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The Behavior of Phosphorus Reagents Towards Substituted Diazine and Hydrazine Derivatives

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Summary. The reaction of dibenzoyldiazine with phosphorus ylides afforded the new 2-[(benzoylhydrazono)phenylalkyl]but-2-enedioic acid dialkylesters. Moreover, ethyl-2(triphenylphosphoranylidene)propionate reacts with dibenzoyldiazine to give the olefinic compound and triphenylphosphine oxide. On the other hand, oxovinylidene-triphenylphosphorane reacts with dibenzoyldiazine to give a new phosphorane adduct. Trialkyl phosphites react with dibenzoyldiazine to yield the dialkyl phosphonate products. The reaction of dibenzoylhydrazide with *Wittig* reagents gave rise to the new 3,7-diphenylpyrazolo[1,2-α]pyrazole-1,5-diones. Possible reaction mechanisms are considered, and the structural assignments are based on analytical and spectroscopic results.

Keywords. Ylides; Trialkyl phosphites; Diazines; Hydrazides.

Introduction

Diverse biological and pharmacological activities have been reported for diazines and their related compounds [1]. Furthermore, they form part of the structure of azapeptides [2], biologically active antibiotic compounds [3a, b], potent anticancer [3c], and antimalerial agents [3d], and have also been extensively used as versatile precursors in acyclic [4] and heterocyclic synthesis [5]. This together with our interest in organophosphorus chemistry [6–10] triggered the synthesis of new phosphorus compounds incorporating such important nuclei that may possibly lead to biological activity. The present study deals with the reaction of stabilized phosphonium ylides **1a**–**1c**, active phosphacumulene ylide **2**, trialkyl phosphites **3a**–**3b** with dibenzoyldiazine (**4a**) and *N*,*N*-dibenzoylhydrazide (**4b**) (Scheme 1).

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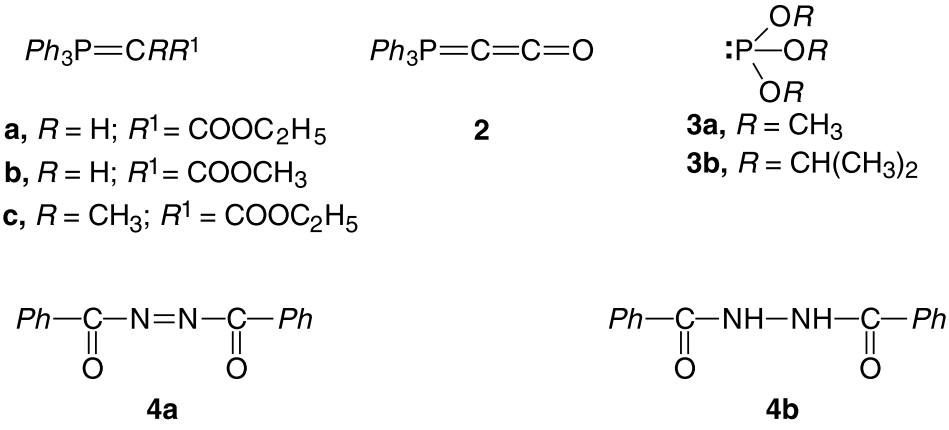
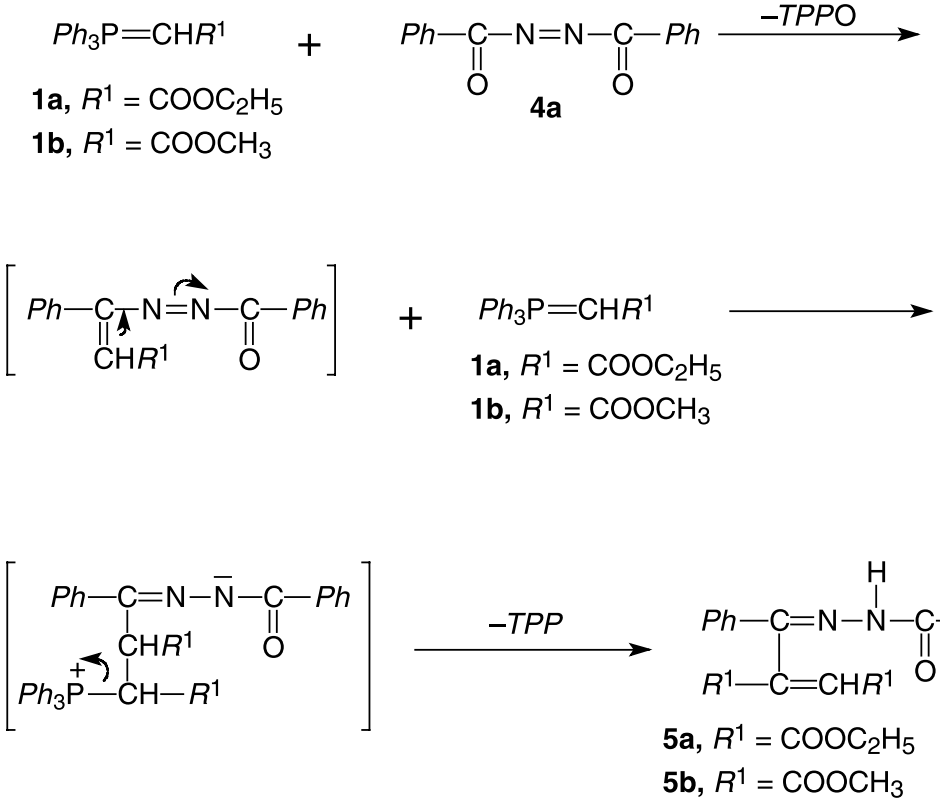


