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SHORT COMMUNICATIONS

diaza-Wittig Reactions of Diketoesters Phosphazines: Synthesis of Tetrasubstituted Fluoroalkyl-Containing Pyridazines

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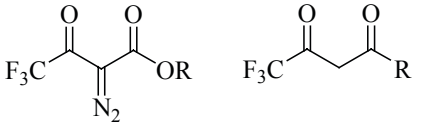
Pyridazines attract much attention due to their biological activity [1], some of them are used in the treatment of Parkinson, Alzheimer, and other neurodegenerative diseases [2, 3]. Therefore the development of new methods of preparation of this class compounds is an urgent problem of the synthetic organic chemistry.

In keeping with published reports 3,4,6-trisubstituted pyridazines can be synthesized in good yields from 2-vinyl derivatives of 2-diazoketones by the intramolecular *diaza*-Wittig reaction [4–9]. The only example of the synthesis of the tetrasubstituted pyridazine with the use of analogous procedure was described in [10], where by the *diaza*-Wittig reaction of the posphazine of 4-diazopyrrolidinetrione with ethyl acetoacetate bicyclic pyrrolo[3,4-*c*]pyridazine was obtained.

The aim of our study was the elucidation of the possibility to obtain 3,4,5,6-tetrasubstituted pyridazines by the intermolecular *diaza*-Wittig reaction of phosphazines of acyclic diazoketoesters with 1,3-diketones and ketoesters .

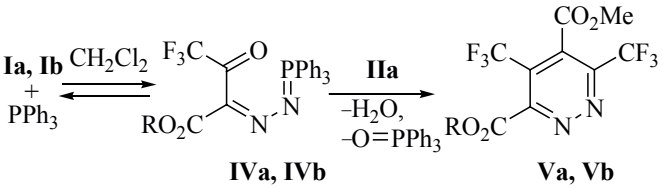
We used as diazo substrates methyl and ethyl 2-diazo-3-oxo-4,4,4-trifluorobutanoates (**Ia, Ib**), and as 1,3-dicarbonyl compounds ketoesters **IIa, IIb** and diketones **IIc, IId**. In the preparation of the phosphazines from diazoketoesters **I** we applied the triphenylphosphine (**IIIa**) commonly used in the Staudinger reaction [11–13] and more nucleophilic [14] tris(dimethylamino)phosphine (**IIIb**).



Ia, Ib **IIa–IId**

I, R = Me (**a**), Et (**b**); **II**, R = OMe (**a**), OEt (**b**), Me (**c**), *t*-Bu (**d**).

The reaction of diazoketoesters **Ia, Ib** with ketoester **IIa** was carried out similarly to procedure [10] using PPh_3. It presumably proceeded with the intermediate formation of triphenylphosphazines **IVa, IVb** and was of low efficiency. The monitoring of the reaction progress by ^1H NMR spectroscopy showed that under these conditions a fairly complex mixture of products formed containing alongside the target compounds also a diazoacetic ester phosphazine and the other reaction products, and according to the data of ^1H NMR spectrum of the reaction mixture the yield of pyridazines **V** did not exceed 30–32%.



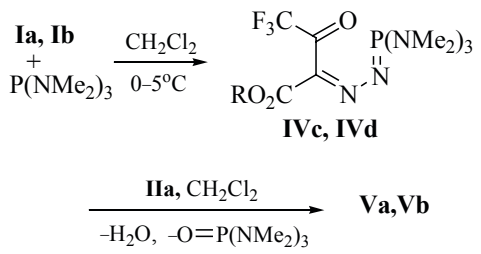
IVa, IVb **Va, Vb**

The relatively low yield of pyridazines **V** and the occurrence of the side processes in the reaction with the use of the triphenylphosphine is apparently due to the ready dissociation of the triphenylphosphazines **IV** formed in the first stage into the initial components, PPh_3 and diazoketoesters **I** [5, 12, 13]. This decreases the efficiency of the subsequent *diaza*-Wittig reaction, and in the presence in the reaction mixture of a little water formed in the stage of condensation it makes possible the

parallel proceses: the hydrolysis of fluoroalkyl-containing diazoketoesters **I** [5] and/or of phosphazines **IVa, IVb** [13, 14]. In this connection in further experiments phosphine **IIIb** was used since it provided phosphazines more stable against thermolysis and hydrolysis [9].

The reaction of diazoketoesters **Ia, Ib** with tris(dimethylamino)phosphine (**IIIb**) proceeded with heat evolution and furnished as a result phosphazines **IVc, IVd** in 95–97% yield. The analysis of the ^{1}H NMR spectra of the reaction mixture showed that in contrast to the reaction with PPh_3, phosphine **IIIb** reacted with diazoketoesters **I** virtually quantitatively and irreversibly. The structure of phosphazines **IVc, IVd** was confirmed by ^{1}H and ^{13}C NMR spectra, their purity, by the elemental analyses, and in further experiments phosphazines **IVc, IVd** were used without additional purification.

