ISSN 1070-4280, Russian Journal of Organic Chemistry, 2012, Vol. 48, No. 7, pp. 924–927. © Pleiades Publishing, Ltd., 2012.
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Phosphazenes: I. Reactions with Electron-Deficient Alkenes

T. A. Yangirov[a], G. R. Zubairova[a], R. M. Sultanova[a], R. Z. Biglova[a], V. A. Dokichev[a], and Yu. V. Tomilov[b]

[a] *Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia*
e-mail: dokichev@anrb.ru

[b] *Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia*

Received February 24, 2012

Abstract—Triphenylphosphazenes reacted with methyl vinyl ketone, methyl acrylate, methyl methacrylate, and dimethyl maleate to give the corresponding substituted dihydropyrazoles.

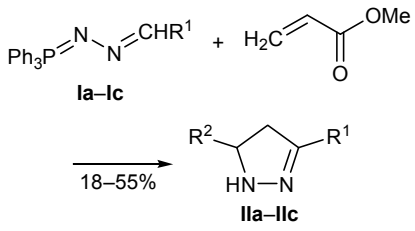
DOI: 10.1134/S1070428012070068

Well known 1,3-dipolar cycloaddition of diazo compounds to unsaturated compounds provides a convenient method for the synthesis of dihydropyrazole derivatives [1–3] which attract interest as intermediate products for the preparation of polyfunctional physiologically active substances [4–6]. For example, 2,5-di- and 3,4,5-trimethoxydihydropyrazole analogs of combretastatin A4 exhibit anticancer activity [5], while 3-(2-furyl)dihydropyrazoles act as antidepressants and anticonvulsants [6]. The use of aliphatic diazo compounds in organic synthesis is limited due to their instability and risk of explosion [7]. Phosphazenes are adducts derived from organophosphorus compounds and diazo compounds available via Staudinger reaction [8]; they are used for the identification of unstable diazo compounds and preparation of various organic compounds [9, 10]. However, there are no published data on the use of phosphazenes as synthetic equivalents of diazo compounds in 1,3-dipolar cycloaddition to unsaturated compounds. It was shown recently that triphenylphosphine activates the cycloaddition of methyl diazoacetate to methyl acrylate [11], and we presumed that phosphazenes may be formed as intermediates in 1,3-dipolar cycloaddition of diazo compounds to those containing a C=C bond.

In the present work we examined the reaction of phosphazenes with electron-deficient alkenes and synthesized some new dihydropyrazole derivatives from formaldehyde (triphenyl-λ^5-phosphanylidene)hydrazone (**Ia**), 1-[(triphenyl-λ^5-phosphanylidene)hydrazinylidene]propan-2-one (**Ib**) and methyl [(triphenyl-λ^5-phosphanylidene)hydrazinylidene]acetate (**Ic**). Unlike the corresponding diazo compounds, reactions of triphenylphosphazenes **Ia**–**Ic** with olefins can be carried out at a temperature of up to 110°C. According to the data of thermogravimetric analysis, decomposition of crystalline compounds **Ia**–**Ic** starts at 140, 120, and 110°C, respectively (see figure); under these conditions, a weight loss of 1% is observed.

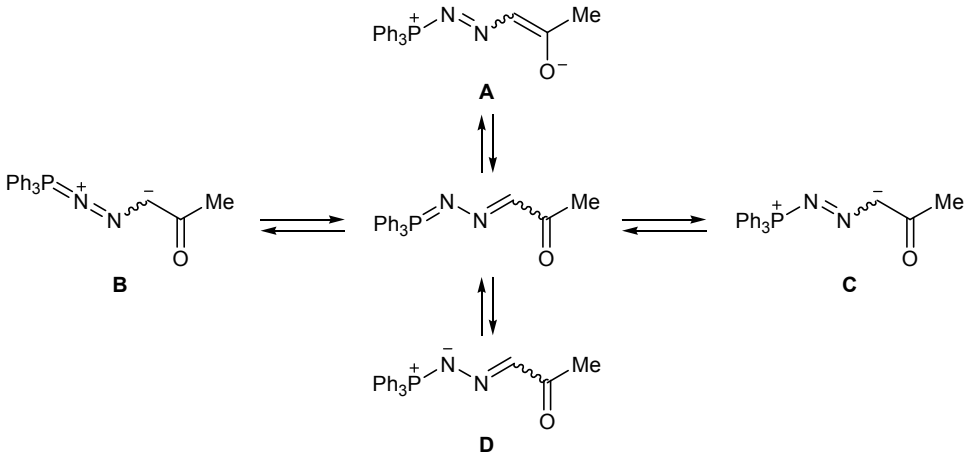
The reactions under study were carried out with equimolar amount of the reactants in benzene at 70°C (reaction time 5 h). Phosphazenes **Ia**–**Ic** reacted with methyl acrylate to form methyl 4,5-dihydro-1*H*-pyrazole-3(5)-carboxylates **IIa**–**IIc** in 48, 18, and 55% yield, respectively (Scheme 1). The yield of **IIa**–**IIc** was considerably improved by raising the reaction temperature or extending the reaction time. Methyl 4,5-dihydro-1*H*-pyrazole-5-carboxylate (**IIa**) was formed in quantitative yield in the reaction of phosphazene **Ia** with methyl acrylate at 70°C (16 h) or at 100°C (toluene, argon, sealed ampule, 5 h). The poor yield (18%) of compound **IIb** may be rationalized assuming that 1-[(triphenyl-λ^5-phosphanylidene)hydra-

