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PREPARATION OF TRIFLUOROMETHYLATED ALLYLIC ALCOHOLS FROM TRIFLUOROACETALDEHYDE AND ORGANOMETALLIC COMPOUNDS

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SUMMARY

A number of allylic alcohols bearing a trifluoromethyl group at the α- or γ-position, and α-trifluoromethylated γ-enols and -ynols were prepared by the reaction of trifluoroacetaldehyde with a variety of organometallic compounds. Most of the Reformatsky- or Grignard-type reactions required promotion by ultrasonic irradiation.

INTRODUCTION

Recently perfluoroalkyl containing organic compounds have received much attention, particularly those bearing a trifluoromethyl group, due to their unique biological activities [1]. However, the direct introduction of a perfluoroalkyl group into organic molecules often proves to be quite difficult and the synthetic procedures available are quite limited.

As part of our continuing study to prepare new useful perfluoroalkyl containing synthetic intermediates by ultrasound promoted perfluoroalkylation [2,3,4], we now report a practical synthetic method for the preparation of trifluoromethyl containing allylic alcohols as well as related enols and ynols from trifluoroacetaldehyde.

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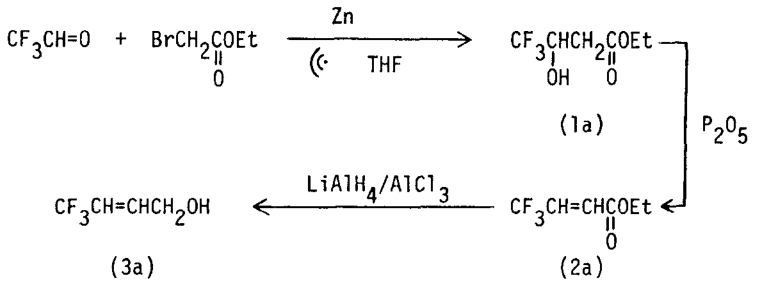
Many routes to a wide variety of allylic alcohols are already known and their synthetic utility is well established [5]. Such, however, is not the case for perfluoroalkyl containing allylic alcohols, which are also expected to be versatile intermediates for perfluoroalkylated organic molecules, as very little work was been carried out to date [2,6].

RESULTS AND DISCUSSION

Preparation of γ-trifluoromethylated allylic alcohols

A Reformatsky-type reaction between trifluoroacetaldehyde and ethyl bromoacetate [6] proceeded at room temperature by the assistance of ultrasonic irradiation. Commercially available zinc powder without any activation and the solvent, tetrahydrofuran, dried over molecular sieve 4A were used. Ethyl 4,4,4-trifluoro-3-hydroxybutyrate (1a) was thus obtained in 62% yield. This trifluoromethylated hydroxyester was dehydrated to the α,β-unsaturated ester (2a) by heating with phosphorus pentoxide [6]. The E/Z ratio of the product was determined by ^{19}F nmr, the identification being based on the well-established coupling constants for substituted trifluoromethyl compounds; $J_{CF_3\text{-}H(trans)} \sim 0.1$, $J_{CF_3\text{-}H(cis)} \sim 2$, and $J_{CF_3\text{-}H(gem)} \sim 8$ [7-9].

The trifluoromethylated acrylic ester (2a) was reduced to the γ-trifluoromethylated allylic alcohol (3a) using lithium aluminum hydride and aluminum chloride in diethyl ether [6].



$$CF_3CH{=}O + BrCH_2\underset{\overset{\|}{O}}{C}OEt \xrightarrow[\text{((· THF}]{Zn} CF_3\underset{OH}{C}HCH_2\underset{\overset{\|}{O}}{C}OEt$$

(1a)

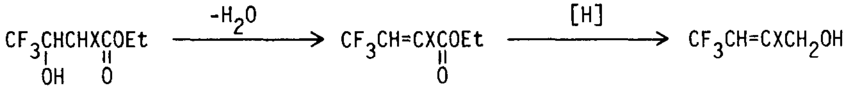
$$\xrightarrow{P_2O_5} CF_3CH{=}CH\underset{\overset{\|}{O}}{C}OEt$$

(2a)

$$\xrightarrow{LiAlH_4/AlCl_3} CF_3CH{=}CHCH_2OH$$

(3a)

In addition to ethyl bromoacetate, ethyl bromofluoroacetate or ethyl 2-bromopropionate were used and the corresponding γ-trifluoromethyl-β-substituted allylic alcohols (3b, 3c) were obtained via (1b), (1c) and (2b), (2c) (Table 1 and 2).



