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Addition of Phthalimide and Acetone to Phosphorylated Methylene Quinones

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Abstract—New method for synthesis of phosphorylated methylene quinones via bromination of the sterically hindered phenol [prepared via benzylation of secondary chlorophosphines with 4-(methoxymethyl)-2,6-di-*tert*-butylphenol] with *N*-bromosuccinimide followed by dehydrobromination with trimethyl orthoformate has been developed. Tertiary phosphine oxides containing the fragment of sterically hindered phenol and amine or acetonyl group have been synthesized for the first time in the reaction of phosphorylated methylene quinones with *N*- and *C*-nucleophiles.

Keywords: phosphorylated methylene quinone, secondary chlorophosphine, trialkyl orthoformate, benzylation, phthalimide, bromination

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Phosphorylated sterically hindered phenols and methylene quinones are of increased interest in view of their application in the synthesis of polyfunctional organic compounds, potential biological activity, and complex formation properties [1–6]. Development of novel methods for preparation of highly reactive phosphorylated methylene quinones is a topical issue. We have recently described a new method for synthesis of such compounds, based on the successive reactions of secondary chlorophosphines with 4-hydroxy-3,5-di-*tret*-butylbenzylidenchloride and trimethyl orthoformate [1]. In this work we reported on another approach towards synthesis of phosphorylated methylene quinones and their reactions with *N*- and *C*-nucleophiles.

4-Methyl-2,6-di-*tert*-butylphenol derivatives containing an easily leaving group (Hlg, NMe_2, Ac, or OMe) in α-position have been recognized for promotion of benzylation of certain P(III) acids derivatives such as dialkyl and trialkyl phosphites and secondary chlorophosphines [7–11]. The reaction of secondary chlorophosphines with 4-methoxymethyl-2,6-di-*tert*-butylphenol has not been studied earlier.

It was found that the reaction of compounds **1a** and **1b** with 4-methoxymethyl-2,6-di-*tert*-butylphenol **2** led to the formation of diphenyl(diethyl)-4-hydroxy-3,5-di-*tert*-butylbenzylphosphine oxides **4a** and **4b** in high yield. The reaction proceeded at heating of equimolar amounts of the reagents (Scheme 1).

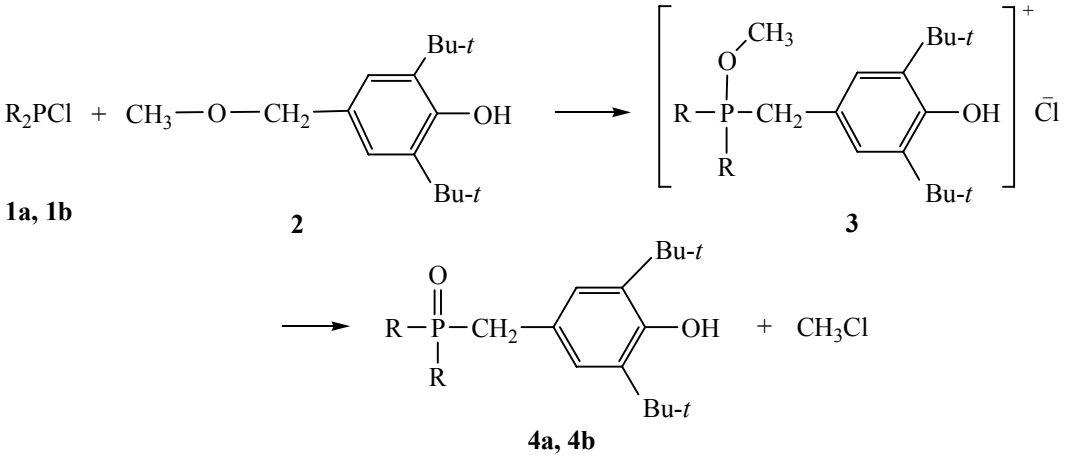
We suggested that chlorophosphines **1a** and **1b** exhibited nucleophilic properties; they reacted with phenol **2** to form quasi-phosphonium salts **3** further stabilized according to the second stage of the Arbuzov–Michaelis reaction to form phosphine oxides **4a** and **4b**.

