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CHEMISTRY

Diarylphosphoryl-Containing β-Diketones: Methods of Synthesis and Transformation into Pyrazoles

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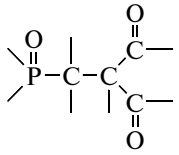
Functionalized phosphine oxides containing oxoalkyl substituents where phosphoryl and carbonyl groups are separated by the ethylene fragment have attracted much recent attention. For example, 4-(diorganylphosphoryl)-4-methylpentan-2-ones **(I)** can be used as fire retardants for poly(vinyl chloride), the best results having been obtained for diarylphosphoryl compounds [1]. Later, phosphorylmonoketones of type **I** have been demonstrated to be efficient extractants of lanthanides from acid solutions, better than such a known bidentate organophosphorus extractant as *N*,*N*-dibutylcarbamoylmethylphosphine oxide $Ph_2P(O)CH_2C(O)N(Bu\text{-}n)_2$ [2].

The introduction of an additional functional group into the oxoalkyl group of γ-oxoalkylphosphine oxide molecule could be one of the most promising variants to extend the area of practical application of the phosphine oxides, in particular, to increase their extraction capacity. In our opinion, diorganylphosphoryl derivatives of β-diketones are the most interesting from this point of view.

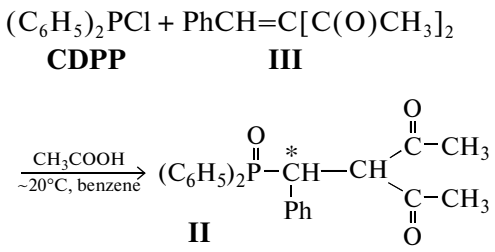


Moreover, bifunctionalized phosphine oxides of such a kind can behave as intermediates for preparing original potentially biologically active heterocyclic systems containing diorganylphosphoryl substituents.

However, only one organophosphorus compound of such a kind has been reported in the literature to date, namely, 3-[α-(diphenylphosphoryl)benzyl]pentane-2,4-dione **(II)**, which was isolated in minor yield by the action of dry HCl on the adduct of 3-benzylidenepentane-2,4-dione **(III)** with $MeOPPh_2$ [3].

In this work, by the example of compound **II**, we suggest for the first time simple and efficient variants of preparation of diorganylphosphorylated β-diketones, using available chlorophosphines as initial organophosphorus compounds.

It was found that the modified Conant reaction—the reaction of chlorodiphenylphosphine (CDPP) with α,β-enones in the presence of acetic acid in benzene at ambient temperature—is suitable for the synthesis of not only appropriate diphenylphosphorylated monoketones [4, 5] but also diphenylphosphoryl-containing diketones when alkylidenediones, for example benzylidenedione **III**, are used as initial compounds (Scheme 1).



Scheme 1.

This reaction allows the preparation of target compound **II** in a rather high yield (85.1%); however, its rate is relatively low. Therefore, we developed another

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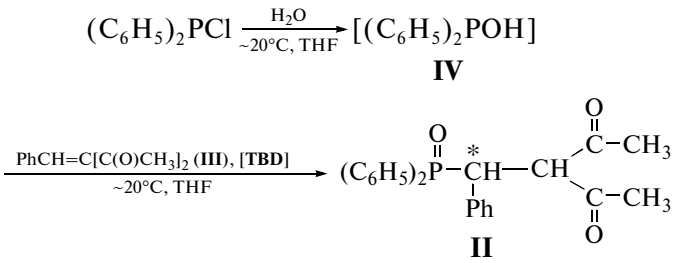
two-step one-pot method for preparing diketone **III**, starting from the same initial compounds, CDPP and benzylidenedione **II** (Scheme 2).

