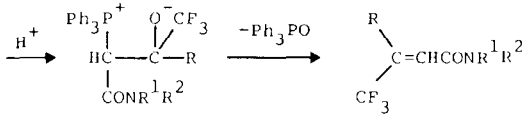


1 **2**



3 **4**

a: R^1, $R^2 = -(CH_2)_5-$; R = Ph

b: R^1, $R^2 = -(CH_2)_5-$; R = Me

c: R^1, $R^2 = -(CH_2)_5-$; $R = Bu^nC{\equiv}C-$

d: R^1, $R^2 = -(CH_2)_5-$; $R = PhC{\equiv}C-$

e: $R^1 = R^2 = Et$; R = Ph

f: $R^1 = R^2 = Et$; R = Me

g: $R^1 = R^2 = Et$; $R = Bu^nC{\equiv}C-$

h: $R^1 = R^2 = Et$; $R = PhC{\equiv}C-$

The fluorinated triphenylphosphoranes **1** were found to be very stable and did not react with aldehydes because of the strong electron-withdrawing effect of the perfluoroacyl group; only the intramolecular Wittig reaction occurred at 240 °C, giving fluoroacetylenes [7]. As nucleophiles, the lithium reagents are capable of regiospecific attack on the trifluoroacyl groups of the phosphoranes **1** to form ylide-anions **2**, and after protonation with acetic acid, the intramolecular Wittig reaction occurred spontaneously to give products **4** in 72–90% yield.

The results are summarized in Table 1. All products are new and were characterized by microanalysis, IR, NMR and mass spectroscopy.

This new one-pot synthesis of the title compounds is quite convenient for the exclusive preparation of the *Z*-isomer (**4a**, **4e**), or a mixture of the two isomers. On the basis of data reported in the literature [8], the chemical shift of the trifluoromethyl group in the *Z*-isomer appears at 6–8 ppm lower than those of the corresponding *E*-isomer; hence the relative proportions of the *Z*- and *E*-isomers could be ascertained. These isomers could be useful in the synthesis of trifluoromethylated biologically active compounds.

Experimental

All boiling (melting) points are reported uncorrected. IR spectra were recorded as films on a Shimadzu IR-440 spectrometer. NMR spectra (TMS for ^1H NMR and TFA for ^{19}F NMR as external references, positive for upfield shifts) were obtained on a Varian EM-360 spectrometer (60 MHz). Mass spectra were measured on a Finnigan GC–MS-4021 mass spectrometer.

TABLE 1

Preparation of trifluoromethyl-2-enyl and 2,4-enynyl amides (**4**)

Compound	R	R^1	R^2	Reaction temp.[a] (°C)	Yield[b] (%)	Z/E[c]
4a	Ph	$-(CH_2)_5-$		−30	80	100:0
4b	Me	$-(CH_2)_5-$		0	90	73:27
4c	$Bu^nC{\equiv}C-$	$-(CH_2)_5-$		10	72	58:42
4d	$PhC{\equiv}C-$	$-(CH_2)_5-$		10	78	53:47
4e	Ph	Et	Et	−30	85	100:0
4f	Me	Et	Et	0	81	72:28
4g	$Bu^nC{\equiv}C-$	Et	Et	10	84	52:48
4h	$PhC{\equiv}C-$	Et	Et	10	74	51:49

[a]Reaction temperatures for ylide-anion formation.
[b]Isolated yields.
[c]Ratio of *Z*- to *E*-isomer was estimated on the basis of the ^{19}F NMR spectra.

General procedure for the preparation of trifluoromethyl-2-enyl and 2,4-enynyl amides (4)

The lithium reagent (4 mmol) was added dropwise to a solution of **2** (4 mmol) in anhydrous THF (16 ml) at −30 °C, 0 °C or 10 °C under nitrogen with stirring. After stirring for 2 h, acetic acid (1 ml) was added which led to the disappearance of the characteristic colour of the ylide-anion. The mixture was allowed to warm to 20 °C and stirred for a further 3 h. Diethyl ether (20 ml) was added. The organic layer was washed with water until neutral and then dried with anhydrous Na_2SO_4. Evaporation of the solvent gave a residue which was isolated by column chromatography eluting with petroleum (60–90 °C)/ethyl acetate (3:1) to give products **4**. The following analyses were obtained.