Scheme 1

Results and Discussion

We have found that dibenzoyldiazine (**4a**) reacts with two equivalents of ethoxycarbonylmethylenetriphenylphosphorane (**1a**) in dry benzene at room temperature to give colourless crystals formulated as 2-[(benzoylhydrazono)phenylmethyl]but-2-enedioic acid diethylester (**5a**). Triphenylphosphine oxide and triphenylphosphine were also isolated from the reaction medium (Scheme 2). Compound **5a** is



Scheme 2

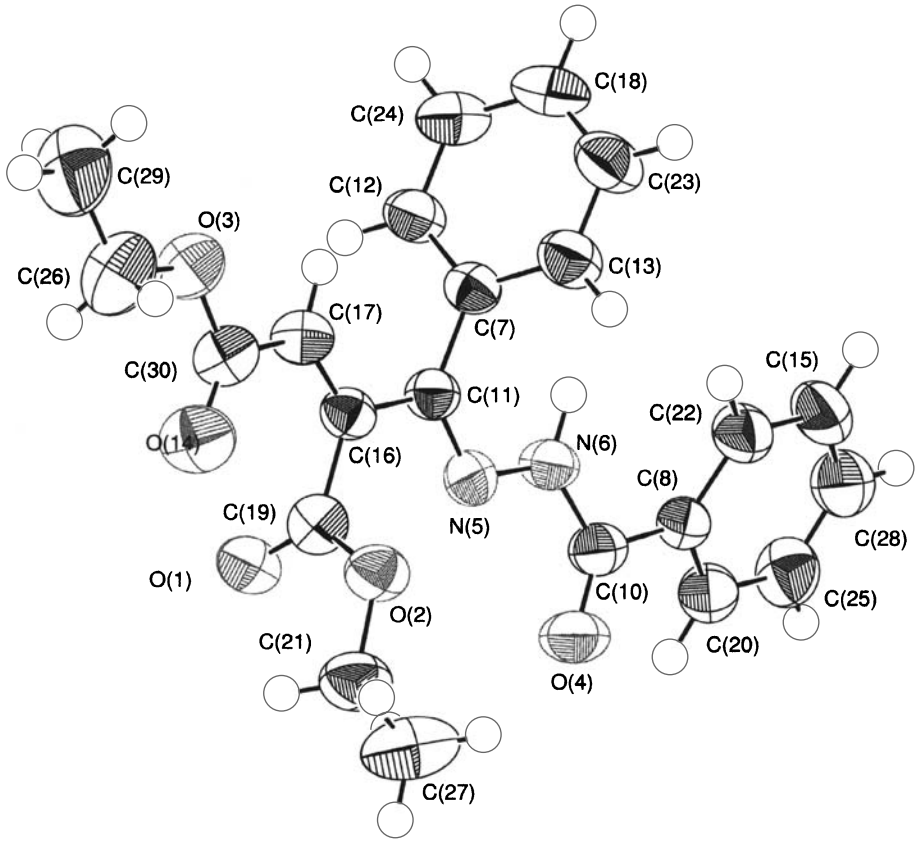


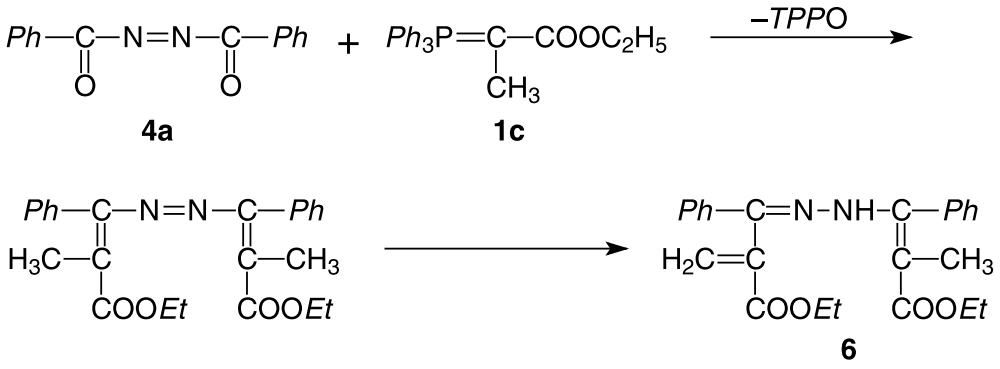
Fig. 1. Molecular structure of **5a** with the atomic numbering scheme; anisotropic displacement parameters are drawn at the 30% level and the hydrogen atoms are shown as spheres of arbitrary radii

