Journal of Fluorine Chemistry, 49 (1990) 401–408

Received February 7, 1990, accepted April 17, 1990

4-FLUORO-2-BUTYNAL. PREPARATION AND SOME EXAMPLES OF DIENOPHILIC PROPERTIES

A. KHANOUS, A. GORGUES*

Laboratoire de Synthèse Organique et d'Electrochimie, Ensemble Scientifique, Université d'Angers, 2 Boulevard Lavoisier, 49045 Anger Cedex (France)

and J. COUSSEAU*

Laboratoire de Chimie Organique, Ensemble Scientifique, Université d'Angers, 2 Boulevard Lavoisier, 49045 Angers Cedex (France)

SUMMARY

4-Fluoro-2-butynal FCH_2-C≡C-CHO (**5**) is prepared in good yield by formolysis of the corresponding fluoro-acetal FCH_2-C≡C-CH$(OEt)_2$ (**4**) The dienophilic properties of (**5**) are investigated towards 2,3-dimethyl-1,3-butadiene (**6**), cyclopentadiene (**7**) and 1,3-cyclohexadiene (**8**) [possible hazards during the reaction with (**6**)] The results emphasize the activating effect of the FCH_2 group on the electrophilic character of the -C≡C- bond in (**5**)

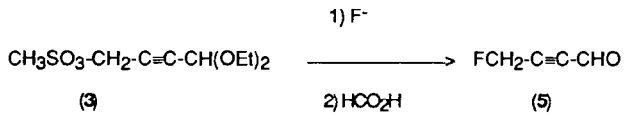
INTRODUCTION

Electrophilic alkynes are attractive synthetic intermediates, especially when the -C≡C- bond bears an aldehyde group [1-4]. Following our studies in this field, we became interested in 4-fluoro-2-butynal (**5**) which can be a useful reagent for synthesizing fluoromethyl substituted molecules. In particular, Diels-Alder reactions of (**5**) seemed to be promising since dienophilic properties of the CHO-activated triple bond might be enhanced by the vicinal position of the highly electronegative fluorine atom [5-7] We report here the preparation and the careful isolation of the rather unstable [8] fluorotetrolic aldehyde (**5**), and show the latter to be a fairly good dienophile

0022-1139/90/$3 50

RESULTS AND DISCUSSION

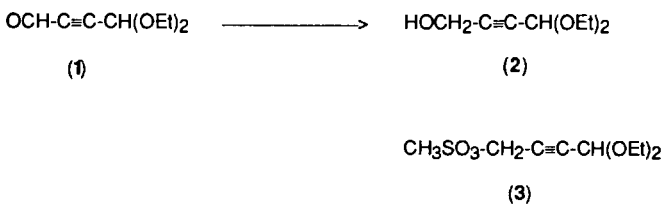
The synthetic route we used for obtaining (5) utilizes two key steps substitution of the methanesulfonate group for the fluoro group from 1,1-diethoxy-4-methylsulfonyloxy-2-butyne (3), followed by the formolysis of the obtained fluorinated acetal (4) into the expected (5)



Preparation of CH_3SO_3-CH_2-C≡C-$CH(OEt)_2$ (3)

Previously this compound (3) was obtained by reaction of 1-methylsulfonyloxy-2- propyne and triethyl orthoformate according to the Howk-Sauer's procedure [9] In fact this method did not appear to us to be quite reproducible and safe, an important degradation, generally accompanied with explosion, was observed in the end of the distillation of (3) whose yield did not exceed 20%

We preferred the following sequence .



4,4-Diethoxy-2-butynal (1), readily obtained by formolysis of 1,1,4,4-tetraethoxy-2-butyne [10], is reduced in good yield by $NaBH_4$ in methanol at 0°C, thus leading to 4,4-diethoxy-2-butyn-1-ol (2) (over 90% as crude product) Then the alcohol (2) is transformed into the corresponding methanesulfonate (3) in 90% yield, according to the Crossland-Servis method [11], the crude product is pure enough for being used in the following step

Preparation of FCH_2-C≡C-CHO (5)