Compound **4a**: 80% yield; b.p., 113 °C/2 mmHg; *Z*-isomer only IR (film) cm^{-1}: 1640 (s); 1450 (m). ^1H NMR (CCl_4) δ: 1.42–1.72 (m, 6H); 3.37–3.57 (m, 4H); 6.30 (s, 1H); 7.36 (m, 5H) ppm. ^{19}F NMR (CCl_4) δ: −16.7 (s, 3F) ppm MS *m/e*: 283 (M^+, 5%); 214 ($M^+ - CF_3$, 100%); 199 ($M^+ - C_5H_{10}N$, 72%). Analysis: Calcd. for $C_{15}H_{16}F_3NO$: C, 63.60; H, 5.69; N, 4.94%. Found: C, 63.31; H, 5.49; N, 4.79%.

Compound **4b**: 90% yield; $Z/E = 73:27$; *Z*-isomer; b.p., 80 °C/2 mmHg; m.p., 45–46 °C. IR (film) cm^{-1}: 1625 (s). ^1H NMR (CCl_4) δ: 1.49–1.77 (m, 6H); 2.02 (s, 3H); 3.42–3.63 (m, 4H); 6.17 (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: −11.0 (s, 3F) ppm. *E*-isomer: b.p., 68 °C/2 mmHg. IR (film) cm^{-1}: 1630 (s). ^1H NMR (CCl_4) δ: 1.40–1.69 (m, 6H); 1.95 (s, 3H); 3.33–3.54 (m, 4H); 6.40 (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: −7.0 (s, 3F) ppm. MS *m/e*: 221 (M^+, 16%); 152 ($M^+ - CF_3$, 83%); 137 ($M^+ - C_5H_{10}N$, 51%). Analysis: Calcd. for $C_{10}H_{14}F_3NO$: C, 54.29; H, 6.38; N, 6.33%. Found: C, 54.33; H, 6.24; N, 6.22%.

Compound **4c**: 72% yield; b.p., 138 °C/2 mmHg; $Z/E = 58:42$. IR (film) cm^{-1}: 2200 (w); 1640 (s). ^1H NMR (CCl_4) δ: 0.92 ($E+Z$) (t, 3H, $J = 7.0$

Hz); 1.39–1.81 (*E*+*Z*) (m, 10H); [2.39 (*Z*)+2.36 (*E*)] (t, 2H, *J*=5.8 Hz); 3.28–3.70 (*E*+*Z*) (m, 4H); [6.45 (*Z*)+6.74 (*E*)] (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: [−13.3 (*Z*)+(−10.0) (*E*)] (s, 3F) ppm. MS *m/e*: 287 (M^+, 56%); 288 (M^++1, 100%). Analysis: Calcd. for $C_{15}H_{20}F_3NO$: C, 62.70; H, 7.02; N, 4.88%. Found: C, 62.87; H, 6.89; N, 4.97%.

Compound **4d**: 78% yield; b.p., 170 °C/2 mmHg; *Z*/*E*=53:47. IR (film) cm^{-1}: 2200 (w); 1640 (s); 1450 (m). ^{1}H NMR (CCl_4) δ: 1.02–1.24 (*E*+*Z*) (m, 6H); 3.16–3.51 (*E*+*Z*) (m, 4H); [6.60 (*Z*)+6.80 (*E*)] (s, 1H); 7.33 (m, 5H) ppm. ^{19}F NMR (CCl_4) δ: [−13.8 (*Z*)+(−10.6) (*E*)] (2, 3F) ppm. MS *m/e*: 308 (M^++1, 56%); 307 (M^+, 82%); 223 ($M^+ - C_5H_{10}N$, 100%). Analysis: Calcd. for $C_{17}H_{16}F_3NO$: C, 66.44; H, 5.25; N, 4.56%. Found: C, 66.63; H, 4.92; N, 4.43%.