The reaction of phosphazines **IVc, IVd** with ketoester **IIa** was carried out at 18–20°C over 72 h or at heating in dichloromethane (39–40°C) within 6 h. After the workup of the reaction mixture and chromatographic purification pyridazines **Va, Vb** were isolated in preparative yields of 44–50%.



IVc, IVd

Va,Vb

Investigating the reactions of phosphazines **IVa, IVb** with diketone **IIc** we varied reaction time and temperature to estimate the effect of these variations on the efficiency of the formation of 5-acetyl-substituted pyridazines **VIa, VIb**.

The highest yields of pyridazines **VIa, VIb** (35–46% by the data of ^{1}H NMR) were obtained in the reaction carried out in acetonitrile at the temperature of the reaction mixture 80–81°C in the presence of dehydrating agents (magnesium or calcium sulfates). The increased temperature of the reaction mixture favors the higher yield of bis(trifluoromethyl)-substituted pyridazines **VI** (yield of pyridazine **VIa** at 80°C 46% compared with 11% at 39–40°C). Yet the attempts to use weak organic or inorganic bases (Et_3N, Na_2CO_3, K_2CO_3) for the intensification of the condensation stage resulted in a significant decrease in the yield of tetrasubstituted pyridazines **VI** (yield of pyridazine **VIa** in the presence of Et_3N was 14% in contrast to 46% in the absence of the base).

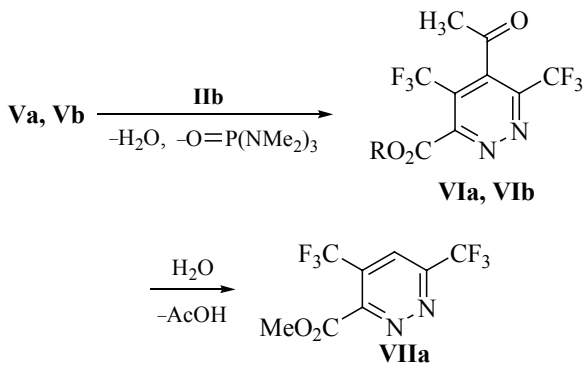
By the more detailed investigation of the composition of the reaction mixtures we established that alongside the target pyridazines **VI** they contained the products of deacylation of the latter, trisubstituted pyridazines **VII** (up to 25–37% by the data of ^{1}H NMR). The hydrolytic cleavage of the acetyl group occurs evidently owing to the presence of water formed in the stage of the condensation. It is also presumable that this process is catalyzed by bases for the yields of the 5-acetyl-substituted pyridazines essentially decrease in the presence of bases. At the same time the addition into the reaction mixture of drying agents ($CaSO_4$ or $MgSO_4$) led to the increased yields of tetrasubstituted pyridazines **VI** and to decreased yields of deacylated products **VII** (yields of pyridazine **VIa** in the presence of calcium sulfate and without it were 39 and 11% respectively).

It was also shown that the reaction of phosphazine **IVa** with diketone **IId** containing in its structure the sterically loaded *tert*-butyl group provided the corresponding pyridazine **VId** in a low yield (9%).

The structure of pyridazines **Va, Vb** and **VIa, VIb** was established from ^{1}H, ^{13}C NMR spectra, their composition, from elemental analyses. The signals of atoms C^3 at 152.8, 153.1 and of C^6 at 148.7 and 148.6 q ($^2J_{C–F}$ 35.9 Hz) in the spectra of pyridazines **Va, Vb**, and also 152.8, 153.1 (C^3), 148.1 q (C^6, $^2J_{C–F}$ 35.9 Hz) in the spectra of **VIa, VIb** are located in the region of the ^{13}C NMR spectra characteristic of unsubstituted [15] and trisubstituted pyridazines [5, 7, 9].

The presence of the signals from the ester and acetyl carbonyl groups in the ^{13}C NMR spectra of pyridazines **Va, Vb** and **VIa, VIb** at 162.6, 162.2 and 194.2, 194.4 ppm respectively shows that the condensation of the 1,3-dicarbonyl fragment forming the cyclic pyridazine system does not affect these groups but occurs chemoselectively at the carbonyl group linked to the trifluoromethyl group.

Hence we established for the first time that the reaction of phosphazines of fluoroalkyl-containing diazoketoesters with fluorinated acyclic 1,3-diketones and ketoesters provides by a tandem process (*diaza*-Wittig reaction and condensation) tetrasubstituted fluoroalkyl-containing pyridazines. This method makes it possible to obtain 5-alkoxycarbonyl- and 5-acetyl-4,6-bis(trifluoromethyl)-substituted pyridazines in the preparative yields up to 50%.



