ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 12, pp. 1840–1843. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © M.B. Supurgibekov, L. Hennig, B. Schulze, V.A. Nikolaev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 12, pp. 1866–1869.

SHORT COMMUNICATIONS

Stereochemical Aspect of the Intramolecular Diaza-Wittig Reaction

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Received June 25, 2008

DOI: 10.1134/S1070428008120221

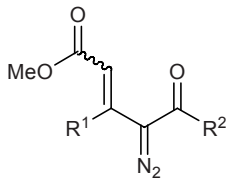
Reactions of fluoroalkyl-substituted vinyl diazo carbonyl compounds with triphenylphosphine are accompanied by spontaneous intramolecular cyclization of the initially formed phosphazene, and pyridazines are formed as a result of tandem process [1–3]. However, no analogous transformations occur with fluorine-free vinyl diazo carbonyl compounds. Taking into account that fluoroalkyl-containing vinyl diazo carbonyl compounds are usually characterized by *cis* configuration* of the double bond [1, 4] and that their fluorine-free analogs are *trans* isomers [5, 6], the most probable reason for their different reactivities is different arrangement of functional groups (CO_2Alk, CN_2) at the double C=C bond. The goal of the present work was to compare chemical transformations of diastereoisomeric fluoroalkyl-containing and fluorine-free phosphazenes derived from vinyl diazo carbonyl compounds.

As substrates we selected phosphazenes **IIIa**, **IIIb**, **IVa**, **IVb**, and **V** with *cis* and *trans* configuration of the double C=C bond, which were synthesized from diazo ketones **Ia** and **Ib** and diazo ester **II** and triphenylphosphine and tris(dimethylamino)phosphine.

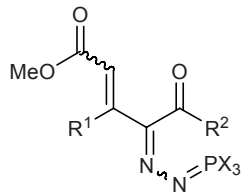
The relative configuration of stereoisomeric vinyl diazo ketones **Ia** and **Ib** was determined by NMR spectroscopy using NOE, COLOC, and HMQC techniques, and the configuration of diazo ester **II** was assigned on the basis of the coupling constants for protons at the double bond (2-H and 3-H) and X-ray diffraction data. It is known that configuration of the double C=C bond does not change in the Staudinger reaction of vinyl diazo carbonyl compounds with phosphines.

The reaction of the pure *cis* isomer of vinyl diazo ketone **Ia** with triphenylphosphine gave 4-trifluoromethyl-substituted pyridazine **VI** in more than 70% yield, while intermediate *cis*-phosphazene **IIIa** could not be isolated from the reaction mixture, in keeping with our previous data [3]. In analogous reaction with a mixture of *cis* and *trans* isomers **Ia** and **Ib** at a ratio of ~1 : 1 we isolated 43% of pyridazine **VI** together with pure *trans*-phosphazene **IIIb** (39%) (Scheme 1). The structure and relative configuration of the latter was determined by spectral data and X-ray analysis.

More nucleophilic tris(dimethylamino)phosphine reacted with a mixture of *cis*- and *trans*-isomeric vinyl diazo ketones **Ia** and **Ib** (~1 : 1) to give a mixture of *cis*- and *trans*-phosphazenes **IVa** and **IVb** in an overall yield of 92%, their ratio being the same as for initial diazo ketones **Ia** and **Ib** (~1 : 1, according to the



