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Preparation of 1-Aryl-4-(trifluoromethyl)penta-1,3-dienes by Wittig-Horner Condensation

Valérie Martin [a] , Huguette Molines [a b] & Claude Wakselman [a]

[a] CERCOA-CNRS , 2, rue Henry Dunant, F-94320, THIAIS, France

[b] Laboratoire de Chimie des Hétérocycles , Université P et M Curie , BP 43, 4, Place Jussieu, F-75525, Paris Cedex

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PREPARATION OF 1-ARYL-4-(TRIFLUOROMETHYL)PENTA-1,3-DIENES BY WITTIG-HORNER CONDENSATION

Valérie Martin, Huguette Molines[+] and Claude Wakselman

CERCOA-CNRS, 2, rue Henry Dunant, F-94320 THIAIS, France.

Abstract : A direct route to 1-aryl-4-(trifluoromethyl)penta-1,3-dienes is described using the Wittig-Horner reaction of diethyl (3-(trifluoromethyl)-but-2-enyl)phosphonate anion with aromatic aldehydes or trifluoroacetophenone.

Fluorinated organic compounds have received an increased attention during the past years[1] due to the modification of reactivity when an hydrogen atom or a methyl group are replaced by a fluorine atom or a trifluoromethyl group in a

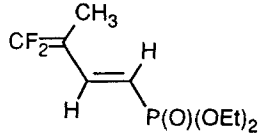
[+] Present address : Laboratoire de Chimie des Hétérocycles, Université P et M Curie, BP 43, 4, Place Jussieu F-75525 Paris Cedex.

biological molecule[2]. Especially there continues to be a great interest in the selective synthesis of trifluoromethylated molecules[3, 4, 5].

Wittig and Wittig-Horner reactions have been employed for the preparation of trifluoromethyl containing olefines from fluorinated aldehydes or ketones [6, 7, 8, 9, 10]. An alternative method is the use of an alkylphosphonate bearing a trifluoromethyl group[11].

Here we describe the preparation of 1-aryl-4-(trifluoromethyl)penta-1,3-dienes **3**[12] by Wittig-Horner reaction of carbonyl compounds with diethyl (3-(trifluoromethyl)but-2-enyl)phosphonate[15] (**1**) and sodium hydride in THF (Figure 1).

The aldehyde must be present in the mixture since the beginning of the reaction, otherwise an elimination process occurs and only diene **4** is formed from the phosphonate anion. We checked that the diethyl phosphonate **1** in presence of base gave only **4**.



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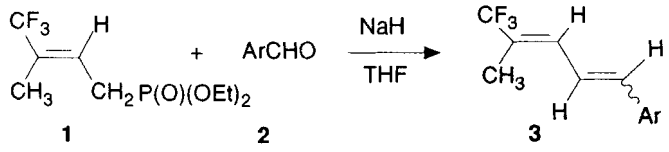
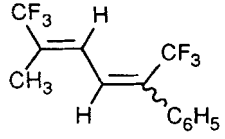
For this reason, only non enolisable aldehydes could be used. The condensation has been done with aromatic aldehydes and dienes **3** were isolated in fairly yields (Figure 1). Best results were obtained when 2 equivalents of aldehyde were used and with sodium hydride as base. The use of LDA or potassium hydride did not increase the yield. High selectivity in favour of *E,E*-isomer was observed and in the case of **3b** and **3c** no *E,Z*-isomer was detected. Identification of the **3a** stereoisomers has been done by ^1H



	a	b	c	d	e
Ar	C_6H_5	$pNO_2C_6H_4$	1-Naphthyl		
E,E:E,Z	91:9	100	100	94:6	87:3
isolated yield%	44	62	18	52	52