chromatographically pure and possesses a sharp melting point. The structure assigned to **5a** was based mainly on the X-ray analysis together with correct microanalysis, IR, ^{1}H NMR, and mass spectral data (*cf.* Experimental). In order to identify unambiguously the structure of the reaction product **5a**, an X-ray structure determination [11–15] of crystalline **5a** was performed (Fig. 1).

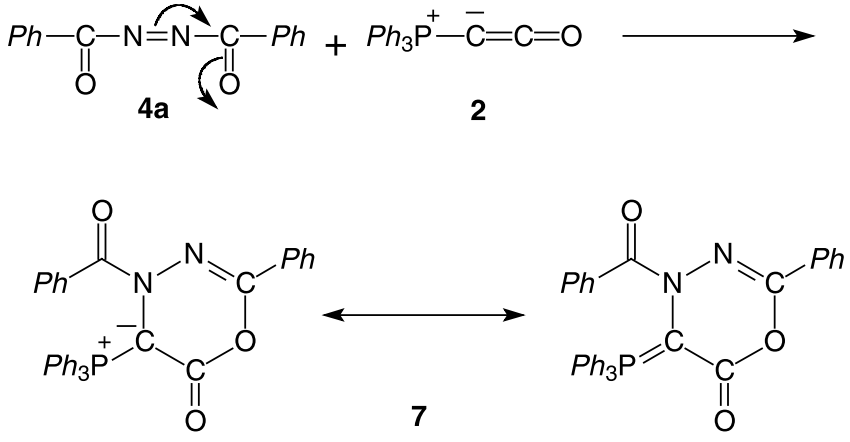
Similarly, carbmethoxymethylenetriphenylphosphorane (**1b**) reacts with **4a** (**1b:4a** = 2:1) to give adduct **5b** in 87% yield. Triphenylphosphine oxide and triphenylphosphine were also isolated from the reaction mixture (Scheme 2). Structure **5b** was deduced from correct microanalysis, IR, ^{1}H NMR, and MS spectral data (*cf.* Experimental).

