Wittig Reaction of a Series of Diazodiketones: Synthesis and Structure of Fluorine-Containing Vinyldiazoketones

Valerija M. Zakharova,[a] Lothar Hennig,[b] Valerij A. Nikolaev*[a]

[a] St. Petersburg State University, Department of Organic Chemistry, University pr. 26, 198504 St. Petersburg, Russia
E-mail: vnikola@VN6646.spb.edu

[b] Universität Leipzig, Institut für Organische Chemie, Johannisallee 29, 04103 Leipzig, Germany
E-mail: hennig@organik.chemie.uni-leipzig.de

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Abstract: Reaction of (alkyloxycarbonyl)- and (benzoyl)-methylenetriphenylphosphoranes with fluorine-containing diazodiketones leads to olefination of the perfluoroacyl carbonyl group and formation of fluorinated vinyldiazoketones. The analogous reaction with non-fluorinated diazodiketones does not proceed under the same conditions. The resulting fluorine-containing vinyldiazoketones have an *E*-configuration regardless of the nature and size of the substituents.

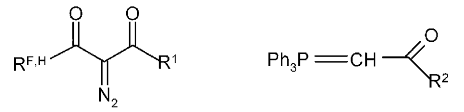
Key words: aliphatic diazo compounds, Wittig reaction, fluorine-containing vinyldiazoketones, 1,3-diketones, diazo transfer reaction

The Wittig reaction is one of the most powerful means to introduce carbon–carbon double bonds into organic molecules. It is applicable to a large number of aliphatic, aromatic, carbo- and heterocyclic compounds possessing different functional groups which do not interfere with this effective and widely used process.[1,2]

However, analysis of the literature showed that of all the carbonyl compounds previously used in the Wittig reaction, aliphatic diazocarbonyl compounds have been rarely investigated.[3–5] Therefore, the application of the Wittig reaction to diazocarbonyl substrates could increase the scope of this process as well as enhance the synthetic potential of aliphatic diazo compounds since the target products – vinyldiazocarbonyl compounds – are very attractive for organic synthesis.[3,5–7]

The main objective of our project was to investigate the reaction of fluoroalkyl-containing and non-fluorinated 2-diazo-1,3-diketones **1** (**F**- and **H**-diazodiketones) with Wittig reagents to elucidate both the chemo- and stereoselectivity of this process and thereby to elaborate an effective approach to the structure of vinyldiazoketones. For this purpose a range of **F**- and a few **H**-diazodiketones (**1a**–**j**) were chosen with both alkyl and aryl substituents; also the steric effect (Me, Bu, *t*-Bu, Ar) exhibited by the substituent adjacent to the diazo group was investigated (Figure 1).

Investigations were carried out with easily accessible (alkoxycarbonyl)methylenetriphenylphosphoranes **2a**,**b**. Several (acyl)methylenephosphoranes **2c**–**e** were also used in the reaction with diazocarbonyl compounds **1** in order to estimate the scope and limitations of the process.

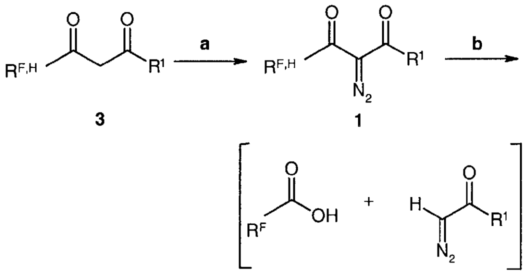


1 **2**

1a	$R^F = CF_3$	R^1 = Me	**1f**	$R^F = CF_3$	R^1 = *p*-Tol	**2a**	R^2 = OMe
1b	CF_3	Et	**1g**	CF_3	ß-$C_{10}H_7$	**2b**	OEt
1c	CF_3	*n*-Bu	**1h**	C_3F_7	Ph	**2c**	Ph
1d	CF_3	*t*-Bu	**1i**	R^H = Me	Me	**2d**	H
1e	CF_3	*n*-Pentyl	**1j**	Me	*t*-Bu	**2e**	Me

Figure 1

All starting diazodiketones **1** were obtained in a one-step procedure from the corresponding 1,3-diketones **3** using a diazo transfer reaction (Scheme 1).[8]



Scheme 1 a) $ArSO_2N_3$/base, CH_2Cl_2, 20 °C; b) H_2O/base; side reaction in the case of R^F

Since fluorinated diazodiketones **1a**–**h** are easily hydrolyzed even in the presence of traces of alkali and water,[9] their synthesis was carried out using a modified diazo transfer reaction,[10] which prevents the reaction mixture coming into contact with moisture at all stages of the process. Furthermore, several bases (trimethylamine, DBU, and potassium fluoride on aluminum oxide)[11] were tested as catalysts in the reaction with diketone **3a** to optimize the yields of **F**-diazodiketones **1**. The best results (49–54% yield), with the not easily accessible **F**-diazodiketone **1a**, were accomplished using DBU in a solution of dichloromethane (Table 1).