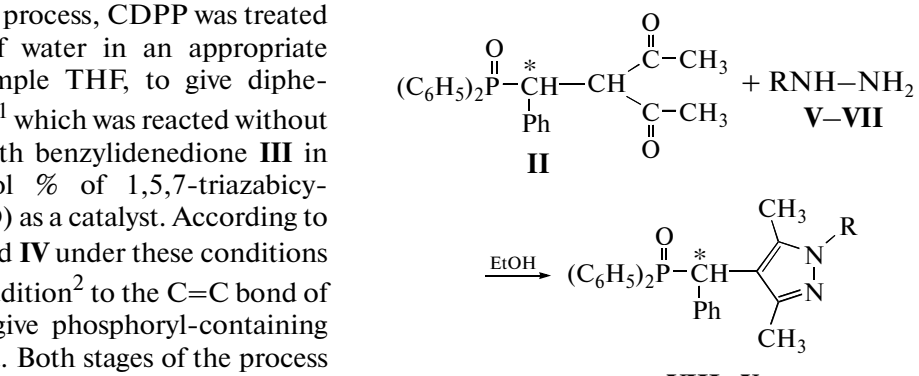


Scheme 2.

At the first stage of this process, CDPP was treated with a twofold excess of water in an appropriate organic solvent, for example THF, to give diphenylphosphinous acid (**IV**),[1] which was reacted without additional purification with benzylidenedione **III** in the presence of 10 mol % of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a catalyst. According to $^{31}P\{^1H\}$ NMR spectra, acid **IV** under these conditions undergoes regiospecific addition[2] to the C=C bond of benzylidenedione **III** to give phosphoryl-containing diketone **II** in 86.9% yield. Both stages of the process are carried out at ambient temperature, and the total reaction time does not exceed 24 h.

The suggested alternative methods for the synthesis of diphenylphosphorylated pentan-2,4-dione **II**, especially the one-pot process based on acid **IV**, are simple, industrially feasible and, if necessary, can be readily used for the preparation of other diarylphosphoryl-containing β-diketones.

β-Diketones and some of their derivatives are known to react readily with hydrazine and substituted hydrazines to form pyrazoles [7]. The reaction of diphenylphosphorylated diketone **II** with hydrazine hydrate (**V**) and monosubstituted hydrazines (**VI** and **VII**) in ethanol is also regioselective and yields phosphoryl-containing 3,5-dimethylpyrazoles (**VIII**–**X**, respectively) (Scheme 3). This is the first example of the preparation of substituted pyrazoles containing diorganylphosphoryl group in the side chain of the heterocycle.



Scheme 3.

Diketone **II** and unsubstituted hydrazine **V** readily react even at ambient temperature. The reactions of *N*-isopropylhydrazine **VI** and especially *N*-phenylhydrazine **VII** proceed less vigorously than with unsubstituted hydrazine and require refluxing for several hours to complete.

The structure of the synthesized diphenylphosphorylated pyrazoles **VIII**–**X** was confirmed by the data of ^1H NMR spectra and, in the case of 1-phenyl derivative **X**, also by $^{31}P\{^1H\}$ NMR and mass spectra.

In the ^1H NMR spectrum of N-unsubstituted pyrazole derivative **VIII**, the chemical shifts of methyl groups at the 3- and 5-positions of the pyrazole ring coincide, which results from the prototropic tautomerism of 1,2-pyrazoles [8]. Thus, the effect of the chiral benzyl carbon atom does not appear in the ^1H NMR spectrum of this compound as distinct from the spectrum of initial diketone **II**, whose methyl groups are diastereotopic and show different chemical shifts in ^1H NMR spectra [3]. On the contrary, in the ^1H NMR spectra of 1-substituted pyrazole derivatives **IX** and **X**, the methyl groups at the 3- and 5-positions of the pyrazole ring have different chemical shifts, the

[1] Acid **IV** was isolated in almost quantitative yield, its purity according to $^{31}P\{^1H\}$ NMR spectra was ~97%, which is identical to that of the commercially available but very expensive product offered by Aldrich and Acros.

[2] According to the literature data, the addition of diorganylphosphinic acids, including acid **IV**, to α-benzylideneketones at ambient temperature in the absence of catalysts occurs, on the contrary, at the C=O group of benzylideneketone molecule [6].

largest Δδ is observed for 1-phenyl-substituted compound **X**. The presence of asymmetric center in the molecule of pyrazole **IX** causes the diastereotopy of the methyl groups of the 1-isopropyl moiety, which appear in the ^{1}H NMR spectrum as two doublets. It is noteworthy that changes in structure on passing from diketone **II** ($\delta_{^{31}P}$ = 31.0 ppm [3]) to 1-phenylpyrazole derivative **X** ($\delta_{^{31}P}$ = 32.0 ppm) have only slight effect on the chemical shift of ^{31}P nuclei in these compounds. The results of mass spectral analysis of compound **X** correspond to those expected for pyrazole derivatives.