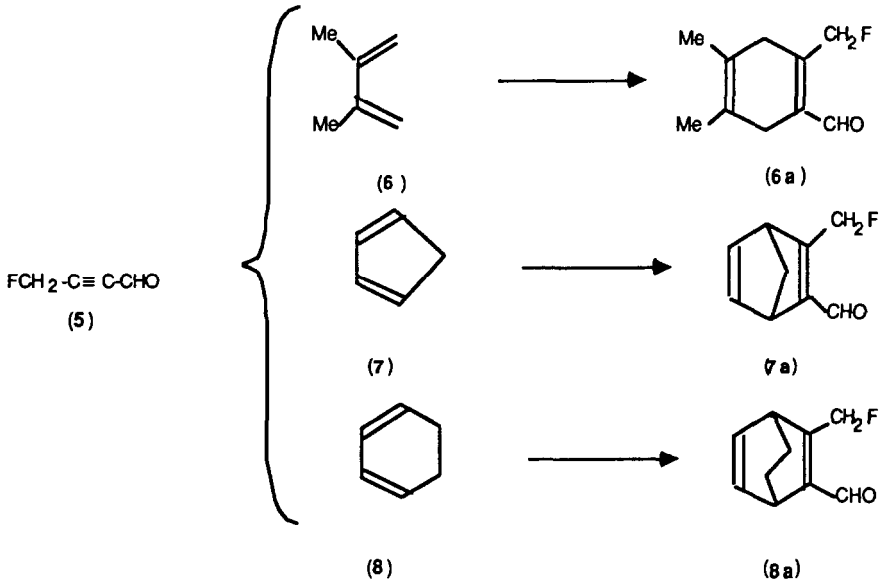
Using Bu_4NF $3H_2O$ (TBAF) as fluorinating agent [12] allows us to obtain the fluoro- acetal (4) from the corresponding methanesulfonate $CH_3SO_3CH_2$-C≡C-$CH(OEt)_2$ (3), the reaction proceeds smoothly in toluene at 95°C, giving rise to the compound (4) with a 70% yield (crude product) in 40 h

4-Fluoro-2-butynal (5) was readily formed by formolysis [2] of (4) (followed by ^1H NMR) in the presence of an excess of dry formic acid The isolation of (5) is somewhat difficult and requires

several steps. Firstly, after dissolving the reaction mixture in cold diethyl ether, the unreacted formic acid is gently neutralized with aq. Na_2CO_3, and the aqueous phase is extracted many times with diethyl ether. Then, after drying and evaporating under normal pressure, the pressure is reduced little by little under nitrogen and the residue is distilled off, affording (5) as a light yellow, very lachrymatory, liquid which rapidly darkens unless stored at -20°C.

Diels-Alder reactions

The dienophilic character of (5) was investigated towards 2,3-dimethyl-1,3-butadiene (DMB) (6), cyclopentadiene (CPD) (7) and 1,3-cyclohexadiene (CHD) (8) These reactions were performed, both from the formic acid medium where (5) is formed after the formolysis of the acetal (4) and/or from isolated pure (5) under neutral conditions; in the latter case, when (6) is the diene, the reaction must be stopped before completion in order to avoid explosive decomposition



The results (Table I) clearly show that (5) is a good dienophile, the expected Diels-Alder cycloadducts (6a), (7a) and (8a) being readily obtained

As expected from the classification of dienes reactivity towards tetracyanoethylene and maleic anhydride as the dienophiles [13], cyclopentadiene (7) is the most reactive diene, while 2,3-dimethyl-1,3-butadiene (6) and 1,3-cyclohexadiene (8) display roughly similar reactivities Under acidic conditions, compared to neutral ones, the Diels-Alder reaction rates are slightly enhanced by acid catalysis [1,4] but the yields are lowered in the case of acid sensitive dienes and/or cycloadducts (Table I).

TABLE I

Formation of the cycloadducts (6a), (7a) and (8a)

	Acidic medium			Neutral medium		
	Temp (°C)	Time (hr)	Yield (%)	Temp. (°C)	Time (hr)	Yield (%)
(6a)	40	1	degrad.	40	48	80
(7a)	r.t.	(*)	40	-25-0	0.2	87
(8a)	40	30	94	40	36	90

(*) instantaneous.

In an attempted experimental rationalization of comparative dienophilicity of α–acetylenic aldehydes R-C≡C-CHO towards (8) (neutral conditions), fluorotetrolic aldehyde (5) (R=CH_2F) appears as an activated alkyne far less reactive than the highly electron deficient alkynals with R = CHO, CO_2Et, $CONMe_2$, but slightly better than the fairly good dienophile with R= $CH(OEt)_2$ [2,4] (Table II).