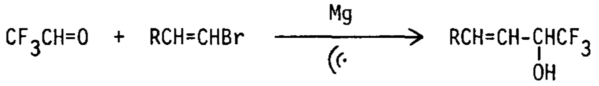
$$CF_3\underset{OH}{CH}CHX\underset{O}{\overset{\|}{C}}OEt \xrightarrow{-H_2O} CF_3CH{=}CX\underset{O}{\overset{\|}{C}}OEt \xrightarrow{[H]} CF_3CH{=}CXCH_2OH$$

(1b) X=F (2b) X=F (3b) X=F

(1c) $X=CH_3$ (2c) $X=CH_3$ (3c) $X=CH_3$

Preparation of α-trifluoromethylated allylic alcohols

Another type of trifluoromethylated allylic alcohol, 1,1,1-trifluoro-3-buten-2-ols (4) were prepared by the Grignard reaction between vinyl bromides and trifluoroacetaldehyde. In this case too, ultrasonic irradiation was very effective and several kinds of α-trifluoromethylated allylic alcohols were obtained in good yields (Table 3).



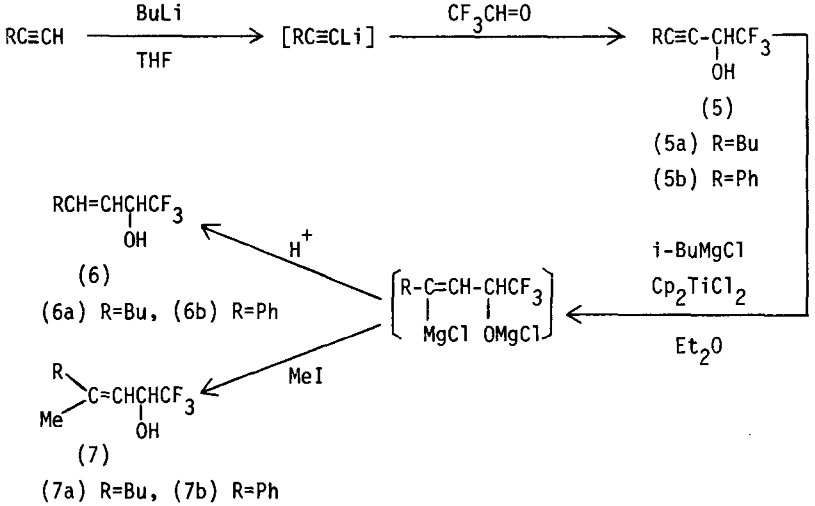
$$CF_3CH{=}O + RCH{=}CHBr \xrightarrow[)))]{Mg} RCH{=}CH\text{-}\underset{OH}{C}HCF_3$$

(4)

(4a) R=H, (4b) R=Me

(4c) R=Ph, (4d) $R=SiMe_3$

Another route to α-trifluoromethylallyl alcohols is the 'hydromagnesiation' [10] of α-trifluoromethyl-β-ynols, which are available by the reaction of lithioalkynes with trifluoroacetaldehyde as shown below:



$$RC{\equiv}CH \xrightarrow[THF]{BuLi} [RC{\equiv}CLi] \xrightarrow{CF_3CH=O} RC{\equiv}C\text{-}\underset{OH}{C}HCF_3$$

(5)

(5a) R=Bu

(5b) R=Ph

$$\xrightarrow[Et_2O]{i\text{-}BuMgCl,\ Cp_2TiCl_2} \left[\underset{MgCl}{R\text{-}C}{=}CH\text{-}\underset{OMgCl}{C}HCF_3\right]$$

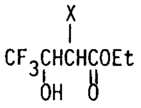
$$\xrightarrow{H^+} RCH{=}CH\underset{OH}{C}HCF_3 \quad (6)$$

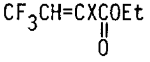
(6a) R=Bu, (6b) R=Ph

$$\xrightarrow{MeI} \underset{Me}{\overset{R}{>}}C{=}CH\underset{OH}{C}HCF_3 \quad (7)$$

(7a) R=Bu, (7b) R=Ph

TABLE 1





Properties of $CF_3CH(OH)CH(X)C(=O)OEt$ (1) and $CF_3CH{=}CXC(=O)OEt$ (2)

