Stereoselective synthesis of trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles

Yanchang Shen * and Shu Gao

Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, Shanghai 200032, China

A stereoselective synthesis of trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles by the reaction of fluorinated ylide-anion resulting from nucleophilic addition of organolithium or Grignard reagents to trifluoromethylated phosphoranes with *N*-chlorosuccinimide is described.

Introduction

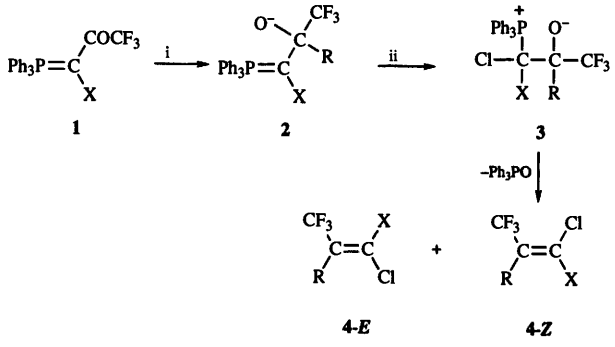
Alkenyl chlorides constitute structural features of a number of marine natural products; for example, *Plocamium violaceum* and *Desmia hornemanni* which show biological activities.[1] They have been used as electrophiles in carbon–carbon bond-forming reactions such as coupling with terminal alkynes catalysed by $PdCl_2(PhCN)_2$ and CuI in piperidine for the stereospecific synthesis of enynes.[2] Introduction of a fluorine atom or perfluoroalkyl group into compounds with biological properties often leads to pronounced activity enhancement, and organofluorine compounds have been applied increasingly in pharmaceuticals, agrochemicals and other fields.[3] Usually they are prepared from trifluoromethyl ketones by Wittig condensation or by a Wittig–Horner reaction.[4] However, these methods are known to lack stereoselectivity.[2b] Starting from carbonyl- or dicarbonyl-methylenetriphenylphosphoranes, the intramolecular Wittig reaction is a well known methodology for the synthesis of alkynes,[5] particularly fluoro species.[6] Due to the strong electron-withdrawing effect of the carbonyl group, carbonyl- or dicarbonyl-triphenylphosphoranes are very stable and are unable to react with aldehydes or ketones. Therefore it is of interest to use these fluorinated phosphoranes as reagents in a Wittig reaction towards the synthesis of fluorinated alkenes and to develop a convenient method for the synthesis of title compounds since they may be expected to be useful intermediates for the synthesis of fluorine-containing biologically active compounds.

Results and discussion

In our previous paper,[7] we reported that these fluorinated phosphoranes could be activated by nucleophilic addition of organolithium compounds to the carbonyl group neighbouring to the trifluoromethyl group, leading to the formation of ylide-anions. The active species, ylide-anions, reacted with aldehydes or were protonated to give trifluoromethylated allylic alcohol or perfluoroalkylated α,β-unsaturated carbonyl compounds. In our continuing investigation into the exploitation of the synthetic utility of fluorinated ylide-anions in organic synthesis, we now report a stereoselective synthesis of triflormethylated α-chloro-α,β-unsaturated esters and nitriles *via* ylide-anions resulting from nucleophilic addition of organolithium compounds or Grignard reagents to the carbonyl group neighbouring the trifluoromethyl group.

The reaction sequence is shown in Scheme 1.

Fluorinated phosphoranes **1** are very stable because of the strong electron-withdrawing effect of the carbonyl group making them unreactive toward aldehydes or ketones. However, they did react with a variety of organolithium and Grignard reagents affording, after chlorination and elimination of triphenylphosphine oxide, trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles.



Scheme 1 *Reagents:* i, RM; ii, NCS

The organolithium or Grignard reagents regiospecifically attack the trifluoroacetyl group of fluorinated phosphoranes **1** to give the ylide-anion **2** which reacts with *N*-chlorosuccinimide (NCS) to produce the chloro-substituted betaines **3**; these spontaneously decompose to the trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles together with triphenylphosphine oxide.

The results are summarized in Table 1.