The reaction of diazodiketones **1a**–**j** with phosphoranes **2a**–**e** was studied under usual Wittig reaction conditions (18–20 °C, Et_2O solution; Scheme 2).[1,2]

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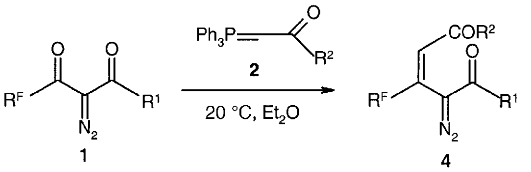
Compound	R^H/R^F	R^1	Yield (%) (Base)
1a	CF_3	Me	54 (DBU); 27 (Me_3N); 49 (KF/Al_2O_3)
1b	CF_3	Et	58 (DBU)
1c	CF_3	Bu	66 (DBU)
1d	CF_3	*t*-Bu	48 (DBU)
1e	CF_3	Pentyl	82 (DBU)
1f	CF_3	*p*-Tolyl	66 (DBU)
1g	CF_3	β-$C_{10}H_7$	64 (DBU)
1h	C_3F_7	Ph	55 (DBU)
1i	Me	Me	65 (Et_3N)
1j	Me	*t*-Bu	58 (Et_3N)



Scheme 2

It was found that **F**-diazodiketones **1a**–**h** react easily with (alkoxycarbonyl)methylenephosphoranes **2a**,**b** giving rise to fluorine-containing vinyldiazoketones **4a**–**h** with moderate to good yields in three to four hours (Table 2).

The reaction of (benzoyl)methylenephosphorane **2c** with **F**-diazodiketones **1a**,**c** in toluene (6 d for **1a**; 14 d for **1c**) also results in vinyldiazoketones **4k**,**l**, but only in low yields (Table 2).

Table 2 Yields of Fluorinated Vinyldiazoketones **4a**–**h**,**k**,**l**

Compound	R^F	R^1	R^2	Yield (%)[a]
4a	CF_3	Me	OMe	79
4b	CF_3	Et	OEt	65
4c	CF_3	Bu	OMe	84
4d	CF_3	*t*-Bu	OMe	76
4e	CF_3	Pentyl	OMe	69
4f	CF_3	*p*-Tolyl	OMe	63
4g	CF_3	β-$C_{10}H_7$	OEt	72
4h	C_3F_7	Ph	OMe	42
4k	CF_3	Me	Ph	32
4l	CF_3	Bu	Ph	18

[a] Satisfactory microanalyses were obtained: C ± 0.35, H ± 0.17, N ± 0.38, with exception for **4a**,**b**,**l** (in C) and **4f**–**h** (in N).

The **F**-diazo compounds **4a**–**h**,**k**,**l** were purified by chromatography on silica gel and characterized by a variety of spectroscopic methods (Table 3).

Attempts to carry out the Wittig reaction of **F**-diazodiketone **1c** with (formyl)- and (acetyl)methylenephosphoranes **2d**,**e** failed. In both cases no products similar to vinyldiazoketones **4** were identified in the reaction mixture, by TLC, even after a few days. Even varying the reaction conditions (inverse order of reagent addition, substitution of Et_2O by THF or benzene, lowering the reaction temperature, etc.) did not change the result.

The reaction of non-fluorinated diazodiketones **1i**,**j** with Wittig reagent **2a** was also attempted. However, it was found that these **H**-diazodiketones as well as **H**-α-diazo-β-ketoesters[12] did not react with (alkoxycarbonyl)methylenephosphorane **2a** under the usual conditions.

The resulting fluorinated vinyldiazoketones **4a**–**h**,**k**,**l** are bright yellow oils, which are stable for many months when refrigerated at –5 to –10 °C. The structure of the previously unknown fluorine-containing vinyldiazoketones **4** was established by means of IR, ^1H, ^{13}C, and ^{19}F NMR spectroscopy (Table 3), and their composition was confirmed by elemental analysis.