According to the data of preliminary testing in the Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences, diphenylphosphorylated diketone **II** prepared in this work, in contrast to corresponding monoketones, can extract platinum group metals from acid solutions, and this fact confirms the promise of further synthetic studies in this direction.

As for phosphoryl-containing pyrazoles **VIII**–**X**, the presence of potentially pharmacophoric groups in these molecules make these original heterocyclic compounds interesting in the context of their possible application in medicine.

EXPERIMENTAL

The ^{1}H and ^{31}P{^{1}H} NMR spectra of the compounds were recorded on a Bruker AV-400 spectrometer operating at 400.13 MHz for ^{1}H and 161.98 MHz for ^{31}P{^{1}H}. The solvent was $(CD_3)_2SO$ or $CDCl_3$. Residual proton signals of the deuterated solvent were used as the internal reference for ^{1}H NMR, and 85% H_3PO_4 was used as the external reference for ^{31}P{^{1}H} NMR spectra.

Initial benzylidenedione **III** (Aldrich) was used without additional purification. Chlorodiphenylphosphine (Acros) was purified by vacuum distillation prior to use.

Benzene was dried by distillation over P_2O_5 prior to use. Other organic solvents used in the work were purified by common procedures [9].

All manipulations with CDPP were carried out in an argon atmosphere.

Mass spectra were obtained on a Finnigan SSQ 7000 mass spectrometer.

Elemental analysis was performed in the Laboratory of Microanalysis, Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences.

Synthesis of 3-[α-(diphenylphosphoryl)benzyl]pentane-2,4-dione (II). (a) Benzylidenedione **III** (2.16 g, 11.15 mmol) was added dropwise to a solution of 2.46 g (11.14 mmol) of CDPP in 10 mL of anhydrous benzene. Then, a solution of 0.73 g (12.16 mmol) of glacial acetic acid in 10 mL of anhydrous benzene was added with magnetic stirring, the reaction mixture was kept in the dark at ambient temperature for 48 h, and the resultant precipitate was separated, recrystallized from ethyl acetate, and dried in a vacuum (~10 mmHg) for 2 h at 120°C to give 3.7 g of 3-[α-(diphenylphosphoryl)benzyl]pentane-2,4-dione (**II**). Yield 85.1%, mp 189–190°C. Lit.: mp 182–184°C [3].

For $C_{24}H_{23}O_3P$ anal. calcd. (%): C, 73.83; H, 5.94; P, 7.93.

Found (%): C, 73.88; H, 5.69; P, 7.95.

(b) Chlorodiphenylphosphine (1.098 g, 0.00498 mol) was added dropwise to a solution of 0.2 g (0.0111 mol) of distilled water in 7 mL of THF, and the mixture was magnetically stirred for 15 min. The solvent, excess water, and resultant HCl were removed by keeping the reaction mixture first in a vacuum of a water-jet pump (~15 mmHg) at 30–35°C for 0.5 h and then in a vacuum of a rotary vane pump (~1 mmHg) at 50–55°C for 1 h. The residue was dissolved in 12 mL of THF, a solution of 0.937 g (0.00498 mol) of benzylidenedione **III** and 68 mg (0.498 mmol) of TBD in 10 mL of THF were added dropwise to that solution, and the mixture was magnetically stirred for 2 h at ambient temperature and allowed to stand overnight. The solvent was removed in a vacuum, the residue was dissolved in 10 mL of chloroform, the resultant solution was filtered through 3 g of basic Al_2O_3, the solvent was removed from the filtrate in a vacuum, the residue was triturated with hexane, and the resultant crystalline product was washed with distilled water (2 × 10 mL) and dried in air to give 1.69 g of 3-[α-(diphenylphosphoryl)benzyl]pentane-2,4-dione (**II**). Yield 86.9%, mp 190.5–191.5°C (hexane–chloroform).

For $C_{24}H_{23}O_3P$ anal. calcd. (%): C, 73.83; H, 5.94; P, 7.93.