Ia, **Ib**, **II**

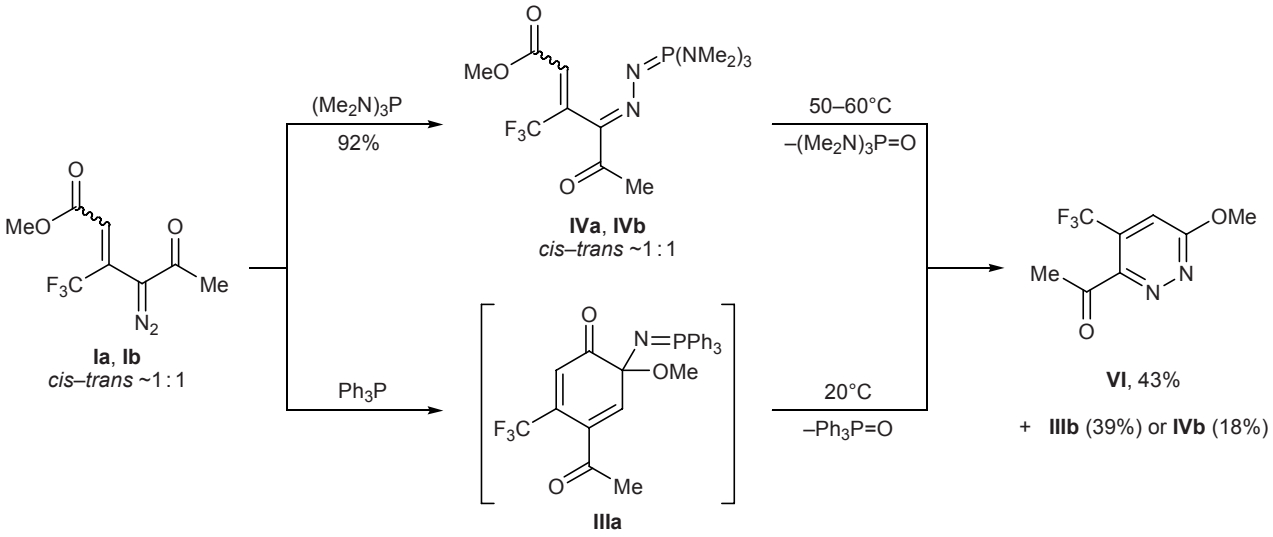


IIIa, **IIIb**, **IVa**, **IVb**, **V**

I, $R^1 = CF_3$, R^2 = Me, *cis* (**a**), *trans* (**b**); **II**, R^1 = H, R^2 = OMe, *trans*; **III**, $R^1 = CF_3$, R^2 = Me, X = Ph, *cis* (**a**), *trans* (**b**); **IV**, $R^1 = CF_3$, R^2 = Me, $X = NMe_2$, *cis* (**a**), *trans* (**b**); **V**, R^1 = H, R^2 = OMe, X = Ph, *trans*.

* Hereinafter, *cis* and *trans* arbitrarily denote mutual orientation of the CO_2Alk and $C=N_2$ groups at the double C=C bond with no account taken of group seniority.

Scheme 1.



^{1}H NMR data). Phosphazenes **IVa** and **IVb** turned out to be less reactive that their analogs **IIIa** and **IIIb** derived from triphenylphosphine, and they did not undergo subsequent diaza-Wittig reaction at room temperature (18–20°C). On the other hand, heating of a mixture of stereoisomeric phosphazenes **IVa** and **IVb** in benzene at 65–68°C resulted in the formation of 45% of pyridazine **VI**, and 18% of unreacted *trans* isomer **IVb** was recovered from the reaction mixture. The structure of phosphazene **IIIb**, *cis*/*trans*-phosphazenes **IVa**/**IVb**, and pyridazine **VI** was determined by ^{1}H and ^{13}C NMR spectroscopy.

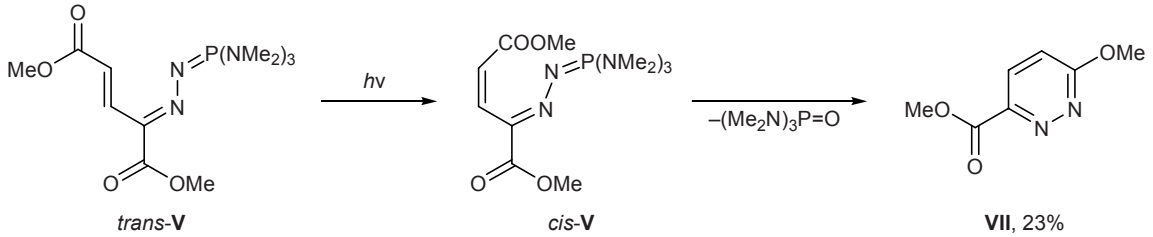
The above experimental data suggest that initially formed *cis*-phosphazenes **IIIa** and **IVa** undergo spontaneous intramolecular diaza-Wittig reaction, and the two-step process finally yields pyridazine **VI**. Phosphazines **IIIb** and **IVb** having *trans*-configured double C=C bond do not undergo diaza-Wittig reaction and remain unchanged. This assumption was confirmed by photochemical isomerization of *trans*-phosphazene **V** to the corresponding *cis* isomer and subsequent cyclization of the latter to pyridazine **VII** (Scheme 2). After irradiation (quartz light filter, $\lambda > 210$ nm) of *trans*-**V** in benzene for 20 h, we isolated 23% of pyridazine **VII** and 76% of unreacted initial phosphazene **V**.

We can conclude that the reactivity of fluorinated and fluorine-free vinyl diazo carbonyl compounds is governed by configuration of the double C=C bond: phosphazenes with *cis* orientation of functional groups (CO_2Alk, CN_2) at the double C=C bond readily undergo intramolecular diaza-Wittig reaction with formation of the corresponding pyridazines, whereas *trans* isomers do not react.