The IR spectra of **F**-vinyldiazoketones **4a**–**h**,**k**, revealed strong diazo group absorption bands at 2080–2095 cm^{-1}; this is a 50–60 cm^{-1} shift to lower frequency in comparison to the starting **F**-diazodiketones **1**.[10] Valence vibrations of non-fluoroalkyl-substituted (**H**-acyl) carbonyl groups are located almost at the same position (1640–1670 cm^{-1}) as the initial diazo compounds **1** (1640–1680 cm^{-1}),[10] demonstrating that only the perfluorinated acyl group of **F**-diazodiketone **1** takes part in the Wittig reaction.

Diagnostic signals for the diazo group in ^{13}C NMR spectra for **F**-vinyldiazoketones **4a**–**h**,**k** were observed at 61–66 ppm. They are shifted to a higher field (15–20 ppm) compared to **F**-diazodiketones **1**.[10] A new set of signals corresponding to the two C-alkene atoms (C=CHCOR^2 group) with the typical coupling pattern ($^2J_{C\text{-}F}$ = 33 and $^3J_{C\text{-}F}$ = 5 Hz) appeared at 127–130 ppm and 125–131 ppm, whereas the signal of the perfluoroacetyl carbonyl group of **F**-diazodiketones **1** at 170–171 ppm disappeared. Non-fluoroalkyl-substituted carbonyl groups are located at 183–195 ppm.[10]

Thus, both the ^{13}C NMR and IR spectra unambiguously suggest that the reaction of **F**-diazodiketones **1a**–**h** with methylenetriphenylphosphoranes **2a**–**c** proceeds chemoselectively at the perfluoroacyl carbonyl group while the **H**-acyl group remains intact during the reaction.

Only one set of signals was found in the ^1H and ^{13}C NMR spectra of **4a**–**h** in $CDCl_3$ solution at room temperature, therefore it is possible to conclude that only one regio- and stereoisomer of each vinyldiazoketone is formed in this case.

Vinyldiazoketones **4k**,**l**, possessing a bulky benzoyl substituent at the double bond, gave two sets of signals in the ratio ca. 3:1 and 2:1 in the ^{1}H and ^{13}C NMR spectra (Table 3). Most likely, what is observed in this case is an equilibrium between the s-*Z* and s-*E* stereoisomers at the CO–CN_2 bond;[13] the broadening of some signals (Table 3) supports this speculation to some extent. Also, we cannot exclude the existence of an equilibrium in the solution with vinyldiazo-3*H*-pyrazole.[14]

In accordance with the literature data, Wittig reaction of unsymmetrically substituted α-fluoroalkyl carbonyl compounds normally results in the formation of olefins with *E* configuration at the new double bond.[15,16] Therefore, one can expect that vinyldiazoketones **4** should also have an *E* configuration.

This assumption was verified by an additional study of vinyldiazoketones **4a**–**h**,**k** using HOESY experiments on ^{1}H