On the basis of data reported in the literature[8] the trifluoromethyl group is *trans* with respect to the X group (CO_2R or CN) (*i.e.* for compounds **4-*Z***) when the ^{19}F chemical shifts of trifluoromethyl group are upfield; while for the corresponding *cis* compounds (*i.e.* compounds **4-*E***) the chemical shifts are downfield. Hence the relative proportions of *Z*- and *E*-isomers could be ascertained. The stereochemical results in Table 1 indicate that the groups attached to the chloroalkenes may play an important role in determining the stereoselectivity of the reaction. The stereoselectivity may be rationalized as shown in Scheme 2.

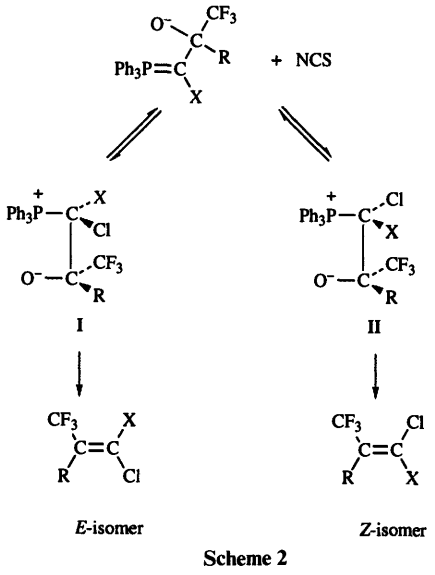
The reaction is initiated by electrophilic attack of NCS on the ylide-anion, forming two diastereoisomeric betaines **I** and **II** in equilibrium. The energies of the betaines depend upon the steric interference between the individual pairs of 'eclipsed' substituents. As a result of the different energies of the betaines the equilibrium can shift toward isomer **I** or isomer **II**. The relative steric bulk of CF_3 and R groups, and hence their interaction with Cl and X, seems to control the stereochemical results.

(1) In the case where X = CO_2Bu^t, a bulky group, the ratios of *E*-isomer decrease as the group size of R is decreased [**4a** (Bu^s) to **4f** (PhC≡C)]. In the case of compound **4a** the largest groups (Bu^s and CO_2Bu^t) are located *trans* with respect to one another in intermediate **3** and the resulting preferred conformation with lower energy undergoes decomposition to give the *E*-isomer, while in the case of compound **4f** the location of the largest groups (CF_3 and CO_2Bu^t) in a *trans* configuration in intermediate **3** resulted in the conformation with somewhat

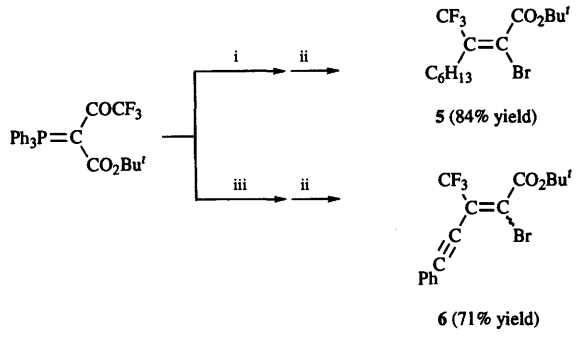
Table 1 Trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles prepared

Compound	X	RM	Reaction temp[a] (T/°C)	Yield[b] (%)	E:Z[c]
4a	CO_2Bu^t	Bu^sLi	−40	79	100:0
4b	CO_2Bu^t	$PhCH_2MgCl$	−30	83	78:22
4c	CO_2Bu^t	$C_6H_{13}MgCl$	0	79	76:24
4d	CO_2Bu^t	BuLi	−60	70	73:27
4e	CO_2Bu^t	PhMgCl	0	85	56:44
4f	CO_2Bu^t	PhC≡CLi	0	65	30:70
4g	CN	BuC≡CLi	0	71	100:0
4h	CN	PhC≡CLi	0	70	100:0
4i	CN	Bu^sLi	−50	74	78:22
4j	CN	BuLi	−60	62	52:48

[a] The temperature of reaction of phosphorane **1** with RM. [b] Isolated yield. [c] The ratios of *E*- and *Z*-isomers were based on NMR spectra.