Subsequent bromination of compounds **4** with *N*-bromosuccinimide (NBS) and dehydrobromination of the so formed bromo(4-hydroxy-3,5-di-*tert*-butylphenyl)methanediphenyl(diethyl)phosphine oxides **5** aided by trimethyl orthoformate provided the target phosphorylated methylene quinones **6** with yield of 65–70% (Scheme 2).

Aiming to obtain new polyfunctional organic compounds, we performed addition of *N*- and *C*-nucleophiles such as phthalimide and acetone to methylene quinones **6**.

It was shown that compounds **6a** and **6b** reacted with phthalimide in the presence of triethylamine in DMF solution to give diphenyl(diethyl)(1,5-dihydro-2,7-dioxo-7*H*-benz[*c*]azol-1-yl)(4-hydroxy-3,5-di-*tert*-

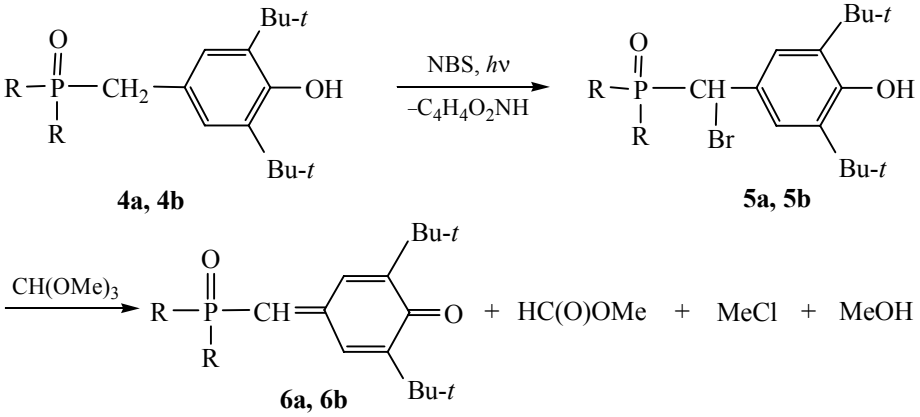
Scheme 1.



1a, 1b **2** **3** **4a, 4b**

R = Ph (**a**), Et (**b**).

Scheme 2.



4a, 4b **5a, 5b** **6a, 6b**

R = Ph (**a**), Et (**b**).

butylphenyl)methanephosphine oxides **7a** and **7b**. Those compounds were converted into diphenyl(diethyl)amino(4-hydroxy-3,5-di-*tert*-butylphenyl)methanephosphine oxides **8a** and **8b** via the modified Gabriel reaction [12] (Scheme 3).

In addition, acetonylation of phosphorylated methylene quinone **6a** in the presence of dimethylamine as a base was performed for the first time. Refluxing of compound **6a** in a mixture of acetone and 33% aqueous solution of dimethylamine led to the formation of diphenyl(4-hydroxy-3,5-di-*tert*-butylphenyl)-(2-oxopropyl)methanephosphine oxide **9** in 98% yield. The suggested mechanism of the basic catalysis of the performed reaction is shown in Scheme 4.

The structure and composition of the prepared compounds were confirmed by elemental analysis as well as NMR and IR spectroscopy data.