Table 3 NMR Spectroscopic Data for Vinyldiazoketones **4a**–**h**,**k**,**l**

Compound	IR (cm^{-1})			^{1}H NMR, δ (ppm), *J* (Hz)	^{12}C NMR, δ (ppm), *J* (Hz)	^{19}F NMR, δ (ppm), *J* (Hz)
	CN_2	CO	COR^{1}			
4a	2080	1650	1720	2.16 (s, 3 H), 3.72 (s, 3 H), 6.52 (s, 1 H)	25.72, 52.63, 65.47, 122.73 (q, $^{1}J_{C-F}$ = 275.8), 126.81 (q, $^{3}J_{C-F}$ = 4.6), 128.01 (q, $^{2}J_{C-F}$ = 34.5), 163.64, 188.16	–67.30
4b	2095	1675	1730	1.55 (t, *J* = 7.7, 3 H), 1.31 (t, *J* = 6.9, 3 H), 2.51 (q, *J* = 7.7, 2 H), 4.25 (q, *J* = 7.0, 2 H), 6.59 (s, 1 H)	8.27, 14.07, 31.46, 61.79, 65.11, 122.24 (q, $^{1}J_{C-F}$ = 275.9), 127.31 (q, $^{3}J_{C-F}$ = 4.2), 127.86 (q, $^{2}J_{C-F}$ = 33.3), 163.22, 191.51	–67.02
4c	2080	1660	1730	0.93 (t, *J* = 7.7, 3 H), 1.37 (m, 2 H), 1.65 (m, 2 H), 2.48 (t, *J* = 7.0, 2 H), 3.69 (s, 3 H), 6.58 (s, 1 H)	14.05, 22.53, 26.76, 38.12, 52.84, 65.15, 122.58 (q, $^{1}J_{C-F}$ = 275.9), 126.94 (q, $^{3}J_{C-F}$ = 4.6), 128.00 (q, $^{2}J_{C-F}$ = 32.9), 163.98, 191.23	–67.11
4d	2080	1650	1720	1.28 (s, 9 H), 3.77 (s, 3 H), 6.60 (s, 1 H)	26.45, 44.65, 52.41, 61.91, 122.28 (q, $^{1}J_{C-F}$ = 275.9), 126.78 (q, $^{3}J_{C-F}$ = 4.6), 130.21 (q, $^{2}J_{C-F}$ = 33.3), 163.59, 195.91	–77.44
4e	2095	1670	1735	0.91 (t, *J* = 7.7, 3 H), 1.30 (m, 2 H), 1.31 (m, 2 H), 1.66 (m, 2 H), 2.47 (t, *J* = 7.3, 2 H), 3.79 (s, 3 H), 6.58 (s, 1 H)	14.19, 22.71, 24.41, 36.62, 38.39, 52.87, 64.88, 122.53 (q, $^{1}J_{C-F}$ = 275.9), 126.96 (q, $^{3}J_{C-F}$ = 4.6), 128.87 (q, $^{2}J_{C-F}$ = 33.0), 164.00, 191.30	–66.85
4f	2080	1670	1730	2.35 (s, 3 H), 3.63 (s, 3 H), 6.44 (s, 1H), 7.19 (d, *J* = 7.6, 2 H), 7.49 (d, *J* = 7.6, 2 H)	2.61, 52.36, 65.75, 122.28 (q, $^{1}J_{C-F}$ = 275.9), 125.12 (q, $^{3}J_{C-F}$ = 4.6), 127.84, 129.29, 129.70 (q, $^{2}J_{C-F}$ = 33.1), 133.75, 143.10, 163.57, 186.52	–66.23
4g	2090	1640	1725	1.11 (t, *J* = 7.0, 3 H), 4.05 (q, *J* = 6.9, 2 H), 6.49 (s, 1 H), 7.51–7.59 (m, 7 H)	13.88, 61.67, 66.13, 122.37 (q, $^{1}J_{C-F}$ = 275.9), 124.05, 125.88 (q, $^{3}J_{C-F}$ = 4.6), 126.99, 127.86, 128.27, 128.56, 128.63, 129.12, 129.15 (q, $^{2}J_{C-F}$ = 32.2), 132.28, 133.75, 135. 00, 163.15, 186.66	–74.28
4h	2085	1645	1725	3.75 (s, 3 H), 6.56 (s, 3 H), 7.45 (t, *J* = 7.7, 2 H), 7.54 (t, *J* = 7.6, 1 H), 7.62 (d, *J* = 7.7, 2 H)	52.62, 66.21, 108.66 (tq, $^{1}J_{C-F}$ = 266.1, $^{2}J_{C-F}$ = 38.3), 114.37 (tt, $^{1}J_{C-F}$ = 258.9, $^{2}J_{C-F}$ = 31.3), 117.66 (qt, $^{1}J_{C-F}$ = 288.8, $^{2}J_{C-F}$ = 34.2), 127.57, 128.18 (t, $^{2}J_{C-F}$ = 25.3), 128.78, 129.23, 129.51 (t, $^{3}J_{C-F}$ = 7.9), 132.33, 135.38, 136.62, 163.41, 186.35	–80.57 (t, *J* = 8.5, 3 F), –112.11 (s, 2 F), –126.50 (s, 2 F)
4k	2095	1675	1675	2.16 (s, 3 H), 7.41 (br s, 1 H), 7.49 (t, *J* = 7.2, 2 H), 7.60 (t, *J* = 7.2, 1 H), 7.91 (d, *J* = 7.2, 2 H)	25.77, 65.91, 122.54 (q, $^{1}J_{C-F}$ = 275.8), 128.72 (q, $^{2}J_{C-F}$ = 33.3), 128.76, 129.00, 129.23, 131.29 (q, $^{3}J_{C-F}$ = 4.2), 136.47, 188.01, 189.36	–66.54 (br)
4l				0.85 (t, *J* = 7.6, 3 H), 1.22 (m, 2 H), 1.52 (m, 2 H), 2.41 (t, *J* = 6.9, 2 H), 7.38 (s, 1 H), 7.50 (t, *J* = 7.7, 2 H), 7.60 (t, *J* = 7.7, 1 H), 7.91 (d, *J* = 7.7, 2 H)		

and ^{19}F nuclei. A clear interaction between fluorine atoms of the R^F-group and the hydrogen atom on the double bond was established. Furthermore, a weak interaction of the same F-atoms with hydrogens in the non-fluorinated R^1 group of **F**-vinyldiazoketones **4f**,**h** was found. Therefore, one can conclude that vinyldiazoketones **4** have the expected *E*-configuration (Figure 2).