Scheme 2



Scheme 3 *Reagents:* i, $C_6H_{13}MgBr$; ii, NCS; iii, PhC≡CLi, LiBr

lower energy which undergoes decomposition to give a mixture of two isomers.

(2) In the case where X = CN, a small group, the ratios of *E*-isomer decrease as the group size of R is increased [**4g** (BuC≡C) to **4i** (Bu^s)]. In the case of compounds **4g** and **4h**, the largest groups (CF_3 and Cl) are located *trans* to one another and the resulting preferred conformation with lower energy undergoes decomposition to give the *E*-isomer, while in the case of compound **4i** the energy difference between isomers **I** and **II** is not too much and a mixture of two isomers was obtained.

In summary, steric factors or non-bonded interactions determine which intermediate **I** or **II** is preferred, the largest group being *trans* with respect to the next largest.

It is noteworthy that in this one-pot reaction the bromine ion had to be avoided, otherwise the bromo compound was obtained. For example, the reactions shown in Scheme 3 were found to occur. This result may be rationalized by the halogen-exchange reaction[9] to generate NBS [eqn. (1)].

$$NCS \xrightarrow{Br^-} NBS \qquad (1)$$

Experimental

Bps are uncorrected. IR spectra of all products were obtained as films on a Shimadzu IR-440 spectrometer. ^{19}F NMR spectra were recorded on a Varian EM-360 spectrometer (60 MHz) with CF_3CO_2H as external standard, positive for upfield shifts. ^1H NMR spectra were obtained on a Varian EM-360 or a Bruker AM-300 (300 MHz) instrument with $SiMe_4$ as reference; $CDCl_3$ was used as solvent; *J*-values are in Hz. Mass spectra were measured on a Finnigan GC-MS-4021 mass spectrometer.

Grignard reagents

These were prepared from the corresponding chloro compounds and magnesium.

Lithium reagents

Bu^nLi and Bu^sLi were obtained from Aldrich Chemical Company. R′-C≡CLi were prepared by the reaction of terminal acetylenes (4 mmol) and butyllithium (4 mmol) in tetrahydrofuran (THF) (10 cm^3) for 15 min at 0 °C.

General procedure for the preparation of trifluoromethylated α-chloro-α,β-unsaturated esters and nitriles 4a–j

Lithium reagent or Grignard reagent (4 mmol) was added dropwise to a stirred solution of the ylide **1** (4 mmol) in dry THF (16 cm^3) at −60, −50, −40, −30 or 0 °C (see Table 1) under nitrogen. The reaction mixture was stirred for 1 h at the same temperature to form the ylide-anion **2**, after which NCS (5 mmol) was added. The mixture was allowed to reach 20 °C after which it was stirred for 2 h and then diluted with diethyl ether (20 cm^3). The organic layer was separated, washed repeatedly with water to neutral pH, dried and evaporated. The residue was chromatographed on silica gel and eluted with light petroleum (distillation range 60–90 °C)–ethyl acetate (98:2) to give compounds **4**.

***tert*-Butyl 2-chloro-4-methyl-3-(trifluoromethyl)hex-2-enoate 4a.** *E-Isomer*; bp 74 °C/10 mmHg; ν_{max}/cm^{-1} 1740, 1635, 1460, 1340, 1100 and 860; δ_H 3.06–2.76 (m, 1 H), 1.77–1.34 (m, 2 H), 1.51 (s, 9 H), 1.21 (d, *J* 7.2, 3 H) and 0.93 (t, *J* 7.1, 3 H); δ_F −18.94 (s, 3 F); *m*/*z* 287 (M^+ + 1, 10%), 231 (11), 230 (26), 215 (5), 213 (20) and 57 (100) (Found: C, 49.9; H, 6.3. $C_{12}H_{18}ClF_3O_2$ requires C, 50.27; H, 6.33%).