Scheme 1.

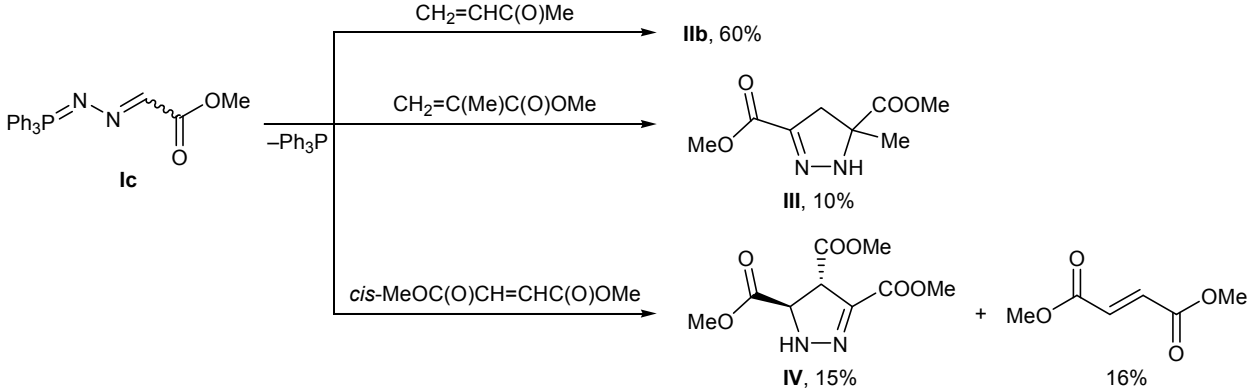


I, R^1 = H (**a**), Ac (**b**), MeOC(O) (**c**); **II**, R^2 = H, R^3 = MeOC(O) (**a**); R^2 = MeOC(O), R^3 = Ac (**b**); R^2 = R^3 = MeOC(O) (**c**).

Scheme 2.



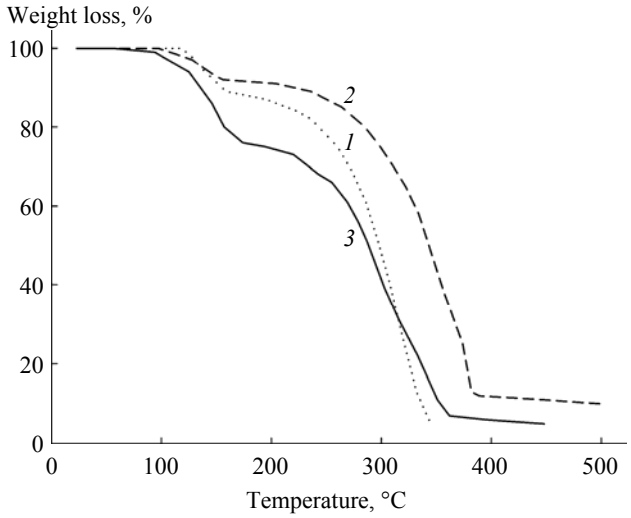
Scheme 3.



zinylidene]propan-2-one (**Ib**) exists mainly as thermodynamically more stable zwitterionic structure **A** (Scheme 2) which could not produce dihydropyrazoles in reactions with electron-deficient alkenes [12, 13].