Compd.[a] No.	X	B.p. (°C/mmHg)	Yield (E/Z) (%)	^{19}F nmr[b] CF_3 δ ppm
1a	H	93-95/20[c)]	62	2.67
1b (nc)	F	90-92/18	52	-1.72, -0.80(major)[d)]
1c (nc)	Me	123-125/25	67	-1.67, -0.47(major)[d)]
2a	H	112-113	69 (92/2)	E: 3.3 ($J_{CF_3\text{-}CH\ gem}$ 4.3 Hz, $J_{CF_3\text{-}CH\ vic}$ 1.0 Hz) Z: 3.6 ($J_{CF_3\text{-}CH\ gem}$ 3.8 Hz, $J_{CF_3\text{-}CH\ vic}$ 1.0 Hz)
2b (nc)	F	126-129	58 (4/96)	E: 3.0 ($J_{CF_3\text{-}F}$ 7.9 Hz); Z: 2.6 ($J_{CF_3\text{-}F}$ 19.6 Hz)
2c (nc)	Me	125-128	61 (91/9)	E: 3.1 ($J_{CF_3\text{-}H\ gem}$ 4.1 Hz); Z: 3.4 ($J_{CF_3\text{-}H\ gem}$ 3.6 Hz)

[a] Elementary analysis for (1b)(2b) and (1c)(2c) was done for their destined compounds (3b) and (3c).

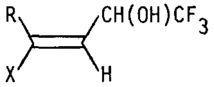
[b] All ^{19}F nmr were run in $CDCl_3$ and chemical shifts are quoted in ppm from external CF_3CO_2H.

[c] Lit: 90-93 °C/20 mmHg [6].

[d] Two signals due to erythro- and threo-isomers appeared.

The alkynylation of trifluoroacetaldehyde proceeded smoothly without aid of ultrasound and 1,1,1-trifluoro-3-octyn-2-ol (5a) and 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (5b) were obtained from 1-hexyne and phenylacetylene in 72 and 74% yield respectively.

Hydromagnesiation of a carbon-carbon triple bond with isobutylmagnesium chloride and a catalytic amount of titanocene dichloride followed by protonation or alkylation is reported to give stereoselectively a carbon-carbon double bond [10]. In our study of the reactions of α-trifluoromethylated ynols, the products (6) and (7) were found to be formed in the Z-form exclusively, based on their nmr spectra (Table 4).



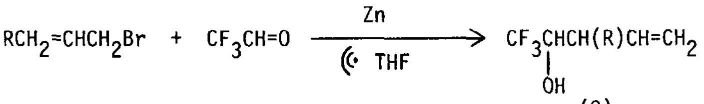
R=Bu, Ph

(6) X=H, (7) X=Me

Preparation of α-trifluoromethylated γ-enols and γ-ynols

Allyl- or propargylmetallic compounds are known to be some of the most useful intermediates in synthetic chemistry. We have found in this case too that ultrasonic irradiation promotes the metallation of allyl or propargyl halides, and the following reaction with trifluoroacetaldehyde.

Allyl bromide and zinc together with trifluoroacetaldehyde in tetrahydrofuran, for example, reacted smoothly under ultrasonic irradiation to give 1,1,1-trifluoro-4-penten-2-ols (8a) in excellent yield.



$$RCH_2{=}CHCH_2Br + CF_3CH{=}O \xrightarrow[\text{((THF}]{Zn} \underset{\displaystyle OH}{CF_3CH}CH(R)CH{=}CH_2$$

(8)

(8a) R=H

(8b) R=Me

(8c) R=Ph

Other substituted allyl bromides, such as 2-butenyl bromide and 3-phenylallyl bromide gave the similar trifluoromethylated homoallyl alcohols (8a) and (8c) respectively (Table 5).

TABLE 2

Properties of $CF_3CH=CXCH_2OH$ (3)

Compd.		B.p.	Yield	ir (OH)	^{19}F nmr[a]	Found (Calcd)	
No.	X	(^oC/mmHg)	(%)	(cm^{-1})	CF_3 δ ppm	C (%)	H (%)
3a	H	128-129[b]	96	3325	-13.0	———	———
3b (nc)	F	76-78/28	97	3340	-12.0	33.78 (33.35)	2.56 (2.80)
3c (nc)	Me	81-83/16	94	3330	-14.0	42.48 (42.87)	5.31 (5.04)

[a] See Table 1, [b]; [b] Lit: 127-129 °C [6]

TABLE 3

Properties of $RCH=CHCH(OH)CF_3$ (4)

