A facile one-pot synthesis of trifluoromethyl vinyl ethers

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Abstract

Enynyl, cycloalkenyl and heterocyclic vinyl ethers may be synthesized with high stereoselectivity by the reaction of organolithium compounds with fluorinated α-alkoxyl-β-ketophosphonium salts in 40–85% yield (three steps).

Introduction

Vinyl ethers are potentially useful intermediates in synthetic organic chemistry since they can undergo a variety of synthetically useful organic transformations and have been widely used in the synthesis of biologically active compounds [1]. As their fluorinated analogues, some fluorine-containing vinylic ethers show alkylating properties towards nucleophilic agents [2] and perfluoroalkenyl ethers of bile alcohols reduce the interfacial tension between perfluorooctyl bromide and the emulsifying agent Pluronic F-68 [3]. For this reason, reactions leading to the formation of fluorinated vinyl ethers have attracted much attention. However few reports have appeared in the literature concerning the preparation of trifluoromethylated vinyl ethers [4]; indeed, the trifluoromethylated enynyl, cycloalkenyl and heterocyclic vinyl ethers have not been reported previously. Hence, it is of much value to develop an effective method for the preparation of the title compounds.

Experimental

All boiling points are reported uncorrected. Infrared spectra of liquid products were obtained as films on a Shimadzu IR-440 spectrometer. NMR spectra (δ in ppm from TMS for ^{1}H NMR and from external TFA for ^{19}F NMR, positive for upfield shifts) were obtained on a Varian EM-360 at 60 MHz. Mass spectra were recorded on a Finnigan GC-MC-4021 mass spectrometer.

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General procedure for the preparation of trifluoromethylated vinyl ethers (6)

Phosphorane (**2**) generated from the corresponding phosphonium salt (3 mmol) and n-butyllithium (3 mmol) in THF (30 ml) was stirred at −20 °C under nitrogen while methyl iodide (3 mmol) was slowly added. After stirring at 20 °C for 30 min, a second portion of n-butyllithium (3 mmol) was added at −20 °C. The mixture was stirred for a further 30 min, cooled to −78 °C and trifluoroacetic anhydride (1.8 mmol) slowly added until the characteristic ylidic colour disappeared. After this addition and stirring at −78 °C for 15 min, an excess of phenyllithium (2.5 mmol) was added. The mixture was allowed to warm to room temperature and stirred for a further 2 h. The product (**6a**) was isolated by column chromatography on silica gel using petroleum ether (60–90 °C)/ethyl acetate (20:1) as the eluant.

Compound **6a**: 62% yield; b.p., 118 °C/2 mmHg. IR (film): 1670(s); 1120(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 1.57 (3H, q, $J=2$ Hz); 7.06–7.26 (10H, m). ^{19}F NMR (CCl_4/TFA) δ: −19.2 (3F, s). MS *m/e*: 278 (M^+, 71%); 263 (M^+-Me, 4%); 94 ($PhO^+ + 1$, 56%). Analysis: Calcd. for $C_{16}H_{13}F_3O$: C, 69.08; H, 4.67%. Found: C, 69.18; H, 5.11%.

Compound **6b**: 66% yield; b.p., 92 °C/2 mmHg. IR (film): 1665(s); 1120(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 1.78 (3H, q, $J=2$ Hz); 2.20 (3H, s); 5.82 (1H, d, $J=2$ Hz); 6.10 (1H, d, $J=2$ Hz); 7.14 (5H, s). ^{19}F NMR (CCl_4/TFA) δ: −18.3 (3F, s). MS *m/e*: 283 ($M^+ + 1$, 100%); 282 (M^+, 39%); 267 (M^+-Me, 6%). Analysis: Calcd. for $C_{15}H_{13}F_3O_2$: C, 63.85; H, 4.61%. Found: C, 63.54; H, 4.72%.