Figure 1

NMR at 300 MHz using irradiation. Coupling constant between H (C1) and H (C2) is higher in *E,E*-isomer (15 Hz) than in *E,Z*-isomer (11.5 Hz). We also noticed that the chemical shift of hydrogen (C2) is downfield in the *E,E*- (6.87 ppm) compared to the *E,Z*-isomer (6.33 ppm). The aromatic aldehyde must be electrophilic enough not to observe the competitive elimination process. In the case of **2c** a mixture of compound **4** and diene **3c** in ratio 77:23 was obtained and with *p*-methoxybenzaldehyde no Wittig-Horner condensation took place. This method was also applied to trifluoroacetophenone. Diene **3f** was isolated in 54% yield as a mixture of *E,Z*- and *E,E*-isomers in a 78:22 ratio.



3f

Experimental

Melting point was determined on a Mettler FP-61 apparatus. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer. ^{1}H NMR (200.13 MHz) spectra were recorded on a Bruker AC-200e FT spectrometer and ^{19}F NMR (56.4 MHz) on a Varian EM360L instrument. NMR chemical shifts δ in deuterochoroform are reported in ppm, positive downfield from internal trimethylsilane for ^{1}H and negative upfield from trichlorofluoromethane for ^{19}F. Elemental analyses were performed by the Service de Microanalyses, Université P. et M. Curie, Paris. Ether was diethyl ether. THF and pentane were distilled over sodium just before use. Petroleum ether was 45-65°C one. Brine was a saturated aqueous sodium chloride solution. Preparative chromatographies were performed on silica gel column (Merck 70-230 Mesh).

1-Aryl-4-(trifluoromethyl)penta-1,3-dienes (3); General Procedure :

To a suspension of sodium hydride (7.5 mmol; 1.5 equivalent; 60% in mineral oil, washed twice with pentane) in THF (10 mL) aldehyde (or trifluoroacetophenone) (10 mmol; 2 equivalents) was added under argon. The mixture was cooled to -10 °C and diethyl (3-(trifluoromethyl)but-2-enyl)-phosphonate (5 mmol; 1 equivalent) was dropwise added. The mixture was then stirred at room temperature for 2 h. After cooling to 0 °C saturated aqueous ammonium chloride solution (20 mL) and then few drops of hydrochloric acid (10%) until neutralisation were added. The aqueous layer was extracted with ether (3 x 20 mL). The organic layers were washed with brine (30 mL) and dried over magnesium sulfate. After filtration, the solvents were evaporated under vacuum (20 Torr). The residue was purified by column

chromatography on silica gel using petroleum ether/ethyl acetate (95 : 5) as eluant.

1-Phenyl-4-(trifluoromethyl)penta-1,3-diene (3a) : from benzaldehyde (1.17 mL; 11.5 mmol) and diethyl (3-(trifluoromethyl)but-2-enyl)phosphonate (1.5 g; 5.7 mmol) 1-phenyl-4-(trifluoromethyl)penta-1,3-diene (**3a**) was obtained as a colourless liquid and as a mixture of *E,E*- and *E,Z*-isomers (91:9); yield : 0.53 g (44%); R_f 0.88. IR (CCl_4) : ν = 3030, 3010, 2960, 2920, 1640, 1480, 1440, 1360, 1330, 1300, 1280, 1240, 1210, 1180, 1140, 1110, 1080 cm^{-1}. ^1H NMR : δ = 1.97 (s, 3 H, CH_3), 6.33 (br t, *J* = 11.5 Hz, C(2)-H, *E,Z*-isomer), 6.62 (br d, 1 H, *J* = 11.5 Hz, C(3)-H, *E,E*-isomer), 6.77 (d, 1 H, *J* = 15 Hz, C(1)-H, *E,E*-isomer), 6.87 (dd, 1 H, *J* = 15 and 11.5 Hz, C(2)-H, *E,E*-isomer), 6.97 (br d, *J* = 11.5 Hz, C(3)-H, *E,Z*-isomer), 7.32-7.55 (m, 5 H, C_6H_5). ^{19}F NMR : δ = -69 (s). Anal. calculated for $C_{12}H_{11}F_3$: C, 67.92; H, 5.225. Found : C, 67.90; H, 5.42.