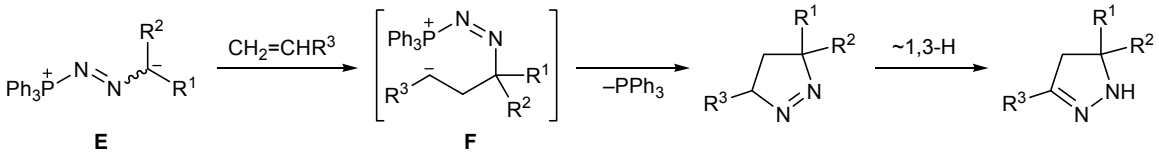
The C=C bond in methyl methacrylate and dimethyl maleate turned out to be low reactive in 1,3-dipolar cycloaddition with methyl 3-[(triphenyl-λ^5-phosphanylidene)hydrazinylidene]acetate (**Ic**), and the yield of the corresponding cycloadducts **III** and **IV** did not exceed 15% (Scheme 3). The reaction of **Ic** with dimethyl maleate was accompanied by formation of 16% of dimethyl fumarate in addition to the expected product, trimethyl *trans*-4,5-dihydro-1*H*-pyrazole-3,4,5-tricarboxylate (**IV**). Dimethyl fumarate was also formed in 19% yield in the reaction of dimethyl maleate with ethyl [(triphenyl-λ^5-phosphanylidene)-hydrazinylidene]acetate under analogous conditions. The absence of diethyl fumarate among the products indicated that dimethyl fumarate is formed via isomerization of dimethyl maleate rather than from phosphazene. The yield of dihydropyrazole **IIb** from phosphazene **Ic** and methyl vinyl ketone was 60%.

The formation of dihydropyrazole derivatives in the reaction of phosphazenes with activated alkenes may be illustrated by Scheme 4. Michael addition [14] of phosphazene as structure **E** at the activated C=C bond



Thermogravimetric analysis of phosphazenes (*1*) **Ia**, (*2*) (**Ib**), and (*3*) **Ic**.

Scheme 4.



of electron-deficient alkene yields intermediate **F** which undergoes intramolecular cyclization with elimination of triphenylphosphine. The subsequent 1,3-hydride shift leads to final 4,5-dihydropyrazole [1, 3].

Unlike diazo compounds, phosphazenes **Ia**–**Ic** reacted with electron-deficient alkenes in a selective fashion with formation of 4,5-dihydro-1*H*-pyrazoles; in no case mixtures of difficultly identifiable compounds [1–3] or by-products resulting from elimination of nitrogen from dihydropyrazole ring (which is typical of dihydropyrazoles under catalytic or thermal conditions [1, 7]) were formed.

Thus, the reaction of phosphazenes with electron-deficient alkenes gives the corresponding 4,5-dihydropyrazoles.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker Avance III (500 and 126 MHz, respectively) spectrometers using tetramethylsilane as internal reference. The IR spectra were measured on a Shimadzu IR Prestige-21 instrument from thin films or samples dispersed in mineral oil. The mass spectra (electron impact, 70 eV) were obtained on a Thermo Finnigan MAT 95 XP high-resolution mass spectrometer (ion source temperature 250°C, batch inlet probe temperature 50–270°C, heating rate 10 deg/min). The melting points were determined on a Boetius hot stage. Dynamic thermogravimetric analysis was performed on a MOM Q-1000 instrument (Paulik–Paulik–Erday), at a heating rate of 5 deg/min; balance sensitivity 1 mg per scale mark. The temperature corresponding to a weight loss of 1% was assumed to be the decomposition start.

The structure of **Ia**, **Ib**, **IIa**, **IIc**, and **III** was confirmed by their IR and ^{1}H and ^{13}C NMR spectra which were consistent with those reported in [15–19].

Formaldehyde (triphenyl-λ^5-phosphanylidene)-hydrazone (Ia). Triphenylphosphine, 5 g (19 mmol), was dissolved in 50 ml of diethyl ether, 50 ml (~30 mmol) of a 0.6 M solution of diazomethane in diethyl ether was added, and the mixture was left to stand for 24 h in the dark. The precipitate was filtered off, washed with 10 ml of diethyl ether, and recrystallized from benzene. Yield 3.6 g (62%).

1-[(Triphenyl-λ^5-phosphanylidene)hydrazinylidene]propan-2-one (Ib). Triphenylphosphine, 12.5 g (48 mmol), was dissolved in 50 ml of diethyl ether, and 4 g (48 mmol) of diazoacetone was added under stirring, After 10 min, the precipitate was filtered off, washed with 10 ml of diethyl ether, and recrystallized from benzene–diethyl ether (1 : 1). Yield 8.2 g (50%).