Compound **6c**: 85% yield; b.p., 116 °C/2 mmHg. IR (film): 2220(w); 1640(s); 1128(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 0.81 (3H, t, $J=6$ Hz); 1.01–1.60 (4H, m); 1.92 (3H, q, $J=2$ Hz); 2.25 (2H, t, $J=6$ Hz); 7.07 (5H, s). ^{19}F NMR (CCl_4/TFA) δ: −17.4 (3F, s). MS *m/e*: 282 (M^+, 62%); 267 (M^+-Me, 11%); 94 ($PhO^+ + 1$, 18%). Analysis: Calcd. for $C_{16}H_{17}F_3O$: C, 68.11; H, 6.02%. Found: C, 68.36; H, 6.31%.

Compound **6d**: 70% yield; b.p., 112 °C/2 mmHg. IR (film): 1660(s); 1120(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 1.57 (3H, q, $J=2$ Hz); 7.10 (9H, s). ^{19}F NMR (CCl_4/TFA) δ: −18.9 (3F, s). MS *m/e*: 313 ($M^+ + 1$, 21%); 312 (M^+, 87%); 277 (M^+-Cl, 5%); 128 (*p*-$ClPhO^+ + 1$, 55%). Analysis: Calcd. for $C_{16}H_{12}ClF_3O$: C, 61.47; H, 3.84%. Found: C, 61.60; H, 3.67%.

Compound **6e**: 77% yield; b.p., 102 °C/2 mmHg. IR (film): 1670(s); 1120(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 1.65 (3H, q, $J=2$ Hz); 6.64–7.14 (7H, s). ^{19}F NMR (CCl_4/TFA) δ: −18.2 (3F, s). MS *m/e*: 318 (M^+, 57%); 128 (*p*-$ClPhO^+ + 1$, 16%). Analysis: Calcd. for $C_{14}H_{10}ClF_3OS$: C, 52.77; H, 3.14%. Found: C, 52.73; H, 3.32%.

Compound **6f**: 62% yield; b.p., 102 °C/2 mmHg. IR (film): 2220(w); 1640(s); 1130(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 0.90 (3H, t, $J=6$ Hz); 1.10–1.65 (4H, m); 1.97 (3H, q, $J=2$ Hz); 2.33 (2H, t, $J=6$ Hz); 7.12 (4H, s). ^{19}F NMR (CCl_4/TFA) δ: −17.2 (3F, s). MS *m/e*: 316 (M^+, 39%); 281 (M^+-Cl, 7%); 128 (*p*-$ClPhO^+ + 1$, 12%). Analysis: Calcd. for $C_{16}H_{16}ClF_3O$: C, 60.69; H, 5.05%. Found: C, 60.89; H, 5.20%.

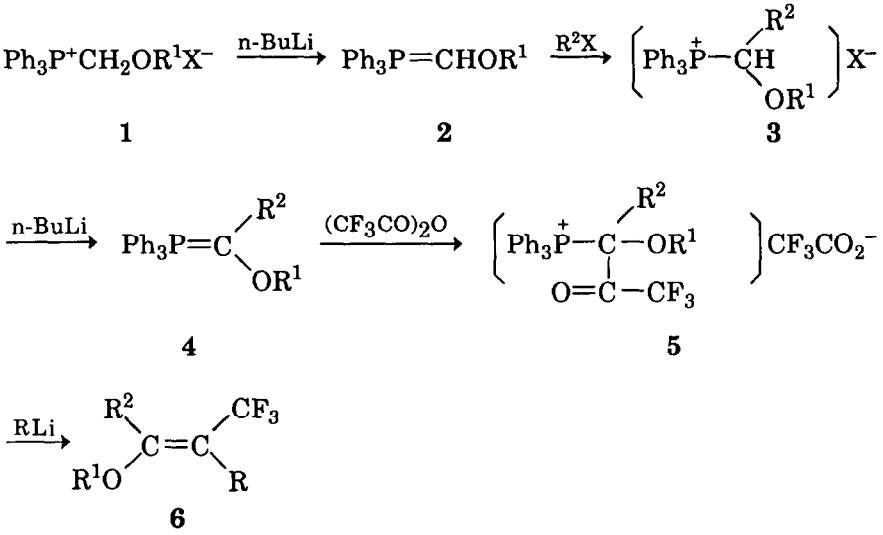
Compound **6g**: 40% yield; b.p., 106 °C/2 mmHg. IR (film): 1680(s); 1110(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 1.60–1.80 (4H, m); 1.80–2.10 (2H, m); 3.92 (2H, t, $J=6$ Hz); 7.10 (5H, s). ^{19}F NMR (CCl_4/TFA) δ: −20.2 (3F, s). MS *m/e*: 242 (M^+, 94%); 173 ($M^+ - CF_3$, 29%). Analysis: Calcd. for $C_{13}H_{13}F_3O$: C, 64.48; H, 5.37%. Found: C, 63.99; H, 5.35%.