R = Me (**a**), Et (**b**)

The use in the reaction of tris(dimethyl)aminophosphazines provided higher yields of pyridazines than the application of the triphenylphosphazine analogs readily dissociating in solution. The presence in the reaction mixture of organic or inorganic bases (Et_3N, Na_2CO_3, K_2CO_3) decreases the yields of tetrasubstituted pyridazines apparently due to the hydrolytic cleavage of the 5-acetyl group from the molecule of the initially formed pyridazine.

Phosphazines IVc,IVd. General procedure. To a solution of 0.8–1.5 mmol of diazo compound **Ia, Ib** in 5–7 ml of dichloromethane cooled with ice was added dropwise within 10–15 min 0.8–1.5 mmol of phosphine **IIIb** in 5–7 ml of dichloromethane. The reaction mixture of yellow color was stirred at room temperature for 10 min, the solvent was completely distilled off in a vacuum (10–12, next 0.1–0.5 mm Hg), obtained phosphazines **IVc, IVd** (practically pure substances according to ^{1}H NMR data) were used in further experiments without additional purification.

For the preparation of analytically pure phosphazines **IVc, IVd** the residue after the removal of solvent was applied to a small column packed with silica gel (5.5 g), elution with a mixture of petroleum ether with ethyl acetate, 1:1 (20 ml). The eluate was dried with anhydrous magnesium sulfate, the residue after the removal of solvents was recrystallized from a mixture of Et_2O and petroleum ether.

Methyl 2-[tris(dimethylamino)phosphoranilidene] azino-3-oxo-4,4,4-trifluorobutanoate (IVc) was obtained from 0.3 g (1.5 mmol) of diazoketoester **Ia** and 0.25 g (1.5 mmol) of phosphine **IIIb**. Yield 517 mg (96%), yellow crystals, mp 82.5–84°C (from mixture Et_2O–petroleum ether), R_f 0.33 (ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 2.71 d (18H, CH_3, $^3J_{P–H}$ 8.9 Hz), 3.83 s (3H, OCH_3). ^{13}C NMR spectrum, δ, ppm: 37.4 d (CH_3, $^2J_{C–P}$ 1.7 Hz), 51.5 (OCH_3), 117.7 q (CF_3, $^1J_{C–F}$ 291.2 Hz), 140.0 d (C=N, $^3J_{C–P}$ 50.9 Hz), 164.8 (COOMe), 174.8 q (CO, $^2J_{C–F}$ 31.9 Hz). Found, %: C 36.67, 36.64; H 6.17, 6.13; N 19.04, 19.05. $C_{11}H_{21}F_3N_5O_3P$. Calculated, %: C 36.77; H 5.89; N 19.49.

Ethyl 2-[tris(dimethylamino)phosphoranilidene] azino-3-oxo-4,4,4-trifluorobutanoate (IVd) was obtained from 0.17 g (0.8 mmol) of diazoketoester **Ib** and 0.13 g (0.8 mmol) of phosphine **IIIb**. Yield 300 mg (97%), yellow crystals, mp 64–66°C (from mixture Et_2O–petroleum ether), R_f 0.48 (ethyl acetate). ^{1}H NMR spectrum, δ, ppm: 1.31 t (3H, CH_2CH_3, $^3J_{H–H}$ 7.1 Hz), 2.71 d (18H, CH_3, $^3J_{P–H}$ 8.9 Hz), 4.30 q (2H, CH_2CH_3, $^3J_{H–H}$ 7.1 Hz). ^{13}C NMR spectrum, δ, ppm: 14.71 (OCH_2CH_3), 37.4 d (CH_3, $^2J_{C–P}$ 1.7 Hz), 60.5 (OCH_2), 117.8 q (CF_3, $^1J_{C–F}$ 291.2 Hz), 140.6 d (C=N, $^3J_{C–P}$ 51.9 Hz), 164.5 (COOMe), 174.8 q (CO, $^2J_{C–F}$ 31.9 Hz). Found, %: C 38.57, 38.76; H 6.20, 6.22; N 18.52, 18.39. $C_{12}H_{23}F_3N_5O_3P$. Calculated, %: C 38.61; H 6.21; N 18.76.

Pyridazine Vb. A mixture of 0.89 g (2.38 mmol) of phosphazine **IVd**, 0.81 g (4.8 mmol) of ketoester **IIa**, and 0.5 g of anhydrous $MgSO_4$ in 5 ml of dichloromethane was stirred at room temperature for 72 h (TLC monitoring), the solvent was distilled off in a vacuum (10–12 mm Hg), the residue (~1.5 g) in 2 ml of the mixture MeOBu-*t* and petroleum ether was filtered through a bed of silica gel (5 g), elution with the mixture MeOBu-*t* and petroleum ether, 1:1 (40 ml). The residue after the removal of the solvent was distilled in a vacuum.