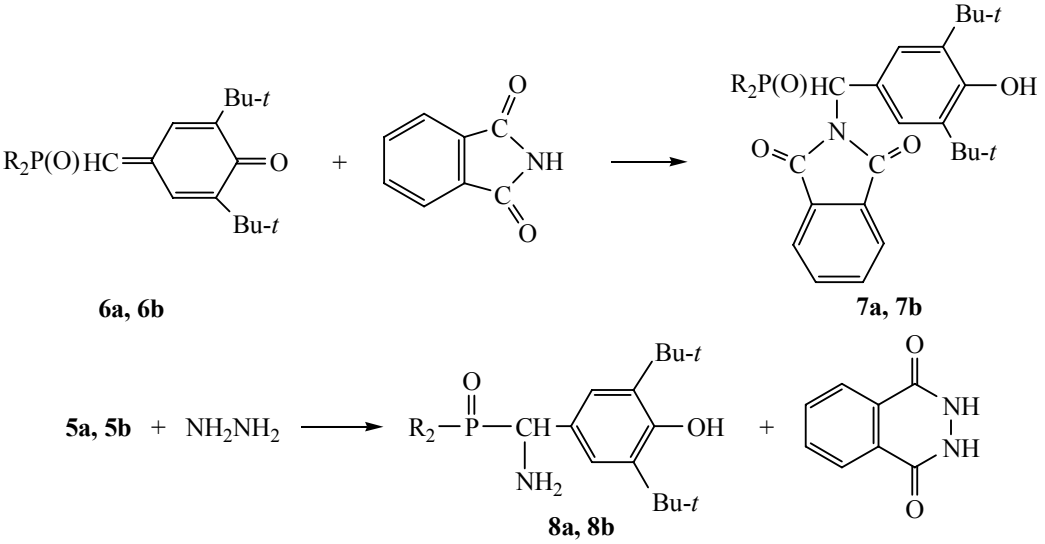
EXPERIMENTAL

^{1}H NMR spectra were recorded using Tesla BS-567A (100 MHz), Bruker WP-250 (250 MHz), or Bruker MSL-400 (400 MHz) spectrometers with the signals of residual protons of the deuterated solvent ($CDCl_3$) as reference. ^{31}P NMR spectra were registered using Bruker MSL-400 (162 MHz) and Bruker WP-250 (101 MHz) instruments with external 85% H_3PO_4 reference.

4-Methoxymethyl-2,6-di-*tert*-butylphenol 2 was prepared via reaction of 4-hydroxy-3,5-di-*tert*-butylbenzylbromide with excess of methanol.

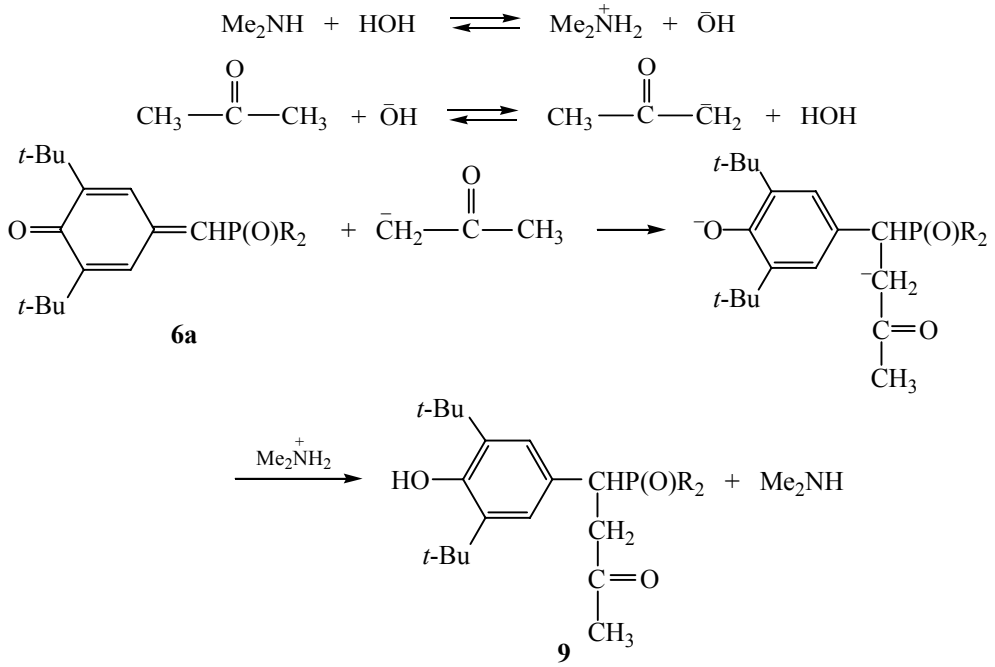
4-(Hydroxy-3,5-di-*tert*-butylbenzyl)diphenylphosphine oxide (4a). A mixture of 4-methoxymethyl-2,6-di-*tert*-butylphenol (2.50 g, 0.01 mol), diphenylchlorophosphine (2.20 g, 0.01 mol), and 2 mL of

Scheme 3.



R = Ph (**a**), Et (**b**).