***tert*-Butyl 3-benzyl-2-chloro-4,4,4-trifluorobut-2-enoate 4b.** Obtained as mixture of E- and Z-*isomers*; bp 85 °C/2 mmHg; ν_{max}/cm^{-1} 1740, 1640, 1370, 1340, 1100 and 840; δ_H 7.40–7.04 (m, 5 H), 3.76 (s, 2 H), 1.52 (s, 0.78 × 9 H, *E*) and 1.48 (s, 0.22 × 9 H, *Z*); δ_F −16.34 (s, 0.78 × 3 F, *E*) and −15.90 (s, 0.22 × 3 F, *Z*); *m*/*z* 321 (M^+ + 1, 13%), 265 (7), 91 (63)

and 57 (100) (Found: C, 56.2; H, 5.1. $C_{15}H_{16}ClF_3O_2$ requires C, 56.17; H, 5.03%).

***tert*-Butyl 2-chloro-3-(trifluoromethyl)non-2-enoate 4c.** Obtained as mixture of E- and *Z-isomers*; bp 60 °C/1.5 mmHg; ν_{max}/cm^{-1} 1745, 1650, 1375, 1340 and 1100; δ_H 2.48–2.23 (m, 2 H), 1.74–1.68 (m, 8 H), 1.49 (s, 9 H) and 1.00–0.74 (m, 3 H); δ_F −15.31 (s, 0.76 × 3 F, *E*) and −14.97 (s, 0.24 × 3 F, *Z*); *m/z* 313 ($M^+ - 1$, 3%), 279 (8), 250 (3), 185 (3) and 57 (100) (Found: C, 53.7; H, 6.9. $C_{14}H_{22}ClF_3O_2$ requires C, 53.42; H, 7.04%).

***tert*-Butyl 2-chloro-3-(trifluoromethyl)hept-2-enoate 4d.** Obtained as mixture of E- and *Z-isomers*; bp 85 °C/10 mmHg; ν_{max}/cm^{-1} 1745, 1650, 1460, 1300 and 1100; δ_H 2.31 (t, *J* 7.5, 2 H), 1.73–1.23 (m, 13 H) and 0.88 (t, *J* 7.0, 3 H); δ_F −16.33 (s, 0.73 × 3 F, *E*) and −15.83 (s, 0.27 × 3 F, *Z*); *m/z* 286 (M^+, 3%), 215 (5), 213 (16) and 57 (100) (Found: C, 50.2; H, 6.3. $C_{12}H_{18}ClF_3O_2$ requires C, 50.27; H, 6.33%).

***tert*-Butyl 2-chloro-4,4,4-trifluoro-3-phenylbut-2-enoate 4e.** Obtained as mixture of E- and *Z-isomers*; bp 71 °C/1.5 mmHg; ν_{max}/cm^{-1} 1740, 1640, 1370 and 1100; δ_H 7.51–7.17 (m, 5 H), 1.58 (s, 0.44 × 9 H, *Z*) and 1.15 (s, 0.56 × 9 H, *E*); δ_F −16.63 (s, 0.56 × 3 F, *E*) and −16.39 (s, 0.44 × 3 F, *Z*); *m/z* 306 (M^+, 1%), 251 (18), 233 (24), 185 (18) and 57 (100) (Found: C, 54.6; H, 4.4. $C_{14}H_{14}ClF_3O_2$ requires C, 54.82; H, 4.60%).

***tert*-Butyl 2-chloro-5-phenyl-3-(trifluoromethyl)pent-2-en-4-ynoate 4f.** Obtained as mixture of E- and *Z-isomers*; bp 95 °C/1 mmHg; ν_{max}/cm^{-1} 2200, 1740, 1580, 1370, 1320 and 1100; δ_H 7.59–7.29 (m, 5 H), 1.57 (s, 0.7 × 9 H, *Z*) and 1.56 (s, 0.3 × 9 H, *E*); δ_F −16.49 (s, 0.3 × 3 F, *E*) and −15.31 (s, 0.7 × 3 F, *Z*); *m/z* 330 (M^+, 13%), 296 (7), 274 (33) and 57 (100) (Found: C, 58.0; H, 4.2. $C_{16}H_{14}ClF_3O_2$ requires C, 58.11; H, 4.27%).