TABLE II

Reaction of CHD (8) with various α-acetylenic aldehydes under neutral conditions

R-C≡C-CHO	Temp. (°C)	Time (hr)	Adduct (%)	Ref.
R = CHO	20	1	75	4
= CO_2Et	20	2	89	2
= $CONMe_2$	46	2	57	2
= CH_2F	40	36	90	this work
= $CH(OEt)_2$	80	10	42	2

EXPERIMENTAL

The IR spectra were run on a Beckman Acculab 2 spectrometer The ^1H NMR (60 MHz) and ^{19}F NMR (84.7 MHz) were recorded respectively with a Varian EM 360 and a JEOL FX-90 instruments. Chemical shifts are reported in δ units downfield relative to internal Me_4Si for ^1H NMR and external $CFCl_3$ for ^{19}F NMR; the coupling constants (J) are expressed in hertz (Hz) High-resolution mass spectra (HRMS) were obtained on a Varian MAT 311 mass spectrometer at an ionization potential of 70 eV. Elemental analyses were carried out by The Service Central d'Analyse (CNRS)

Formic acid used in the formolysis reactions was previously dried over anhydrous $CuSO_4$.

4,4 -Diethoxy-2-butyn-1-ol (2)

To a solution of 4,4-diethoxy-2-butynal (1) [10] (1 44 g, 10 mmol) in methanol (10 mL), cooled to 0°C, is added under stirring sodium borohydride (0.19 g, 5 mmol) by portions in 15 min , and stirring is kept for a further 30 min period. Then the reaction mixture is poured into dichloromethane (40 mL) and washed with water (3 x 20 mL), the aqueous phase is extracted with dichloromethane, and the combined organic extracts are dried (anhydrous Na_2SO_4), giving 1.43 g (90 5%) crude 4,4-diethoxy-2-butyn-1-ol (2); vacuum distillation provides pure (2) (1.1 g, 69.5 %) as a colourless liquid, b p. 88.5-89°C (4 mm Hg) [litt. [14], b p. 100-102° C (1 mm Hg)]. IR (neat). 3420, 2250 and 2295 (possible Fermi resonance). ^1H NMR (CCl_4) 1 23 (t, J=7, 6H), 3.00 (t, J=4 5, 1H), 3.65 (m, 4H), 4.25 (dd, J=4 5 and J= .5, 2H), 5 25 (t, J=1.5, 1H)

4,4 -Diethoxy-1-methanesulfonyloxy 2-butyne (3)

Methanesulfonyl chloride (0.36 g, 3.14 mmol) is added dropwise at -10°C in 30 min. to a stirred solution of 4,4-diethoxy-2-butyn-1-ol (2) (0 45 g, 2 85 mmol) and triethylamine (0.44 g, 4,37 mmol) in CH_2Cl_2 (14 6 mL) After a further stirring for 15 min. at 0°C, the reaction mixture is poured into ice water (20 mL) The extracted organic phase is washed with a diluted aq. H_2SO_4 solution, then with water until pH 7, and dried over anhydrous Na_2SO_4. After evaporation, 0 61 g (90.7%) of 4,4-diethoxy-1-methanesulfonyloxy-2-butyne (3) is obtained (purity checked by ^1H NMR, IR and mass spectrometry). HRMS. m/e $[M-H]^{\cdot +}$ Calcd. for $C_9H_{16}O_5S$: 235 06401; found. 235.0640. IR (neat) : no band near 2200. ^1H NMR (CCl_4)· 1.20 (t, J = 7, 6H), 3 08 (s, 3H), 3 60 (m, 4H), 4.85 (d, J=1.6, 2H), 5.20 (t, J=1.6, 1H).

4,4 -Diethoxy-1-fluoro-2-butyne (4) (nc)

Bu_4NF $3H_2O$ (4.3 g, 13.65 mmol) is added to a solution of methanesulfonate (3) (2 93 g, 12 41 mmol) in toluene (15 mL) This heterogeneous mixture is heated under stirring at 90-95°C, from NMR analysis of the reaction mixture, a 70% conversion of (3) into the fluoro derivative (4) is observed after 40 hrs and does not appear to increase any more Toluene is evaporated under reduced pressure at ca 30°C and replaced by dichloromethane (30 mL) . The reaction mixture is then washed with water and the extracted organic phase dried over anhydrous Na_2SO_4 Pure 4,4-diethoxy-1-fluoro-2-butyne (4) is obtained (1 19 g, 60%) by distillation under reduced pressure b p 64°C (4.5 mm Hg) HRMS. m/e $[M-H]^+$ Calcd. for $C_8H_{13}O_2F$: 159 0821, found 159 0812. IR (neat) : no band at 2200 cm^{-1}. ^1H NMR (CCl_4) 1 2 (t, J = 7, 6H), 3 6 (m, 4H), 4 95 (dd, J_{HH}= 1 4, J_{HF} = 48, 2H), 5 18 (dt, J_{HH}= 1 4, J_{HF} = 4 8, 1H) ^{19}F NMR (CCl_4) -218.5 (td, J_{HF}= 47, J_{HH} = 5 1)