(*E,E*)-1-*p*-Nitrophenyl-4-(trifluoromethyl)penta-1,3-diene (3b) : from *p*-nitrobenzaldehyde (1.16 g; 7.7 mmol) and diethyl (3-(trifluoromethyl)-but-2-enyl)phosphonate (1 g; 3.8 mmol) (*E,E*)-1-*p*-nitrophenyl-4-(trifluoromethyl)+penta-1,3-di ene (**3b**) was obtained as yellow crystals; yield : 0.61 g (62%); mp 90-91 °C; R_f 0.85. IR (CCl_4) : ν = 3020, 2950, 2920, 1640, 1590, 1510, 1360, 1340, 1240, 1180, 1140, 1110, 1070 cm^{-1}. ^1H NMR : δ = 2.08 (s, 3 H, CH_3), 6.78 (br d, 1 H, *J* = 11.5 Hz, C(3)-H), 6.88 (d, 1 H, *J* = 15.6 Hz, C(1)-H), 7.15 (dd, 1 H, *J* = 11.5 and 15.6 Hz, C(2)-H), 7.65 (d, 2 H, *J* = 7.1 Hz, H-2 and 6-aromatic), 8.27 (d, 2 H, *J* = 7.1 Hz, H-3 and 5-aromatic).

^{19}F NMR : δ = -67.6 (s). Anal. calculated for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92. Found : C, 55.95; H, 3.98.

(*E,E*)-1-(1-Naphthyl)-4-(trifluoromethyl)penta-1,3-diene (3c) : from 1-naphthaldehyde (1.2 g; 7.6 mmol) and diethyl (3-(trifluoromethyl)-but-2-enyl)phosphonate (1 g; 3.8 mmol)a mixture of **3c** and **4** in ratio 23:77 (^{19}F NMR analysis) was obtained. Purification by column chromatography gave (*E,E*)-1-(1-naphthyl)-4-(trifluoromethyl)penta-1,3-diene (**3c**) as a white gum; yield : 0.18 g (18%); R_f 0.9. IR (CCl_4) : ν = 3020, 2950, 2920, 1640, 1350, 1340, 1320, 1300, 1290, 1260, 1230, 1180, 1170, 1110, 1070 cm^{-1}. ^1H NMR : δ = 1.92 (s, 3 H, CH_3), 6.56 (d, 1 H, *J* = 11.55 Hz, C(3)-H), 6.70 (d, 1 H, *J* = 17.5 Hz, C(1)-H), 6.91 (dd, 1 H, *J* = 11.55 and 17.5 Hz, C(2)-H), 7.16-8.06 (m, 7 H, H naphthyl). ^{19}F NMR : δ = -67.7 (s). Anal. calculated for $C_{16}H_{13}F_3$: C, 73.27; H, 4.99; Found : C, 73.35; H, 5.14.

2-(4-(trifluoromethyl)penta-1,3-dien-1-yl)furan (3d) : from 2-furaldehyde (0.318 mL; 3.8 mmol) and diethyl (3-(trifluoromethyl)but-2-enyl)phosphonate (0.5 g; 1.92 mmol) 2-(4-(trifluoromethyl)penta-1,3-dien-1-yl)furan (**3d**) was obtained as a mixture of *E,E*- and *E,Z*-isomers (94:6) and as a colourless liquid; yield : 0.2 g (52%); R_f 0.88. IR (CCl_4) : ν = 3070, 3020, 2980, 2970, 2960, 2920, 1640, 1620, 1470, 1380, 1360, 1320, 1290, 1250, 1240, 1200, 1180, 1140, 1110, 1080 cm^{-1}. ^1H NMR : δ = 1.85 (s, 3 H, CH_3), 6.15 (dd, *J* = 12.8 and 13.9 Hz, C(2)-H, *E,Z*-isomer), 6.30 (d, 1 H, *J* = 3.2 Hz, H-3 furan), 6.34 (dd, 1 H, *J* = 1.97 and 3.2 Hz, H-4 furan), 6.55 (br d, 1 H, *J* = 16.1 Hz, C(1)-H, *E,E*-isomer), 6.57 (br d, 1 H, *J* = 11.8 Hz, C(3)-H, *E,E*-isomer), 6.77