Compd.		B.p.	Yield	ir (OH)	^{19}F nmr[a]	Found (Calcd)	
No.	R	(^oC/mmHg)	(%)	(cm^{-1})	CF_3 δ ppm	C (%)	H (%)
4a	H	99-100[b]	70	3330	2.0 d	———	———
4b (nc)	Me	120-123	49	3335	-1.2 d	43.11 (42.86)	4.86 (5.04)
4c (nc)	Ph	76-77/1	57	3335	2.0 d	59.76 (59.41)	4.63 (4.49)
4d (nc)	$SiMe_3$	76-77/67	62	3325	-1.0 d	49.56 (49.41)	7.86 (7.70)

[a] See Table 1, [b] ; [b] Lit: 91.5 °C [11].

TABLE 4

Properties of $RC(R')=CHCH(OH)CF_3$: $RCH=CHCH(OH)CF_3$ (6) and $RC(Me)=CHCH(OH)CF_3$ (7)

Compd.		B.p.	Yield	ir (OH)	^{19}F nmr[a]	Found (Calcd)	
No.	R	(^oC/mmHg)	(%)	(cm^{-1})	CF_3 δ ppm	C (%)	H (%)
6a (nc)	Bu	82-84/23	60	3330	1.3 d	53.02 (52.74)	7.42 (7.19)
6b (nc)	Ph	78-80/3	53	3340	0.3 d	59.18 (59.41)	4.72 (4.49)
7a (nc)	Bu	82-85/21	72	3330	0.8 d	55.31 (55.09)	7.86 (7.71)
7b (nc)	Ph	84-86/2	63	3335	0.6 d	60.96 (61.11)	4.99 (5.13)

[a] See Table 1, [b]

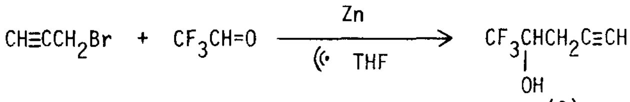
TABLE 5

Properties of $CH_2=CHCH(R)CH(OH)CF_3$

Compd.		B.p.	Yield	ir (OH)	^{19}F nmr[a]	Found (Calcd)	
No.	R	(^oC/mmHg)	(%)	(cm^{-1})	CF_3 δ ppm	C (%)	H (%)
8a (nc)	H	100-101	76	3335	2.0	42.59 (42.86)	5.30 (5.04)
8b (nc)	Me	60/130	95	3335	-2.8, -3.0	46.95 (46.76)	5.76 (5.89)
8c (nc)	Ph	63-65/1.7	80	3340	-3.5, -5.0	61.42 (61.11)	5.32 (5.13)

[a] See Table 1, [b]

Propargyl bromide and trifluoroacetaldehyde in a zinc-tetrahydrofuran system with ultrasound also reacted smoothly to give α-trifluoromethylated γ-ynol (9).



$$CH{\equiv}CCH_2Br + CF_3CH{=}O \xrightarrow[((\cdot\ THF]{Zn} CF_3\underset{OH}{CH}CH_2C{\equiv}CH$$

(9)

EXPERIMENTAL

Ethyl 4,4,4-trifluoro-3-hydroxybutyrate (1a)

Into a 100 ml 3-necked flask equipped with a dry-ice condenser, a gas inlet tube and a thermometer, were placed commercially available zinc powder (3.92 g, 0.06 g-atom), ethyl bromoacetate (5.01 g, 30 mmol) and tetrahydrofuran (30 ml). Trifluoroacetaldehyde (1.96 g, 20 mmol) generated from the hydrate by heating with conc. H_2SO_4 was bubbled into the mixture under ultrasonic irradiation. After 2 h of irradiation, the reaction mixture was poured into a 2% aq. HCl solution, an oily material separated and this was extracted with diethyl ether. The ethereal extract was dried over magnesium sulfate, and the solvent removed. Distillation gave ethyl 4,4,4-trifluoro-3-hydroxybutyrate in a yield of 62% (2.30 g), bp 93 - 95 ^{o}C/20 mmHg.

Ethyl 4,4,4-trifluoro-2-butenate (2a)

Ethyl 4,4,4-trifluoro-3-hydroxybutyrate (6.96 g, 40 mmol) was placed in a 30 ml round bottle flask and phosphorus pentoxide (3.17 g, 22.4 mmol) was added in one portion. The reaction mixture was stirred for 1 h, and then distilled to give ethyl 4,4,4-trifluoro-2-butenoate in a yield of 69% (4.3 g), bp 112 - 113 ^{o}C.