4-Fluoro-2-butyn-1-al (5) (nc)

A solution of fluoroacetal (4) (3 32 g, 20 mmol) in formic acid (5 52 g, 0.12 mol), previously dried over $CuSO_4$, is heated under stirring at 45°C The complete formolysis of (4), monitored by ^1H NMR, is achieved in 2 5 hours. Then the reaction mixture is poured into diethyl ether (100 mL) cooled to 0°C. Excess of formic acid (0 08 mol) is neutralized at 0°C by slowly adding Na_2CO_3 (5.42 g, 0 05 mol) dissolved in 8 mL water. After CO_2 is evolved, and warming to room temperature, the separated aqueous phase is extracted many times with diethyl ether [until the odor of (5) is not detected] and the combined ethereal extracts are dried over anhydrous Na_2SO_4. The most part of diethyl ether is slowly evaporated under ambient pressure, then the pressure is reduced little by little under nitrogen and the residue is distilled off Pure 4-fluoro-2-butyn-1-al (5) (1.07 g, 62%) is obtained as a light yellow liquid which must be stored at - 20°C ; b p 54°C at ca. 50 mm Hg Anal Calcd for C_4H_3OF: C, 55 82; H, 3 48 Found C, 55 21, H, 3 71. HRMS. m/e $[M]^+$ Calcd 86 01679 ; found 86.0166 ^1H NMR (CCl_4) 5 15 (dd, $^5J_{HH}$= 0 6, $^2J_{HF}$ = 47.4, 2H), 9 27 (dt, $^5J_{HH}$= 0 5, $^5J_{HF}$ = 3.2, 1H) ^{19}F NMR (CCl_4) : -221.7 (td, $^2J_{HF}$= 47, $^5J_{HH}$ =3 4).

Cycloadduct (6a) (nc)

A mixture of fluoro-aldehyde (5) (0.13 g, 1.51 mmol) and DMB (6) (0 136 g, 1.66 mmol) is heated at 40-45°C . The reaction, followed by ^1H NMR, is stopped after heating for 47 hrs when ca 80-85% adduct (6a) is formed (when the conversion yield reaches ca 90-95%, the reaction mixture decomposes with explosion). Cooling the reaction mixture to -20°C gives a crude white solid which is dissolved in diethyl ether (5 mL) and the solution is evaporated. The resulting white solid which still contains traces of starting products (5) and (6) is purified by washing with 2 x 8 mL pentane and dried under vacuum, giving the adduct (6a) (0 203 g, 80%), m p. 62°C HRMS· m/e $[M]^+$ Calcd

for $C_{10}H_{13}FO$. 168 09504, found 168.0954. IR ($CHCl_3$)· 1660 (strong) ^1H NMR ($CDCl_3$): 1 69 (s, 6H) 2.88 (s, 4H), 5 36 (d, J_{HF}=48, 2H), 10 17 (s, 1H).

Cycloadduct (7a) (nc)

(a) Acidic medium

A solution of fluoro-acetal (4) (0.576 g, 3 6 mmol) in dried formic acid (1 02 g, 22 mmol) is heated under stirring at 45°C in a nitrogenous atmosphere until the complete formolysis of (4) is achieved (ca 2h, reaction followed by NMR) Then CH_2Cl_2 (10 mL) and freshly distilled CPD (7) (0.475 g, 7 2 mmol) are added at room temperature Instantaneous Diels-Alder reaction occurs, as it appears from t l.c The reaction mixture is added with a further 10 mL CH_2Cl_2 then washed with water, the organic phase is extracted and dried over anhydrous Na_2SO_4 After evaporation of CH_2Cl_2, the residue is purified by column chromatography on silica gel (ether/pentane · 2/8, then 3/7). The cycloadduct (7a) is obtained as an orange liquid (0 22 g, 40%)