Found (%): C, 73.94; H, 5.77; P, 7.91.

Synthesis of 4-[α-(diphenylphosphoryl)benzyl]-3,5-dimethylpyrazole (VIII). A mixture of 0.1 g (0.26 mmol) of diketone **II**, 0.015 mL (0.26 mmol) of hydrazine hydrate **V** and 5 mL of ethanol was magnetically stirred for 8 h at ambient temperature. The resultant precipitate was separated by filtration, washed with ethanol, and twice with ethyl acetate, and dried in a vacuum over calcined calcium chloride to give 0.05 g of 4-[α-(diphenylphosphoryl)benzyl]-3,5-dimethylpyrazole (**VIII**). Yield 50.5%, mp > 240°C (dec.).

For $C_{24}H_{23}N_2OP$ anal. calcd. (%): C, 74.60; H, 6.00; N, 7.25; P, 8.01.

Found (%): C, 74.03; H, 5.84; N, 6.86; P, 8.35.

^{1}H NMR ($(CD_3)_2SO$, δ, ppm, *J*, Hz): 2.08 (s, 6H, 3- + 5-CH_3), 3.51 (br s, 1H, NH), 4.70 (d, 1H, CHP, $^2J_{H-P} = 10.7$), 7.16–7.80 (m, 15H, C_6H_5).

Synthesis of 4-[α-(diphenylphosphoryl)benzyl]-1-isopropyl-3,5-dimethylpyrazole (IX). A mixture of 0.1 g (0.26 mmol) of diketone **II**, 0.025 mL (0.27 mmol) of isopropylhydrazine **VI** and 5 mL of ethanol was magnetically stirred for 3 h at ambient temperature and then heated at reflux for 3 h. The solvent was removed, and the resultant precipitate was recrystallized from benzene to give 0.06 g of 4-[α-(diphenylphosphoryl)benzyl]-1-isopropyl-3,5-dimethylpyrazole (**IX**). Yield 54.5%, mp 186°C.

For $C_{27}H_{29}N_2OP$ anal. calcd. (%): C, 75.68; H, 6.82; N, 6.54; P, 7.23.

Found (%): C, 75.27; H, 6.39; N, 6.17; P, 7.79.

^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 1.32 (d, 3H, $CH(C\underline{H}_3)_2$, $^3J_{H-H} = 6.4$), 1.34 (d, 3H, $CH(C\underline{H}_3)_2$, $^3J_{H-H} = 5.6$), 1.91 (s, 3H, 3- or 5-CH_3), 2.08 (s, 3H, 5- or 3-CH_3), 4.18–4.27 (m, 1H, $\underline{CH}(CH_3)_2$), 4.65 (d, 1H, CHP, $^2J_{H-P} = 10.8$), 7.08–7.82 (m, 15H, C_6H_5).

Synthesis of 4-[α-(diphenylphosphoryl)benzyl]-3,5-dimethyl-1-phenylpyrazole (X). A mixture of 0.1 g (0.26 mmol) of diketone **II**, 0.035 g (0.32 mmol) of phenylhydrazine **VII** and 5 mL of ethanol was heated at reflux for 6 h. The solvent was removed, and the residue was recrystallized from benzene to give 0.06 g of 4-[α-(diphenylphosphoryl)benzyl]-3,5-dimethyl-1-phenylpyrazole (**X**). Yield 50.1%, mp > 240°C (dec.).

For $C_{30}H_{27}N_2OP$ anal. calcd. (%): C, 77.90; H, 5.88; N, 6.06; P, 6.70.

Found (%): C, 77.54; H, 5.71; N, 5.68; P, 6.93.

^{1}H NMR ($(CD_3)_2SO$, δ, ppm, *J*, Hz): 1.61 (s, 3H, 3- or 5-CH_3), 1.97 (s, 3H, 5- or 3-CH_3), 4.76 (d, 1H, CHP, $^2J_{H-P} = 10.7$), 7.06–7.96 (m, 20H, C_6H_5).

$^{31}P\{^1H\}$ NMR ($(CD_3)_2SO$, δ, ppm): 32.0 s.

MS (*m*/*z*): 462.261 $[M]^+$(100%), 220, 201, 144, 118, 91, 77.

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