4,4,4-Trifluoro-2-buten-1-ol (3a)

Lithium aluminum hydride (0.75 g, 20 mmol) in dry ether (10 ml) was added to anhydrous aluminum chloride (0.89 g, 6.7 mmol) in dry ether (20 ml) at 0 ^{o}C. After 15 min of stirring, ethyl 4,4,4-trifluoro-2-butenoate (1.56 g, 10 mmol) in dry ether (6 ml) was added at 0 ^{o}C. After a further

30 min of stirring at 0 °C, the reaction mixture was quenched with Na_2SO_4 saturated aqueous solution. An oily material was extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave 4,4,4-trifluoro-2-buten-1-ol in a yield of 87%, bp 128 - 129 °C.

^{19}F nmr ($CDCL_3$): δ -13.0 (CF_3). ^1H nmr ($CDCl_3$): δ 4.1 (CH_2), 5.90 6.53 (CH=). M^+ 125.

1,1,1-Trifluoro-3-buten-2-ol (4a)

A 100 ml 3-necked flask containing magnesium (1.26 g, 52 mmol), vinyl bromide (5.4 g, 50 mmol) and tetrahydrofuran (45 ml) was equipped with a dry-ice condenser, a thermometer and a gas inlet tube. Trifluoroacetaldehyde (2.94 g, 30 mmol) was bubbled into the above mixture under ultrasonic irradiation. After 3 h of irradiation, the reaction mixture was poured into a 2% aq.HCl solution, and then an oily material was extracted with diethyl ether. Distillation gave 1,1,1-trifluoro-3-buten-2-ol in a yield 70%, bp 99 - 100 °C.

^{19}F nmr ($CDCl_3$) : δ 2.0 (CF_3, d, $J_{CF_3\text{-}CH}$ 5.6 Hz). ^1H nmr ($CDCl_3$): δ 4.43 (CH-OH, q), 4.67 (OH), 5.33 - 6.10 ($CH=CH_2$). M^+ 125.

1,1,1-Trifluoro-3-octyn-2-ol (5a) (nc)

1-Hexyne (6.2 g, 76 mmol), n-butyl lithium (52 ml, 1.5 M in hexane) and trifluoroacetaldehyde (7 g, 71 mmol) were used in the above reaction, and worked up similarly. Distillation gave 1,1,1-trifluoro-3-octyn-2-ol in a yield of 72%, bp 83 - 85 °C/21 mmHg.

^{19}F nmr ($CDCl_3$): δ 2.3 (CF_3, d, $J_{CF_3\text{-}CH}$ 5.6 Hz). ^1H nmr ($CDCl_3$) : δ 0.9, 1.50, 2.30 (9H), 3.70 (OH), 4.73 (CH).

Analysis: Found: C, 53.37; H, 6.39%. $C_8H_{11}OF_3$ requires C, 53.33; H, 6.15%.

1,1,1-Trifluoro-4-phenyl-3-butyn-2-ol (5b) (nc)

Into a solution of phenylacetylene (4.08 g, 40 mmol) and dry ether (30 ml), n-butyllithium (27 ml, 1.5 M in hexane) was added slowly at -78 °C. Trifluoroacetaldehyde (3.7 g, 38 mmol) was bubbled into the above mixture at that temperature. After 2 h of stirring at -78 °C, the reaction mixture was allowed to warm to room temperature and was then poured into a 2% aq. HCl solution. An oily material was separated and extracted with diethyl ether. After the ethereal solution was dried over magnesium sulfate, the solvent was removed. Distillation gave 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol in a yield of 74%, bp 82 °C/1.8 mmHg.

^{19}F nmr (CDCl$_3$): δ 0.3 (CF$_3$, d, $J_{CF_3\text{-}CH}$ 6.6 Hz). ^{1}H nmr (CDCl$_3$): δ 3.83 (OH), 4.87 (CH, q), 7.37 (Ar-H).

Analysis: Found: C, 59.74; H, 3.86%. $C_{10}H_7OF_3$ requires C, 60.01, H, 3.53%.