Scheme 4.



benzene was heated at 150–160°C for 2 h. The reaction was accompanied by vinous coloration of the reaction mixture and gas evolution. After the reaction was complete, the mixture was treated with hexane. The obtained precipitate was filtered off and recrystallized from heptane. Yield 2.89 g (72.2%), mp 175–179°C (heptane) (mp 174–176°C [8]). IR spectrum, ν, cm^{-1}: 3420 br (OH), 1240 (P=O). ^1H NMR spectrum, δ, ppm: 1.42 s (18H, CMe_3), 3.64 d (2H, CH_2P, $^2J_{PH}$ = 14 Hz), 5.73 s (1H, OH), 6.83 d (2H, C_6H_2, $^4J_{HH}$ 2 Hz), 7.58–7.80 m (10H, Ph).

4-(Hydroxy-3,5-di-*tert*-butylbenzyl)diethylphosphine oxide (4b) was prepared similarly from 4-methoxymethyl-2,6-di-*tert*-butylphenol (5.90 g, 0.024 mol) and diethylchlorophosphine (2.95 g, 0.024 mol). Yield

4.30 g (56.0%), mp 134–135°C (heptane) (mp 136–138°C [8]). IR spectrum, ν, cm^{-1}: 3200 br, 1200 (P=O). ^1H NMR spectrum, δ, ppm: 1.10–1.32 m (6H, MeCH$_2$P), 1.45 s (18H, CMe$_3$), 1.71–1.93 m (4H, Me CH$_2$P), 3.02 d (2H, CH$_2$P, $^2J_{PH}$ = 15 Hz), 5.83 s (1H, OH), 6.98 s (2H, C$_6$H$_2$).

4-(Diphenylphosphinylmethylene)-2,6-di-*tert*-butylcyclohexadiene-2,5-one (6a). A suspension of phosphine oxide **4a** (2.94 g, 0.007 mol) and *N*-bromosuccinimide (1.25 g, 0.007 mol) in 100 mL of carbon tetrachloride was microwave-irradiated (300 W) during 5 h. The formed succinimide was filtered off; the filtrate was evaporated in vacuum. The residue was refluxed with trimethyl orthoformate (7.42 g, 0.07 mol) in 10 mL of toluene during 3 h; methyl bromide was liberated. The crystalline product precipitated after the reaction mixture cooling was filtered off, and volatile compounds were distilled off from the mother liquid; the residue was compound **6a** (2.05 g, 69.9%). Mp 218–220°C (isooctane–toluene) (mp 219–221°C [8]). IR spectrum, ν, cm^{-1}: 1650, 1630 (C=O), 1590 (C=CH), 1250 (P=O). ^1H NMR spectrum, δ, ppm: 1.36 s and 1.40 s (18H, CMe$_3$), 6.62 d (1H, CHP, $^2J_{PH}$ = 21.0 Hz), 6.91 s and 8.34 s (2H, C=CH), 7.40–7.99 m (10H, Ph).

4-(Diethylphosphinylmethylene)-2,6-di-*tert*-butylcyclohexadiene-2,5-one (6b) was prepared similarly from phosphine oxide **4b** (2.45 g, 0.0075 mol), *N*-bromosuccinimide (1.35 g, 0.0075 mol), and trimethyl orthoformate (7.95 g, 0.075 mol). Yield 1.57 g (65.0%), mp 174–175°C (heptane) (mp 173–175°C [8]). IR spectrum, ν, cm^{-1}: 1647, 1624 (C=O), 1581 (C=CH), 1252 (P=O). ^1H NMR spectrum, δ, ppm: 1.21–2.42 m (6H, Me), 1.43 s (18H, CMe$_3$), 1.63–2.13 m (4H, CH$_2$P), 6.03 d (1H, CHP, $^2J_{PH}$ = 22.0 Hz), 6.83 s and 8.47 s (2H, C=CH), 8.47 s (1H, C=CH).