Compound **6h**: 57% yield; b.p., 92 °C/2 mmHg. IR (film): 2240(w); 1630(s); 1120(s) cm^{-1}. ^1H NMR (CCl_4/TMS) δ: 0.82 ($E+Z$) (3H, t, $J=6$ Hz); 1.10–1.76 ($E+Z$) (8H, m); 2.10–2.55 ($E+Z$) (4H, m); 3.80–4.00 ($E+Z$) (2H, m). ^{19}F NMR (CCl_4/TFA) δ: [(−18.3)(*E*)+(−21.6)(*Z*)](3F, s). MS *m/e*: 246 (M^+, 60%); 217 ($M^+ - Et$, 20%); 203 ($M^+ - Pr$, 24%); 177 ($M^+ - CF_3$, 13%). Analysis: Calcd. for $C_{13}H_{17}F_3O$: C, 63.43; H, 6.91%. Found: C, 63.41; H, 6.90%.

Results and discussion

Recently we found that fluorinated β-ketophosphonium salts reacted with nucleophiles to give fluoroalkenes [5] and fluoroenynes [6]. In our continuing investigations to exploit the synthetic utility of fluorinated β-ketophosphonium salts in organic synthesis, we now wish to report a convenient one-pot synthesis of trifluoromethyl vinyl ethers.

The reaction sequence is as follows:



6a: R^1 = Ph; R^2 = Me; R = Ph

6b: R^1 = Ph; R^2 = Me; R = Me 

6c: R^1 = Ph; R^2 = Me, R = $Bu^n C{\equiv}C$

6d: R^1 = *p*-ClC_6H_4; R^2 = Me; R = Ph

6e: R^1 = *p*-ClC_6H_4; R^2 = Me; R = 

6f: R^1 = *p*-ClC_6H_4; R^2 = Me; R = $Bu^n C{\equiv}C$

6g: R^1, R^2 = $-(CH_2)_4-$; R = Ph [1]

6h: R^1, R^2 = $-(CH_2)_4-$; R = $Bu^n C{\equiv}C$ [1]

Fluorinated α-alkoxyl-β-ketophosphonium salts (**5**) prepared from the acylation of phosphoranes can readily react with organolithium compounds

TABLE 1

Preparation of trifluoromethylated vinyl ethers (**6**)

Compound	R^1	R^2	R	Method[a]	Yield (%)[b]	*E*:*Z*[c]
6a	Ph	Me	Ph	A	62	100·0
6b	Ph	Me	Me 	A	66	100·0
6c	Ph	Me	$Bu^nC{\equiv}C-$	A	85	100:0
6d	*p*-ClPh	Me	Ph	A	70	100:0
6e	*p*-ClPh	Me		A	77	0:100
6f	*p*-ClPh	Me	$Bu^nC{\equiv}C-$	A	62	100:0
6g	$-(CH_2)_4-$		Ph	B	40	100·0
6h	$-(CH_2)_4-$		$Bu^nC{\equiv}C-$	B	57	61:39

[a]Method A: **1** used as starting material; method B: **3** used as starting material.
[b]Isolated yields.
[c]The ratios of *E*- and *Z*-isomer were estimated on the basis of ^{19}F NMR data (the chemical shift of the trifluoromethyl groups of the *E*-isomer in vinyl ethers is upfield and that of the *Z*-isomer is downfield [4]).

to give trifluoromethyl vinyl ethers in 40–85% yield with high stereoselectivity (Table 1).

This one-pot synthesis of trifluoromethylated vinyl ethers is quite convenient with high stereoselectivity and offers a wide scope since the R group may be alkyl, alkynyl or heterocyclic. Thus, this reaction provides a new method for the preparation of the title compounds which could be useful for elaboration in the synthesis of biologically active compounds.

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