Methyl *cis*-4-diazo-5-oxo-3-trifluoromethylhex-2-enoate **(Ia)** was synthesized by the Wittig reaction from 3-diazo-1,1,1-trifluoropentane-2,4-dione and methyl (triphenyl-λ^5-phosphanylidene)acetate. Yield 75%, bp 30–33°C (0.5 mm), R_f 0.6 (petroleum ether–diethyl ether, 1 : 1) [4]. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): 2.15 s (3H), 3.71 s (3H), 6.51 s (1H).

cis- and *trans*-Isomeric vinyl diazo ketones **Ia** and **Ib** and *trans*-diazo ester **II** were synthesized by the diazo transfer reaction [7, 8] from the corresponding vinyl carbonyl compounds using *p*-acetylaminobenzenesulfonyl azide (*p*-ABSA) and DBU [9] in diethyl ether. In the synthesis of **Ia** and **Ib**, the starting mate-

Scheme 2.



rial was a ~1 : 1 mixture of *cis*- and *trans*-vinyl ketones prepared by reaction of 1,1,1-trifluoropentane-2,4-dione with methyl (triphenyl-λ^5-phosphanylidene)acetate. Compound **II** was synthesized from commercial glutaconic acid dimethyl ester (Aldrich).

Methyl *cis*- and *trans*-4-diazo-5-oxo-3-trifluoromethylhex-2-enoates Ia and Ib were synthesized from 2 g (9.5 mmol) of a mixture of the corresponding vinyl ketones, 3.4 g (14.2 mmol) of *p*-ABSA, and 0.36 g (2.3 mmol) of DBU. Yield 0.96 g (43%), a mixture of *cis* and *trans* isomers at a ratio of 1 : 1, yellow liquid, bp 45–50°C (1–2 mm), R_f 0.34 (petroleum ether–ethyl acetate, 2 : 1). ^{1}H NMR spectrum, δ, ppm: *cis* isomer **Ia**: 2.25 s (3H, CH_3), 3.81 s (3H, OCH_3), 6.60 s (1H, CH); *trans* isomer **Ib**: 2.34 s (3H, CH_3), 3.82 s (3H, OCH_3), 7.01 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: *cis* isomer **Ia**: 25.7, 52.6, 65.4, 122.7 q ($^1J_{CF}$ = 275.8 Hz), 126.8 q ($^3J_{CF}$ = 4.6 Hz), 128.0 q ($^2J_{CF}$ = 34.5 Hz), 163.6, 188.1; *trans* isomer **Ib**: 26.7, 60.7, 66.2, 121.6 q ($^1J_{CF}$ = 275.8 Hz), 127.4 q ($^3J_{CF}$ = 4.6 Hz), 127.6 q ($^2J_{CF}$ = 34.5 Hz), 164.8, 188.9. Mass spectrum, *m*/*z* (I_{rel}, %): 208 $[M - 28]^+$ (87), 193 (100), 183 (12), 180 (25), 165 (47), 151 (30), 137 (40), 123 (20), 107 (52), 75 (30).

Dimethyl *trans*-4-diazopent-2-enedioate (II) was synthesized from 0.1 g (0.63 mmol) of dimethyl glutaconate, 0.19 g (0.7 mmol) of *p*-ABSA, and 0.152 g (0.7 mmol) of DBU [5]. Yield 0.095 g (85%), yellow crystals (from Et_2O), mp 72–73°C, R_f 0.43 (petroleum ether–ethyl acetate, 3 : 1). ^{1}H NMR spectrum, δ, ppm: 3.75 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.73 d (1H, 3-H, ^3J = 16.2 Hz), 7.33 d (1H, 2-H, ^3J = 16.2 Hz).

Reaction of diazo ketones Ia and Ib with triphenylphosphine. A mixture of *cis* and *trans* isomers **Ia** and **Ib** (~1 : 1), 250 mg (1 mmol), was added to a solution of 278 mg (1 mmol) of triphenylphosphine in ~3 ml of diethyl ether, and the mixture was kept for 2 h at room temperature in the dark with protection from atmospheric air. The precipitate was filtered off, washed with cold diethyl ether (2 × 1 ml), and dried under reduced pressure to obtain 195 mg of *trans*-phosphazene **IIIb**. The filtrate was evaporated, and the residue was subjected to column chromatography on silica gel (7 g) using petroleum ether–ethyl acetate as eluent (10 : 1 to 3 : 1, gradient elution) to isolate (in the order of elution) 95 mg of pyridazine **VI** and 15 mg of *trans*-phosphazene **IIIb**.

1-(6-Methoxy-4-trifluoromethylpyridazin-3-yl)-ethanone (VI). Yield 95 mg (43%), colorless liquid, R_f 0.35 (petroleum ether–ethyl acetate, 2 : 1) [3]. ^{1}H NMR spectrum, δ, ppm: 2.83 s (3H, CH_3), 4.30 s (3H, OCH_3), 7.34 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 27.96, 56.19, 116.2 q ($^3J_{CF}$ = 6.0 Hz), 121.3 q ($^1J_{CF}$ 274.0 Hz), 131.2 q ($^2J_{CF}$ = 37 Hz), 150.1, 166.0, 196.4.