(b) Neutral medium

CPD (7) (0.109 g, 1.66 mmol) is added to fluoro-aldehyde (5) (0.13 g,1 51 mmol) cooled to -25°C . The reaction proceeds instantaneously (t.l.c), providing a quantitative formation of adduct (7a) (NMR analysis) which is purified as above by column chromatography Isolated product : 0.206 g, 90% HRMS m/e [M]+ Calcd for C_9H_9FO. 152.06374; found. 152 064 . IR (neat): 1645 (strong), 1710 (shoulder), 1555. ^1H NMR (CCl_4). 2 8 (broad s, bridged CH_2), 3 7 (broad s, bridgehead CH), 4 05 (broad s, bridgehead CH), 5 37 (d, J_{HF} =47.6, 2H), 6 8 (m, 2H), 9.95 (s, 1H) ^{19}F NMR (CCl_4): -218.9 (t , J_{HF}=47). Note: by comparison with ^1H NMR data provided by cycloadducts obtained from reactions between CPD (7) and various α-acetylenic aldehydes [2] , the larger δ_H from the bridgehead CH groups is preferably assigned to the CH group in the ß-position with respect to the CHO group

Cycloadduct (8a) (nc)

(a) Acidic medium

The formolysis of the fluoro-acetal (4) is performed in the same conditions as previously and followed by the addition of CHD (8) (0.432 g, 5.4 mmol). Then the reaction mixture is heated under stirring at 40°C (CH_2Cl_2 refluxing) for 48h After the usual work- up, the crude cycloadduct (8a) (0 572 g, 95 7%) is purified by column chromatography (ether/pentane · 3/7), giving pure (8a) (0 532 g, 90 %) as a colourless liquid.

(b) Neutral medium

A mixture of CHD (8) (0.133 g, 1.66 mmol) and fluoro-aldehyde (5) (0,13 g, 1.51 mmol) is heated at 40°C for 36 hr. Then the reaction mixture is purified by column chromatography as above,

giving the pure cycloadduct (**8a**) (0 225 g , 90%) HRMS m/e $[M]^+$ Calcd for $C_{10}H_{11}FO$: 166 07939; found: 166 0791. IR (neat): 1655 (strong), 1700 (shoulder),1595 ^1H NMR (CCl_4) .1.37 (m, bndged CH_2, 4H), 3 82 (m,bridgehead CH, 1H), 4 26 (m, bridgehead CH, 1H), 5 33 (d, J_{HF}=47 6, 2H), 6 33 (m, 2H), 9 83 (s, 1H). ^{19}F NMR (CCl_4) -217 9 (t, J_{HF}= 47) Note : as in the case of (**7a**), the larger δ_H from bridgehead CH groups may be assigned to the CH group in the ß-position with respect to the CHO group

REFERENCES

1 R.L. Bol'shedvorskaya and L I Vereshchagin, Russian Chem. Rev., Engl. Transl., 42 (1973), 2250

2 A. Gorgues, A. Simon, A Le Coq, A Hercouet and F. Corre, Tetrahedron, 42 (1986), 351.

3 D Stéphan, A Gorgues, A Belyasmine and A Le Coq, J. Chem.Soc . Chem Commun., (1988), 263

4 A Gorgues, D. Stéphan, A. Belyasmine , A Khanous and A Le Coq, Tetrahedron, (1990), in the press.

5 R. N. Haszeldine, J. Chem. Soc., (1952), 3490

6 R. D. Chambers, S Partington and D B. Speight, J. Chem. Soc., Perkin Trans. I, (1974), 2673.

7 R. D. Chambers, C G P. Jones, M J Silvester and D.B. Speight, J Fluorine Chem., 25 (1984), 47

8 For difficulties of isolation, compare to. i) L Brandsma, Preparative Acetylenic Chemistry, Elsevier, Amsterdam, (1971), 170; ii) E R H Jones, J S. Stephenson, W.B. Turner and M.C Whiting, J. Chem. Soc., (1963), 2048

9 R. Epsztein and I Marszak, Bull Soc. Chim. Fr., (1968), 313

10 These two acetals of ADCA are marketed by Janssen Chimica ; for a rewiew, see . A Gorgues, Janssen Chim. Acta, 4 (1986), 21.

11 R.K Crossland and K L Servis, J. Org.Chem., 35 (1970), 3195

12 P.A Grieco, E Williams and T. Sugahara, J.Org. Chem., 44 (1979), 2194

13 C. Rücker, D Lang, J Sauer, H Friege and R Sustmann, Chem. Ber., 113 (1980), 1663

14 T.A. Macrides et V. Thaller, J. Chem. Res., (M), (1981), 2001.