It is worth mentioning that, when **4a** was allowed to react with one equivalent of ylides **1a** or **1b** in dry benzene, adducts **5a** or **5b** were obtained in low yields. A possible explanation of the course of the reaction of phosphonium ylides **1a** and **1b** with **4a** is shown in Scheme 2. Addition of one mole of ylide to the more electronegative carbonyl group in **4a** results in the formation of triphenylphosphine oxide and the unstable olefinic intermediate, which reacts with a second molecule of ylide to give adducts **5a** or **5b** along with triphenylphosphine (Scheme 2).

When **4a** reacts with two equivalents ethyl 2-(triphenylphosphoranylidene)propionate (**1c**) in dry benzene, **6** and triphenylphosphine oxide were isolated in good



Scheme 3

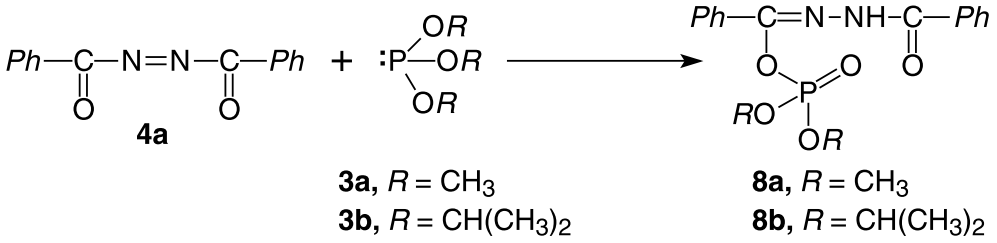


Scheme 4

yields (Scheme 3). The structural assignments for **6** are based upon elemental and mass spectral analysis (IR, ^{1}H and ^{13}C NMR, and MS, *cf.* Experimental).

Next, when **4a** was treated with 2-oxovinylidenetriphenylphosphorane (**2**) in *THF* at 20°C for 8 hours, adduct **7** was isolated. Compound **7** was obtained irrespective whether one or two equivalents of **2** were used (Scheme 4). Its elemental analysis and spectroscopic results were consistent with the assigned structure **7**. The IR spectrum of **7** revealed the presence of strong absorption bands at 1650 cm^{-1} (PhCO–N–), 1740 (C=O, lactone), and 1436 (P-aryl) cm^{-1}. Its ^{1}H NMR spectrum contained aromatic protons at $\delta = 7.57$–7.94 and its ^{13}C NMR spectrum exhibited appropriate signals (*cf.* Experimental). A signal at $\delta = +25.90$ ppm was observed in the ^{31}P NMR spectrum of **7**, which supports structure **7** and fits with the phosphorane structure [16]. The mass spectrum of **7** contains a prominent peak for M^{+} at $m/e = 540$, which corroborates the phosphanylidene structure **7**. A possible explanation of the course of the reaction of the phosphacumulene ylide **2** with **4a** is shown in Scheme 4 [16].

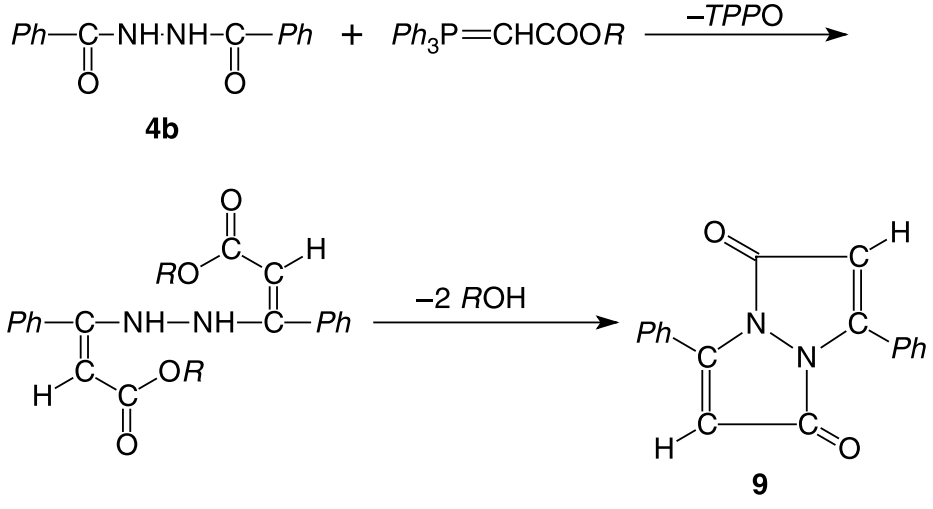
We have also investigated the reaction of **4a** with trialkyl phosphites **3a** and **3b** to establish whether it would behave in a similar manner. Thus, we found that the