2-Chloro-3-(trifluoromethyl)non-2-en-4-ynenitrile 4g. *E*-Isomer; bp 82 °C/10 mmHg; ν_{max}/cm^{-1} 2200, 1580, 1280 and 1100; δ_H 2.43 (t, *J* 6.5, 2 H), 1.80–1.10 (m, 4 H) and 0.87 (t, *J* 7.0, 3 H); δ_F −15.70 (s, 3 F); *m/z* 236 ($M^+ + 1$, 42%), 235 (M^+, 9), 200 (60) and 43 (100) [Found: (M − Cl), 200.0692. (*M* − Cl) requires *m/z*, 200.0687].

2-Chloro-5-phenyl-3-(trifluoromethyl)pent-2-en-4-ynenitrile 4h. *E*-Isomer; bp 78 °C/1.5 mmHg; ν_{max}/cm^{-1} 2200, 1570, 1360, 1265 and 1100; δ_H 7.67–7.31 (m, 5 H); δ_F −16.07 (s, 3 F); *m/z* 255 (M^+, 100%) and 220 (11) [Found: (M − Cl), 200.0335. (*M* − Cl) requires *m/z*, 200.0374].

2-Chloro-4-methyl-3-(trifluoromethyl)hex-2-enenitrile 4i. Obtained as a mixture of *E*- and *Z*-isomers; bp 166 °C; ν_{max}/cm^{-1} 2200, 1600, 1460, 1340 and 1100; δ_H 3.33–2.78 (m, 1 H), 1.88–1.40 (m, 2 H), 1.31–1.15 (m, 3 H) and 0.94 (t, *J* 7.4, 3 H); δ_F −17.91 (s, 0.78 × 3 F, *E*) and −17.32 (s, 0.22 × 3 F, *Z*); *m/z* 211 (M^+, 11%), 201 (100) and 183 (93) (Found: M^+, 211.0461. $C_8H_9ClF_3N$ requires *M*, 211.0376).

2-Chloro-3-(trifluoromethyl)hept-2-enenitrile 4j. Obtained as a mixture of *E*- and *Z*-isomers; bp 160 °C; ν_{max}/cm^{-1} 2200, 1620, 1460, 1340 and 1100; δ_H 2.51 (t, *J* 7.2, 2 H), 1.76–1.16 (m, 4 H) and 0.96 (t, *J* 7.2, 3 H); δ_F −14.47 (s, 0.52 × 3 F, *E*) and −14.03 (s, 0.48 × 3 F, *Z*); *m/z* 212 ($M^+ + 1$, 100%), 169 (28), 142 (7) and 43 (45) [Found: $(M - H)^+$, 210.0371. $C_8H_8ClF_3N$ (*M* − H) requires *m/z*, 210.0297].

***tert*-Butyl 2-bromo-3-(trifluoromethyl)non-2-enoate 5.** E-*Isomer*; bp 95 °C/10 mmHg; ν_{max}/cm^{-1} 1735, 1640, 1370, 1340 and 1100; δ_H 2.32 (t, *J* 7.0, 2 H), 1.52 (9 H, s), 1.68–1.08 (m, 8 H) and 0.88 (t, *J* 7.0, 3 H); δ_F −15.06 (s, 3 F); *m/z* 360 (M^+, 2%), 296 (7), 231 (2), 214 (36) and 43 (100) (Found: C, 46.6; H, 6.4. $C_{14}H_{22}BrF_3O_2$ requires C, 46.81; H, 6.17%).

***tert*-Butyl 2-bromo-5-phenyl-3-(trifluoromethyl)pent-2-en-4-ynoate 6.** Obtained as mixture of E- and *Z-isomers*, *E*/*Z* 14:86; bp 110 °C/1.5 mmHg; ν_{max}/cm^{-1} 2200, 1730, 1370, 1320 and 1100; δ_H 7.62–7.12 (m, 5 H), 1.60 (s, 0.86 × 9 H, *Z*) and 1.54 (s, 0.14 × 9 H, *E*); δ_F −16.24 (s, 0.14 × 3 F, *E*) and −15.41 (s, 0.86 × 3 F, *Z*); *m/z* 374 (M^+, 7%), 321 (96) and 319 (100) (Found: C, 51.2; H, 3.7. $C_{16}H_{14}BrF_3O_2$ requires C, 51.22; H, 3.76%).

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