Methyl *trans*-5-oxo-3-trifluoromethyl-4-(triphenyl-λ^5-phosphanylidenehydrazono)hex-2-enoate (IIIb). Yield 210 mg (39%), yellow crystals, mp 140–140.5°C (decomp., from Et_2O), R_f 0.13 (ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 3.79 s (3H, OCH_3), 6.12 s (1H, CH), 7.45–7.72 m (15H, H_{arom}). Found, %: C 62.33; H 4.50; N 5.55. $C_{26}H_{22}F_3N_2O_3P$. Calculated, %: C 62.6; H 4.5; N 5.6.

Dimethyl *trans*-4-(triphenyl-λ^5-phosphanylidenehydrazono)pent-2-enedioate (V). Triphenylphosphine, 1 mmol, was dissolved in a minimal amount of diethyl ether (~3 ml), 1 mmol of diazo ester **II** was added, and the mixture was left to stand for 4 h at room temperature in the dark with protection from atmospheric air. The precipitate was filtered off, washed with cold benzene (2 × 1 ml), and dried under reduced pressure (1–2 mm) at 18–20°C. Yield 423 mg (87%), yellow crystals (from diethyl ether), mp 108–109°C, R_f 0.16 (petroleum ether–ethyl acetate, 3 : 1). ^{1}H NMR spectrum, δ, ppm: 3.76 s and 3.78 s (3H each, OCH_3), 7.42–7.74 m (16H, C_6H_5, 2-H), 8.12 d (1H, 3-H, ^3J = 16.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.82 and 51.90 (OCH_3), 119.91 (C^2), 127.05 d (C^i, $^1J_{CP}$ = 93.8 Hz), 129.29 d (C^m, $^3J_{CP}$ = 10.9 Hz), 130.07 (C^3), 133.23 (C^p), 134.07 d (C^o, $^2J_{CP}$ = 8.9 Hz), 141.01 d (C=N, $^3J_{CP}$ = 41.9 Hz), 166.68 and 170.40 (C=O). UV spectrum (ethanol), λ, nm (log ε): 219 (3.53), 359 (3.33). Found, %: C 67.29; H 5.14; N 6.47. $C_{25}H_{23}N_2O_4P$. Calculated, %: C 67.3; H 5.2; N 6.3.

Photolysis of phosphazene (V). A solution of 0.43 g (1.24 mmol) of *trans*-**V** in 20 ml of a mixture of petroleum ether and diethyl ether (2 : 1) was irradiated for 20 h at λ > 210 nm (quartz light filter). The precipitate was filtered off, washed with petroleum ether (2 ml), and dried in air. We thus isolated 10 mg of pyridazine **VII**. The mother liquor was evaporated, the residue was applied to 1 g of silica gel and transferred to a column charged with 10 g of silica gel, and the column was eluted with petroleum ether–ethyl acetate (3 : 1 to 1 : 1, gradient elution) to isolate (in the order of elution) 35 mg of pyridazine **VII** and 330 mg (76%) of unreacted phosphazene **V**.

Methyl 6-methoxypyridazine-3-carboxylate (VII). Yield 45 mg (23%), colorless crystals (from diethyl ether), mp 119–120°C, R_f 0.6 (ethyl acetate).

^{1}H NMR spectrum, δ, ppm: 4.05 s (3H, OCH_3), 4.24 s (3H, OCH_3), 7.07 d (1H, 5-H, ^3J = 9 Hz), 8.08 d (1H, 4-H, ^3J = 9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 53.40 and 55.87 (OCH_3), 117.40 (C^5), 130.61 (C^4), 148.09 (C^3), 164.85 (C=O), 166.45 (C^6).

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker DPX-300 spectrometer at 300 and 75 MHz, respectively. The mass spectra (electron impact, 70 eV) were measured on a VG 12-250 instrument with direct sample admission into the ion source. The IR spectra were recorded on a Specord M-80 spectrometer. The progress of reactions was monitored by TLC using Silufol UV-254 plates (Kavalier). Neutral silica gel (Silicagel L, 40–100 μm) was used for preparative column chromatography.

The authors thank Deutscher Akademischer Austausch Dienst (DAAD) for providing Leonard Euler scholarship for M.B. Supurgibekov (a student of the Faculty of Chemistry, St. Petersburg State University) and greatly appreciate Prof. J. Sieler (University of Leipzig, Germany) for performing X-ray analysis of diazoglutaconate **II** and phosphazene **IIIb**.

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