Scheme 5

reaction of **3a** with **4a** in dry benzene proceeds at reflux temperature to give the chromatographically pure 1:1 adduct formulated as the dialkyl phosphate **8a** (Scheme 5). The structure of **8a** was deduced from its elemental analysis, IR, ^{1}H, ^{13}C, and ^{31}P NMR, and mass spectral data (*cf.* Experimental). Similarly, **3b** reacts with **4a** to give the dialkyl phosphate product **8b** in good yield. The structural assignments for **8b** were deduced from spectral analysis (*cf.* Experimental). Furthermore, this study was extended to include the behavior of dibenzoylhydrazide (**4b**) towards phosphonium ylides **1a**, **1b** and trialkyl phosphites **3a**, **3b** to determine the preferential site of attack. We found that **4b** reacts with two equivalents **1a** or **1b** in refluxing toluene in presence of a few drops *DMF* to give **9** in 55% yield. Triphenylphosphine oxide was also isolated from both reaction media. The structure of **9** was assigned on the basis of IR, ^{1}H and ^{13}C NMR, and mass spectral data (*cf.* Experimental).

We propose the reaction course depicted in Scheme 6. The reaction was assumed to proceed through olefination of the two carbonyl groups in **4a** by *Wittig* reagents **1a** or **1b** followed by elimination of two molecules of alcohol under the applied reaction conditions to offord **9**. It is worth mentioning that **4b** is inactive towards trialkyl phosphites **3a** and **3b** under very drastic conditions.



Scheme 6

Conclusion

The results of the present investigation show that the reaction course of dibenzoyldiazine (**4a**) with the active phosphacumulene **2** differs markedly from that of the respective stabilized phosphonium ylides **1a–1c**. In case of the reaction of **2**, 4-benzoyl-2-phenyl-5-(triphenyl-λ^5-phosphanylidene)-4,5-dihydro[1,3,4]oxadiazin-6-one (**7**) was produced. Moreover, the reaction of **4a** with stabilized phosphonium ylides leads to different products depending on the reaction conditions as well as the stability of the addition products. Also, the unexpected behavior of **1a** and **1b** towards dibenzoylhydrazide (**4b**) leading to 3,7-diphenylpyrazolo[1,2-α] pyrazole-1,5-dione (**9**) represents a new finding and supplements the promising aspect of utilizing phosphorus reagents **1** in syntheses.

Experimental

Melting points were measured by means of an electrothermal apparatus. Phosphoranes **1a–1c**, dibenzoyldiazine (**4a**), and dibenzoylhydrazide (**4b**) were prepared according to Refs. [17–19]. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infrared Spectrophotometer Model 157. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Spectrometer at 270 and 67.5 MHz using *TMS* as internal reference. The ^{31}P NMR spectra were taken with a Varian CFT-20 (*vs.* external 85% H_3PO_4 standard). The mass spectra were recorded at 70 eV with a Kratos MS equipment or Varian MAT 311 A Spectrometer. Elemental analyses were performed using the Elmentar varu EL Germany Instrument. Their values agreed favourably with the calculated ones.

*General Procedure for the Reaction of Phosphonium Ylides **1a–1c** with Dibenzoyldiazine (**4a**) to yield **5a**, **5b**, and **6***

A mixture of 0.002 mol **1a–1c** and 0.001 mol dibenzoyldiazine (**4a**) [18] in 30 cm^3 dry benzene was stirred at room temperature for 8 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give the products.