(Z)-1,1,1-Trifluoro-4-phenyl-3-buten-2-ol (6b) (nc)

Into a mixture solution of isobutylmagnesium chloride formed from isobutyl chloride (2.34 g, 25 mmol) and magnesium (0.66 g, 27 mmol) in dry ether (30 ml) at 0 °C, dichlorobis[π-cyclopentadienyl]titanium (0.14 g, 0.56 mmol), and then 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (2 g, 10 mmol) were added slowly at 0 °C. After 1 h of stirring at that temperature, the reaction mixture was poured into a 2% aq. HCl and the oily material which separated was extracted with diethyl ether. After removing the solvent, distillation gave (Z)-1,1,1-trifluoro-4-phenyl-3-buten-2-ol in a yield of 53%, bp 78 - 80 °C/3 mmHg.

^{19}F nmr (CDCl$_3$): δ 0.3 (CF$_3$, d, $J_{CF_3\text{-}CH}$ 6.6 Hz). ^{1}H nmr (CDCl$_3$): δ 4.10 (OH), 4.97 (CH, d, q, $J_{CH\text{-}CH=}$ 9,8 Hz), 5.83 (CH=, d, q, $J_{CH=\text{-}CH=}$12 Hz), 7.0 (=CH, d), 7.50 (Ar-H).

(Z)-1,1,1-Trifluoro-4-phenyl-3-penten-2-ol (7b) (nc)

Into a mixture of isobutylmagnesium chloride formed from isobutyl chloride (3.74 g, 40 mmol) and magnesium (0.97 g, 40 mmol) in dry ether (40 ml) at 0 °C, dichlorobis[π-cyclopentadienyl]titanium (0.22 g, 0.9 mmol) and 1,1,1-trifluoro-4-phenyl-3-butyn-2-ol (2 g, 10 mmol) were added at room temperature. After 4 h of stirring at room temperature, the solvent was removed under reduced pressure for 30 min. Into the reaction vessel, dry tetrahydrofuran (20 ml), then methyl iodide (12.7 g, 90 mmol) were added slowly. After stirring overnight, the reaction mixture was poured into a 2% aq. HCl solution, and the oily material which separated was extracted with diethyl ether. After removing the solvent, distillation gave (Z)-1,1,1-trifluoro-4-phenyl-3-penten-2-ol in a yield of 63%, bp 84 - 86 °C/2 mmHg.

^{19}F nmr ($CDCl_3$): δ 0.6 (CF_3, d, J_{CF_3-CH} 5.4 Hz). ^1H nmr ($CDCl_3$): δ 2.17 (CH_3), 3.17 (OH), 4.47 (CH, d, q, $J_{CH-CH=}$ 9.4 Hz), 5,67 (CH=, d), 7.43 (Ar-H).

1,1,1-Trifluoro-3-methyl-4-penten-2-ol (8b) (nc)

Into a mixture of crotyl bromide (8.2 g, 63 mmol), zinc powder (4.6 g, 0.07 g-atom) and tetrahydrofuran (80 ml), trifluoroacetaldehyde (3.1 g, 32 mmol) was bubbled under ultrasonic irradiation. After 2 h, the reaction mixture was poured into a 2% aq. HCl and worked up as previously described. Distillation gave 1,1,1-trifluoro-3-methyl-4-penten-2-ol in a yield of 95%, bp 60 °C/130 mmHg.

^1H nmr ($CDCl_3$): δ 3.10 (CH_3), 2.60 ($C\underline{H}CH_3$), 3.90 ($C\underline{H}OH$), 4.31 (OH), 5.10, 5.80 ($CH=CH_2$).

1,1,1-Trifluoro-4-pentyn-2-ol (9) (nc)

Into a mixture of propargyl bromide (3.46 g, 29 mmol), zinc powder (2.3 g, 0.035 g-atom) and tetrahydrofuran (60 ml), trifluoroacetaldehyde (1.9 g, 19 mmol) was bubbled under ultrasonic irradiation. After 1 h, the reaction mixture was poured into a 2% aq. HCl and worked up as previously described. Distillation gave 1,1,1-trifluoro-4-pentyn-2-ol in a yield of 65%, bp 95 - 96 °C.

^{19}F nmr ($CDCl_3$): δ 3.2 (CF_3, d, J_{CF_3-CH} 6.6 Hz). ^1H nmr ($CDCl_3$): δ 2.1 ($\equiv CH$, t, J_{CH-CH_2} 3 Hz), 2.57 (CH_2, d, d, J_{CH_2-CH} 7.5 Hz), 4.10 (CH, d, q), 5.37 (CH).

Analysis: Found: C, 43.66; H, 3.81%. $C_5H_5OF_3$ requires C 43.49; H, 3.65%.

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