(dd, 1 H, J = 11.8 and 16.1 Hz, C(2)-H, *E,E*-isomer), 7.33 (d, 1 H, J = 1.97 Hz, H-5 furan, *E,E*-isomer), 7.5 (br d, J = 12.8 Hz, C_3-H, *E,Z*-isomer). ^{19}F NMR : δ = -69.35 (s). Anal. calculated for $C_{10}H_9F_3O$: C, 59.40; H, 4.48. Found : C, 59.26; H, 4.65.

2-(4-(trifluoromethyl)penta-1,3-dien-1-yl)pyridine (3e) : from 3-pyridine-carboxaldehyde (0.726 mL; 7.7 mmol) and diethyl (3-(trifluoromethyl)-but-2-enyl)phosphonate (1 g; 3.8 mmol) 2-(4-(trifluoromethyl)penta-1,3--dien-1-yl)pyridine (**3e**) was obtained as a mixture of *E,E*- and *E,Z*-isomers (87:13) and as a colourless liquid; yield : 0.42 g (52%); R_f 0.89. IR (CCl_4) : ν = 3080, 2990, 2960, 2940, 2920, 1640, 1410, 1380, 1360, 1330, 1320, 1240, 1170, 1140, 1120, 1090, 1070 cm^{-1}. ^1H NMR : δ = 1.90 (s, 3 H, CH_3), 6.63 (d, 1 H, J = 10 Hz, C(3)-H, *E,E*-isomer), 6.70 (d, 1 H, J = 14.3 Hz, C(1)-H, *E,E*-isomer), 6.93 (dd, 1 H, J = 10 and 14.3 Hz, C(2)-H, *E,E*-isomer), 7.2 (dd, 1 H, J = 9.3 and 5 Hz, H-5 pyridine, *E,E*-isomer), 7.38 (dd, 1 H, J = 8.8 and 13.9 Hz, H-5 pyridine, *E,Z*-isomer), 7.52 (d, 1 H, J = 11.4 Hz, C(3)-H, *E,Z*-isomer), 7.53 (dt, 1 H, J = 13.9 Hz, H-4 pyridine, *E,Z*-isomer), 7.70 (dt, 1 H, J = 9.3 and 1.5 Hz, H-4 pyridine, *E,E*-isomer), 8.43 (dd, 1 H, J = 5 and 1.5 Hz, H-6 pyridine, *E,E*-isomer), 8.58 (s, 1 H, H-2 pyridine, *E,E*-isomer), 8.76 (d, 1 H, J = 8.8 Hz, H-6 pyridine, *E,Z*-isomer), 8.83 (s, 1 H, H-7 pyridine, *E,Z*-isomer). ^{19}F NMR : δ = -70.8 (s). Anal. calculated for $C_{11}H_{10}F_3N$: C,61.97; H, 4.73. Found : C, 61.86; H, 4.77.

1,1,1-Trifluoro-2-phenyl-5-(trifluoromethyl)hexa-2,4-diene (3f) : from trifluoroacetophenone (0.65 mL; 4.6 mmol) and diethyl (3-(trifluoromethyl)-