2-[(Benzoylhydrazono)phenylmethyl]but-2-enedioic acid diethylester (**5a**, $C_{22}H_{22}N_2O_5$)

Eluent: petroleum ether/ethyl acetate (80/20, *v*/*v*). Product **5a** was separated as yellow crystals, yield 85%, mp 160–161°C. IR (KBr): $\bar{\nu} = 1730$ (C=O, ester), 1671 (COPh), 3250 (NH) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.25$ (t, 2COOCH$_2$*CH$_3$*), 4.15(q, 2COO*CH$_2$*CH$_3$), 5.60 (s, =CH), 7.25–7.90 (m, 10H Ar), 8.70 (br, NH) ppm; MS(EI): m/z (%) = 394 (M^+, 100), 349 (M^+–OC_2H_5, 30), 321 (M^+–$COOC_2H_5$, 40).

Table 1. X-ray crystallographic analysis of **5a**

Chemial formula	$C_{22}H_{22}N_2O_5$	Formula mass/g mol^{-1}	394.427
Temperature/K	298	Wavelength/Å	0.71073
Crystal system	Triclinic	Crystal description	Prismatic
Space group			
a/Å	9.4963(9)	α/°	95.693(5)
b/Å	10.1708(12)	β/°	11.283(5)
c/Å	11.950(2)	γ/°	95.685(5)
Cell volume/Å^3	1055.6(2)		
θ range/°	2.91–25.35		

X-Ray Crystallographic Study [11–15]: A single crystal of **5a** was grown by conventional crystallization from cyclohexane. The crystal structure was solved and refined, using maXus (Nonius, Delft and Mac Science, Japan). MoK_{α} radiation ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection. A summary of the crystal analysis parameters is given in the Table 1. Details are contained in CCDC file No 293760 at Cambridge Crystallographic Centre.

2-[(Benzoylhydrazono)phenylmethyl]but-2-enedioic acid dimethylester (**5b**, $C_{20}H_{18}N_2O_5$)
Eluent: petroleum ether/ethyl acetate (70/30, *v*/*v*). Product **5b** was separated as yellow crystals, yield 87%, mp 183–184°C. IR (KBr): $\bar{\nu} = 1731$ (C=O, ester), 1686 (COPh), 3100 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3.71$ (s, $2COOCH_3$), 5.64 (s, =CH), 7.25–7.61 (m, 10H, Ar), 8.78 (br, NH) ppm; MS(EI): m/z (%) = 366 (M^+, 100), 307 (M^+–$COOCH_3$, 75), 335 (M^+–OCH_3, 50).

3-[N′-(2-Ethoxycarbonyl-1-phenyl-allylidene)hydrazino]-2-methyl-3-phenyl-acrylic acid ethyl ester (**6**, $C_{24}H_{26}N_2O_4$)
Eluent: petroleum ether/ethyl acetate (60/40, *v*/*v*). Product **6** was separated as white crystals, yield 90%, mp 179–180°C. IR (KBr): $\bar{\nu} = 1659$ (C=O, ester), 1579 (C=N), 1600 (C=C, Ar), 2942 (=CH_2), 3251 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 1.73$ (s, CH_3), 1.91, 2.22 (t, $2COOCH_2\mathit{CH_3}$), 3.80, 4.07 (q, $2COO\mathit{CH_2}CH_3$), 6.03 (br, =CH_2), 7.35–8.42 (m, 10H, Ar), 9.51 (s, NH) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 162.26$ (C=O, ester), 157.08 (C=N), 158.7 (*C*=C–CH_3), 129.7 ($H_2\mathit{C}$=C), 127 (H_2C=*C*), 84.21 (C=*C*–CH_3), 63.87 ($O\mathit{CH_2}CH_3$), 23.67, 20.31 ($2OCH_2$–*C*H_3), 8.7 (C=C–*C*H_3) ppm; MS(EI): m/z (%) = 406 (M^+, 100).

*Reaction of Phosphacumulene Ylide **2** with Dibenzoyldiazine **4a***
A mixture of 0.30 g **2** (0.001 mol) and 0.23 g **4a** (0.001 mol) in 30 cm^3 *THF* was stirred at room temperature for 8 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give **7**.