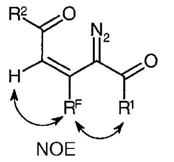


Figure 2

The considerable variation in the reactivity of fluorinated **1a**–**h** and non-fluorinated **1i**,**j** diazodiketones during the Wittig reaction, as well as the discrepancy in the chemical behavior of **H**- and **F**-acyl carbonyl, can be explained by the enhanced electrophilic character of the carbonyl C-atom in the perfluoroacyl substituent. This observation has already been made for ordinary fluoroalkyl containing ketones;[15] it was determined for the first time in this series of diazocarbonyl compounds with two electron-accepting groups at the α,α'-position to the C=O moiety. Moderate yields obtained with (benzoyl)methylenephosphorane **2c**, and negative results with (formyl)- and (acetyl)methylenephosphoranes **2d**,**e** may be attributed to the weak reactivity of these Wittig reagents bearing acyl groups.[17] The process is probably complicated by the easily occurring consecutive reaction of the newly formed conjugated system in vinyldiazoketone **4**, which reacts with one more molecule of phosporanes **2d**,**e** to give polyolefinic structures.

In summary, the reaction of fluoroalkyl-containing diazodiketones with (alkyloxycarbonyl)- and (benzoyl)methylene triphenylphosphoranes proceeds chemoselectively at the perfluoroacyl carbonyl group furnishing the corresponding fluorinated vinyldiazoketones with *E* configuration at the carbon–carbon double bond, in moderate to good yields.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Gemini-300 and Bruker DRX-600 NMR spectrometers at an operating frequency of 300 or 600 MHz (^1H), 75 or 150 MHz (^{13}C) and at 282 MHz (^{19}F) in $CDCl_3$ using TMS and $CFCl_3$ as internal standards. IR spectra were recorded on a spectrophotometer Specord 75IR with KBr pellets. Microanalysis was performed on a Heraeus CHNS Rapid Analyzer. All reactions were carried out in carefully purified and dried solvents, and were monitored by TLC on Silufol UV/VIS 254 nm plates (KAVALIER) using UV light and iodine as visualizing agents. Preparative column chromatography was carried out on neutral silica gel (CHEMAPOL L 40/100 or MERCK 70–230 mesh) with petroleum ether (40–70 °C) and Et_2O as eluents.

2-Diazo-1,3-diketones 1a–j; General Procedure

The diazo transfer reaction to prepare **F**-diazodiketones **1a**–**h** was performed in carefully dried equipment, with moisture excluded at all stages of the process.[10] Reaction with non-fluorinated 1,3-diketones was carried out in the usual manner.[8]

DBU (or another base) (4.5 mmol) was added dropwise to a magnetically stirred solution of 3-nitro-4-methyl-benzenesulfonyl azide (20 mmol) and 1,3-diketone **3** (18 mmol) in CH_2Cl_2 (20 mL) under cooling (0–5 °C) over 5–10 min. The reaction mixture was stirred for 2–3 h, filtered through a short plug of silica gel (3 g), and washed with CH_2Cl_2–hexane (2:1, 5 × 5 mL). Solvents from the combined organic phases were removed in vacuo (or at atmospheric pressure in the case of **1a**), and the residue was purified by distillation under vacuum (for **1i**,**j**) or by column chromatography on silica gel (for **1a**–**h**) to give diazodiketones **1**.

Vinyldiazoketones 4a–h,k,l; General Procedure

F-Diazodiketone **1** (4 mmol) was added dropwise to a stirred suspension of methylene triphenylphosphoranes **2a**,**b**,**d**,**e** (4.8 mmol) in Et_2O (5 mL; toluene for **2c**). After the complete disappearance of **1** from the reaction mixture (3–4 h, in the case of phosphoranes **2c**,**d**,**e** starting diazo compounds **1a**,**c** were still present even after 6–14 d), the solid matter was removed by filtration, the resultant filtrate was concentrated in vacuo, and the residue purified by column chromatography to furnish **F**-vinyldiazoketones **4a**–**h**,**k**,**l** as bright yellow-orange oils. Vinyldiazoketones **4b**,**c**,**e** were additionally purified by repeated column chromatography to give analytically pure samples.

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