but-2-enyl)phosphonate (0.6 g; 2.3 mmol) 1,1,1-trifluoro-2-phenyl-5--(trifluoromethyl)hexa-2,4-diene (**3f**) was obtained as a mixture of *E,E*- and *E,Z*-isomers (22:78) and as a colourless liquid; yield : 0.35 g (54%). IR (CCl_4) : ν = 3020, 3000, 1600, 1480, 1430, 1340, 1320, 1250, 1170, 1140, 1070 cm^{-1}. ^1H NMR : δ = 1.95 (s, 3 H, CH_3), 6.4 (d, 1 H, J = 11.1 Hz, C(4)-H, *E,Z*-isomer), 6.6 (d, 1 H, J = 11.1 Hz, C(4)-H, *E,E*-isomer), 6.98 (d, 1 H, J = 11.1 Hz, C(3)-H, *E,Z*-isomer), 7.04 (d, 1 H, J = 11.1 Hz, C(3)-H, *E,E*-isomer), 7.2-7.33 (m,5 H, C_6H_5). ^{19}F NMR : δ = -54 (s, 3 F, C(2)-CF_3, *E,Z*-isomer), -63.3 (s, 3 F, C(2)-CF_3, *E,E*-isomer), -66.6 (s, 3 F, C(5)-CF_3, *E,Z*-isomer), -67.7 (s, 3 F, C(5)-CF_3, *E,E*-isomer). Anal. calculated for $C_{13}H_{10}F_6$: C, 55.72; H, 3.60. Found : C, 55.85; H, 3.73.

Diethyl (4,4-difluoro-3-methylbuta-1,3-dienyl)phosphonate (4) :

To a solution of diethyl (3-(trifluoromethyl)but-2-enyl)phosphonate (0.6 g; 2.3 mmol) in dry THF (10 mL) was added dropwise an etheral solution of LDA (14 mL; 0.33 M; 4.6 mL) under argon at -10°C. The reaction was monitoring by ^{19}F NMR. When the diethyl phosphonate **1** was no more detected, aqueous saturated ammonium chloride solution (20 mL) and then few drops of 10% hydrochloric acid until neutralisation were added. The aqueous layer was extracted with ether (3 x 20 mL). The organic layers were washed with brine (20 mL) and dried over magnesium sulfate. After filtration the solvents were evaporated under vacuum (20 Torr) and the residue was purified by column chromatography on silica gel using ethyl acetate/pentane (50/50) to give *E*-diethyl (4,4-difluoro-3-methylbuta-1,3-dienyl)phosphonate (**4**) as a yellow liquid; yield : 0.221 g (40%) ; R_f 0.36. IR (CCl_4) : ν = 2990, 2960, 2950, 1600,

1460, 1440, 1380, 1320, 1300, 1230, 1160, 1100, 1090, 1050, 1020 cm^{-1}. ^1H NMR : δ = 1.38 (t, 6 H, J = 7.1 Hz, CH_3), 1.78 (t, 3 H, J = 3 Hz, CH_3C=), 4.14 (dq, 4 H, J = 7.1 and 14.3 Hz, CH_2), 5.69 (dd, 1 H, J = 17.5 Hz, C(1)-H), 7.34 (dd, 1 H, J = 17.1 and 17.5 Hz, C(2)-H). ^{19}F NMR : δ = -84.35 (br d, 1 F, J = 14.4 Hz, F *cis* to CH_3), -84.52 (dq, 1 F, J = 14.4 and 3 Hz, F *trans* to CH_3). Anal. calculated for $C_{13}H_{10}F_6$: C, 55.72; H, 3.60. Found : C, 55.85; H, 3.73.

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12. As far as we know only one of these trifluoromethylated dienes **3** has been described : compound **3a**[13]. The homoallylic alcohol obtained by the ene reaction of trifluoroacetone with allyl benzene [14] has been dehydrated in two directions to give a mixture of **3a** stereoisomers (*E,E*:*E,Z* = 9:2) and 1-phenyl-4-(trifluoromethyl)penta-1,4-diene, in a ratio 1,3 diene:1,4 diene = 92:8. The **3a** stereoisomers have been separated by GLC whereas the homoallylic alcohol precursor has been isolated by HPLC from a complex mixture.

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