Methyl [(triphenyl-λ^5-phosphanylidene)hydrazinylidene]acetate (Ic) was synthesized in a similar way from 6 g (23 mmol) of triphenylphosphine and 2.3 g (23 mmol) of methyl diazoacetate in 15 ml of diethyl ether. Yield 5.5 g (66%), white crystals, mp 110–112°C (decomp.). IR spectrum, ν, cm^{-1}: 2853, 2151, 1690 (N=C), 1681 (C=O), 1520 (P=N), 1437, 1377, 1321, 1261 (C–CO_2), 1078, 916, 854, 719, 692, 577, 509. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.73 s (3H, OCH_3), 7.33 s (1H, CH), 7.45–7.80 m (15H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 51.1 (OMe), 127.5 d (C^i, J_{CP} = 93.7 Hz), 128.8 d (C^o, J_{CP} = 11.6 Hz), 132.46 (C^p), 133.7 d (C^m, J_{CP} = 8.6 Hz), 137.8 d (CH, J_{CP} = 47.7 Hz), 165.8 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 277.1015 (2.1) $[Ph_3P{=}NH]^+$, 262.0906 (100), 183.0358 (63.1), 108.0123 (19.5). Found, %: C 69.60; H 5.32; N 7.45; P 8.39. $C_{21}H_{19}N_2O_2P$. Calculated, %: C 69.61; H 5.25; N 7.73; P 8.56.

Reaction of phosphazens Ia–Ic with electron-deficient alkenes (*general procedure*). A solution of equimolar amounts of phosphazene **Ia**–**Ic** and the corresponding alkene in benzene was stirred for 5 h at 70°C under argon. The solvent was removed under reduced pressure. The yield was determined by signal intensity ratio of the CH proton in dihydropyrazole **II** and nitrometane (internal standard, δ 4.31 ppm) in the ^{1}H NMR spectra.

Methyl 4,5-dihydro-1*H*-pyrazole-3-carboxylate (IIa) was obtained from 0.5 g (1.65 mmol) of **Ia** and 0.1415 g (1.65 mmol) of methyl acrylate in 4 ml of benzene. Yield 48%.

Methyl 3-acetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (IIb). *a*. The reaction of 0.1 g (0.29 mmol) of **Ib** with 0.025 g (0.29 mmol) of methyl acrylate in 2 ml

of benzene gave 18% of **IIb**. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, Me), 3.09 d.d (1H, *cis*-4-H, ^2J = 17.6, $J_{4,5}$ = 12.6 Hz), 3.26 d.d (1H, *trans*-4-H, ^2J = 17.3, $J_{4,5}$ = 5.3 Hz), 3.77 s (3H, MeO), 4.45 d.d (1H, 5-H, J_{trans} = 5.3, J_{cis} = 12.6 Hz), 6.75 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.30 (Me), 32.98 (C^4), 52.65 (OMe), 61.37 (C^5), 149.99 (C^3), 172.0 (5-C=O), 193.89 (3-C=O). Found: *m*/*z* 170.0741 $[M]^{+\cdot}$. $C_7H_{10}N_2O_3$. Calculated: *M* 170.0693.

b. The reaction of 1 g (2.76 mmol) of **Ic** with 0.193 g (2.76 mmol) of methyl vinyl ketone in 4 ml of benzene gave 60% of **IIb**.

Dimethyl 4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylate (IIc) was obtained from 1 g (2.76 mmol) of **Ic** and 0.2376 g (2.76 mmol) of methyl acrylate in 4 ml of benzene. Yield 55%.

Dimethyl 5-methyl-4,5-dihydro-1*H*-pyrazole-3,5-dicarboxylate (III) was obtained from 0.1 g (0.28 mmol) of **Ic** and 0.028 g (0.28 mmol) of methyl methacrylate in 2 ml of benzene. Yield 10%.

Trimethyl *trans*-4,5-dihydro-1*H*-pyrazole-3,4,5-tricarboxylate (IV) was obtained from 0.25 g (0.7 mmol) of **Ic** and 0.1 g (0.7 mmol) of dimethyl maleate in 3 ml of benzene. Yield 17%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.76 s (3H, OMe), 3.78 s (3H, OMe), 3.82 s (3H, OMe), 4.40 d (1H, 4-H, $J_{4,5}$ = 5.4 Hz), 4.76 d (1H, 5-H, $J_{4,5}$ = 5.4 Hz), 6.95 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 52.10 (OMe), 52.46 (C^4), 53.25 (4-CO_2**Me**, 5-CO_2**Me**), 66.15 (C^5), 139.35 (C^3), 161.64 (3-C=O), 169.44 (C=O), 170.16 (C=O).

This study was performed under financial support by the Chemistry and Materials Science Department of the Russian Academy of Sciences (Basic Research Program "Theoretical and Experimental Studies on the Nature of Chemical Bonds and Mechanisms of the Most Important Chemical Reactions and Processes").

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