Compound **4e**: 85% yield; m.p., 65–66 °C; *Z*-isomer only. IR (film) cm^{-1}: 1620 (s); 1450 (m). ^{1}H NMR (CCl_4) δ: 1.17 (t, 6H, *J*=6.6 Hz); 3.27 (q, 4H, *J*=6.6 Hz); 6.30 (s, 1H); 7.33 (m, 5H) ppm. ^{19}F NMR (CCl_4) δ: −16.7 (s, 3F) ppm. MS *m/e*: 272 (M^++1, 100%); 271 (M^+, 12%); 202 ($M^+ - NEt_2$, 83%). Analysis: Calcd. for $C_{14}H_{16}F_3NO$: C, 61.98; H, 5.94; N, 5.16%. Found: C, 61.69; H, 5.74; N, 4.97%.

Compound **4f**: 81% yield; *Z*/*E*=72:28; *Z*-isomer: b.p., 65 °C/2 mmHg. IR (film) cm^{-1}: 1640 (s). ^{1}H NMR (CCl_4) δ: 1.06 (t, 6H, *J*=6.0 Hz); 1.86 (s, 3H); 3.18 (q, 4H, *J*=6.0 Hz); 6.03 (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: −10.8 (s, 3F) ppm. *E*-isomer: b.p., 45 °C/2 mmHg. IR (film) cm^{-1}: 1640 (s). ^{1}H NMR (CCl_4) δ: 1.12 (t, 6H, *J*=6.0 Hz); 1.95 (s, 3H); 3.33 (q, 4H, *J*=6.0 Hz); 6.47 (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: −6.5 (s, 3F) ppm. MS *m/e*: 209 (M^+, 14%); 140 ($M^+ - CF_3$, 36%). Analysis: Calcd. for $C_9H_{14}F_3NO$: C, 51.66; H, 6.75; N, 6.70%. Found: C, 51.64; H, 6.83; N, 6.92%.

Compound **4g**: 84% yield; b.p., 100 °C/2 mmHg; *Z*/*E*=52:48. IR (film) cm^{-1}: 2200 (w); 1645 (s). ^{1}H NMR (CCl_4) δ: 0.57–1.53 (*E*+*Z*) (m, 13H); 2.23 (*E*+*Z*) (t, 2H, *J*=6.0 Hz); 2.93–3.50 (*E*+*Z*) (m, 4H), [6.33 (*Z*)+6.58 (*E*)] (s, 1H) ppm. ^{19}F NMR (CCl_4) δ: [−13.3 (*Z*)+(−9.7) (*E*)] (s, 3F) ppm. MS *m/e*: 276 (M^++1, 58%); 275 (M^+, 60%); 256 (M^+−F, 13%). Analysis: Calcd. for $C_{14}H_{20}F_3NO$: C, 61.07; H, 7.32; N, 5.09%. Found: C, 60.88; H, 7.39; N, 5.15%.

Compound **4h**: 74% yield; b.p., 130 °C/2 mmHg; *Z*/*E*=51:49. IR (film) cm^{-1}: 2200 (w); 1643 (s). ^{1}H NMR (CCl_4) δ: 1.02–1.24 (*E*+*Z*) (*t*, 6*H*, *J*=7.0 Hz); 3.16–3.51 (m, 4H); [6.60 (*Z*)+6.80 (*E*)] (s, 1H); 7.33 (*E*+*Z*) (m, 5H) ppm. ^{19}F NMR (CCl_4) δ: [−13.8 (*Z*)+(−10.5) (*E*)] (s, 3F) ppm. MS *m/e*: 295 (M^+, 59%); 276 (M^+−F, 5%); 223 ($M^+ - NEt_2$, 100%). Analysis: Calcd. for $C_{16}H_{16}F_3NO$: C, 65.07; H, 5.46; N, 4.74%. Found: C, 64.51; H, 5.44; N, 4.72%.

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