4-Benzoyl-2-phenyl-5-(triphenyl-λ^5-phosphanylidene)-4,5-dihydro[1,3,4] oxadiazin-6-one (**7**, $C_{34}H_{25}N_2O_3P$)
Eluent: petroleum ether/acetone (85/15, *v*/*v*). Product **7** was separated as white crystals, yield 85%, mp 205–206°C. IR (KBr): $\bar{\nu} = 1650$ (C=O), 1740 (C=O, lactone), 1436 (P-Aryl) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 7.57$–7.94 (m, 25HAr) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 169.4$ (N–C=O), 166.3 (O–C=O), 154.3 (C=N), 129.30, 128.5, 130.3, 127.8(C–Ph), 132.45 (d, C=P, $J_{CP} = 171.6$ Hz), 133.7, 127.5, 128.3, 131.8 (CO–Ph), 128.6, 128.4, 128.3, 128.2 (PPh_3) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = +25.90$ ppm; MS(EI): m/z (%) = 540 (M^+, 100).

*Reaction of Trialkyl Phosphites **3a** and **3b** with Dibenzoyldiazine **4a***
To a solution of 0.23 g **4a** (0.001 mol) in 30 cm^3 dry benzene trialkyl phosphite **3a** or **3b** (0.002 mol) was added dropwise at room temperature with stirring for 1–4 h. The reaction mixture was concentreted and washed several times with petroleum ether. The solid product was recrystallized from benzene to give **8a** and **8b**.

2-(Benzoylhydrazono)phenylmethyl dimethyl phosphate (**8a**, $C_{16}H_{17}N_2O_5P$)
White crystals, yield 85%, mp 221–222°C. IR (KBr): $\bar{\nu} = 1230$ (P=O), 1045 (P–OCH_3), 1650 (C=O), 3318 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 3{,}80$ (d, $J_{HP} = 13.5$ Hz, $P(O–CH_3)_2$), 7.25–7.85 (m, Ar), 9.25 (s, NH) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = -2.56$ ppm; MS(EI): m/z (%) = 348 (M^+, 100).

2-(Benzoylhydrazono)phenylmethyl diisopropyl phosphate (**8b**, $C_{20}H_{25}N_2O_5P$)
White crystals, yield 80%, mp 202–203°C. IR (KBr): $\bar{\nu} = 1230$ (P=O), 995 ($P(O–iPr)_2$), 1670 (C=O), 3350 (NH) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): $\delta = 4.74$, 4.35 (2m, 2-iPr), 1.26 (m, $(O)P(O–iPr)_2$),

7.50–7.85 (m, Ar), 9.20 (s, NH) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 24.22$ ($OCH(CH_3)_2$), 68.7 (d, $^2J_{CP} = 7.48$ Hz, $P(OCH(CH_3)_2)$), 155 (C=N), 163.0 (C=O), 127.5, 128.9, 134.2, 129.2, 131.9, 128.2 (C_6H_5) ppm; MS(EI): m/z (%) = 404 (M^+, 100).

3,7-Diphenylpyrazolo[1,2-α]pyrazolo-1,5-dione (**9**, $C_{18}H_{12}N_2O_2$)
To mixture of 0.24 g **4b** (0.001 mol) [19] and 0.002 mol **1a** or **1b** in 30 cm^3 dry toluene a few drops of *DMF* were added. The reaction mixture was refluxed for 35 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography using the eluent petroleum ether/ethyl acetate (88/12, *v*/*v*) to give **9** as white crystals, yield 55%, mp 201–202°C. IR (KBr): $\bar{\nu} = 1659$ (C=O), 1600 (C=C, Ar) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 6.5$ (s, 2C=CH), 7.35–8.05 (m, 10H, Ar) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 162$ (C=O), 152.4 (*C*=CH), 95.1 (C=*C*H), 134.4, 128.3, 127.6, 126.3 (C_6H_5) ppm; MS(EI): m/z (%) = 288 (M^+, 100).

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