5-Methoxycarbonyl-4,6-bis(trifluoromethyl)-3-ethoxycarbonylpyridazine (Vb). Yield 406 mg (50%), colorless crystals, mp 52–54°C (from mixture Et_2O–petroleum ether), bp 65–75°C (0.1 mm Hg), R_f 0.60 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.45 t (3H, CH_2CH_3, $^3J_{H–H}$ 7.1 Hz), 4.05 s (3H, OCH_3), 4.58 q (2H, CH_2CH_3, $^3J_{H–H}$ 7.1 Hz). ^{13}C NMR spectrum, δ, ppm: 13.8 (OCH_2CH_3), 54.6 (OCH_3), 60.1 (OCH_2), 120.2 q (CF_3, $^1J_{C–F}$ 276.8 Hz), 120.8 q (CF_3, $^1J_{C–F}$ 277.0 Hz), 124.9 q (C^4, $^2J_{C–F}$ 35.9 Hz), 128.9 (C^5), 148.6 q (C^6, $^2J_{C–F}$ 35.7 Hz), 153.1 (C^3), 161.2 (COOEt), 162.2 (COOMe). Найде-но, %: C 38.36, 38.02; H 2.61, 2.45; N 8.16, 8.24. $C_{11}H_8F_6N_2O_4$. Calculated, %: C 38.15; H 2.33; N 8.09.

Pyridazines VIa, VIb. General procedure. To a solution of 2.55 mmol of phosphazine **IVc, IVd** in 5 ml of acetonitrile was added 0.78 g (5.1 mmol) of trifluoroacetylacetone (**IIb**), ~1 g of anhydrous $MgSO_4$

or $CaSO_4$, and the mixture was stirred at 79–80°C over 20–50 h till the phosphazines **IVc, IVd** disappeared from the reaction mixture (TLC monitoring). The drying agent was filtered off, the solvent was distilled off from the filtrate at 20 mm Hg, unreacted ketone **IIb** was distilled off at 1–2 mm Hg, the residue was subjected to chromatography on a column packed with 8 mg of silica gel, gradient elution with a mixture of MeOBu-*t* with petroleum ether.

5-Acetyl-4,6-bis(trifluoromethyl)-3-ethoxycarbonylpyridazine (VIb). Yield 330 mg (39%), colorless crystals, mp 69–70.5°C (from mixture Et_2O–petroleum ether), R_f 0.53 (petroleum ether–ethyl acetate, 2 : 1). ^{1}H NMR spectrum, δ, ppm: 1.46 t (3H, $CH_2C\underline{H}_3$, $^3J_{H-H}$ 7.3 Hz), 2.67 s (3H, CH_3), 4.59 q (2H, $C\underline{H}_2CH_3$, $^3J_{H-H}$ 7.3 Hz). ^{13}C NMR spectrum, δ, ppm: 13.7 ($OCH_2\underline{C}H_3$), 31.3 (OCH_3), 64.3 (OCH_2), 120.6 q (CF_3, $^1J_{C-F}$ 276.3 Hz), 121.1 q (CF_3, $^1J_{C-F}$ 277.3 Hz), 124.1 q (C^4, $^2J_{C-F}$ 35.9 Hz), 136.7 (C^5), 148.1 q (C^6, $^2J_{C-F}$ 35.7 Hz), 153.3 (C^3), 162.3 (<u>C</u>OOEt), 194.4 (<u>C</u>OMe). Found, %: C 40.25, 40.18; H 2.53, 2.59; N 8.64, 8.73. $C_{11}H_8F_6N_2O_3$. Calculated, %: C 40.01; H 2.44; N 8.48.

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker 300, operating frequencies 300 (^{1}H) and 75.5 MHz (^{13}C), solvent $CDCl_3$, internal reference TMS. Elemental analyses were carried out on an analyzer Heraeus CHNO Rapid Analyser. Reaction mixtures were separated by column chromatography on neutral Silicagel L 40/100 (Aldrich) in the gradient mode, eluents ethyl acetate or the mixture of petroleum ether and MeOBu-*t* in various ratios. The reaction progress was monitored and R_f was measured by TLC on Silufol UV-254 pates (Kavalier, Czechia). Diazodicarbonyl compounds **Ia, Ib** were obtained from commercial ethyl or methyl 4,4,4-trifluorooxobutanoates by the diazotransfer reaction [5], fluoro-containing 1,3-dicarbonyl compounds **IIa–IIc** were obtained by Claisen condensation [16].

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