(1,5-Dihydro-2,7-dioxo-7*H*-benz[*c*]azol-1-yl)(4-hydroxy-3,5-di-*tert*-butylphenyl)methanediphenylphosphine oxide (7a). A solution of phthalimide (0.30 g, 0.002 mol), phosphinylmethylene quinone **6a** (0.84 g, 0.002 mol), and triethylamine (1 mL) in 10 mL of dimethylformamide was stirred at 60°C during 60 min. The reaction mixture was then poured into 100 mL of 10% aqueous solution of sodium chloride. The formed precipitate was filtered off, washed with water, and dried in vacuum desiccator over P_2O_5 till constant mass. Yield 0.93 g (82.30%), mp 209–212°C (heptane–toluene). IR spectrum, ν, cm^{-1}: 3416 br (OH), 1720 (C=O, amide I), 1160 (P=O). ^1H NMR spectrum, δ, ppm: 1.46 s (18H, CMe$_3$), 5.23 br.s (1H, OH), 6.19 d (1H, CHP, $^2J_{PH}$ = 14.0 Hz), 7.27 d (2H, C$_6$H$_2$, $^4J_{PH}$ = 2.0 Hz), 7.40–7.80 m (14H, Ph, C$_6$H$_4$). Found, %: N 2.60, 2.70; P 5.29, 5.38. $C_{35}H_{36}O_4NP$. Calculated, %: N 2.47; P 5.49.

(1,5-Dihydro-2,7-dioxo-7*H*-benz[*c*]azol-1-yl)(4-hydroxy-3,5-di-*tert*-butylphenyl)methanediethylphosphine oxide (7b) was prepared similarly from phthalimide (0.59 g, 0.004 mol), phosphinylmethylene quinone **6b**, and 1 mL of triethylamine. Yield 1.41 g (75.2%), mp 205–207°C (heptane). ^1H NMR spectrum, δ, ppm: 1.14–1.34 m (6H, Me), 1.55 s (18H, CMe$_3$), 1.6–2.4 m (4H, CH$_2$Me), 5.42 s (1H, OH), 5.82 d (1H, CHP, $^2J_{PH}$ = 17.0 Hz), 7.31 s (C$_6$H$_2$), 7.97–8.01 m (4H, C$_6$H$_4$). Found, %: N 3.20, 3.30; P 6.50, 6.30. $C_{27}H_{36}O_4NP$. Calculated, %: N 2.98; P 6.61.

Amino(4-hydroxy-3,5-di-*tert*-butylphenyl)methanediphenylphosphine oxide (8a). A solution of compound **7a** (0.90 g, 0.0016 mol) and hydrazine hydrate (0.8 g, 0.016 mol) in 20 mL of methanol was refluxed during 2 h. The cyclic hydrazide of phthalic acid precipitated at cooling was filtered off. The residue after evaporation of the filtrate was treated with 100 mL of 10% solution of sodium chloride. Yield 0.50 g (72.5%), mp 160–161°C (heptane–toluene). ^1H NMR spectrum, δ, ppm: 1.42 s (18H, CMe$_3$), 2.05 br.s (2H, NH$_2$), 4.77 d (1H, CHP, $^3J_{PH}$ = 12.0 Hz), 5.25 s (1H, OH), 6.92 d (2H, C$_6$H$_2$, $^4J_{PH}$ = 1.0 Hz). Found, %: N 3.05, 3.10; P 7.10, 7.15. $C_{27}H_{34}O_2NP$. Calculated, %: N 3.22; P 7.12.

Amino(4-hydroxy-3,5-di-*tert*-butylphenyl)methanediethylphosphine oxide (8b) was prepared similarly from compound **7b** (0.94 g, 0.002 mol) and hydrazine hydrate (1 g, 0.02 mol). Yield 0.39 g (57.4%), mp 159–162°C. ^1H NMR spectrum, δ, ppm: 1.05–1.21 m (6H, Me), 1.55 s (18H, CMe$_3$), 1.60–1.90 m (4H, PCH$_2$Me), 1.99 s (2H, NH$_2$), 4.20 d (1H, CHP, $^2J_{PH}$ = 9.0 Hz), 5.40 s (1H, OH), 7.26 d (2H, C$_6$H$_2$, $^4J_{PH}$ = 2.0 Hz).

(4-Hydroxy-3,5-di-*tert*-butylphenyl)(2-oxopropyl)methanediphenylphosphine oxide (9). A mixture of solution of phosphinylmethylene quinone **6a** (0.63 g, 0.0015 mol) and 33% aqueous solution of dimethylamine (1.05 g) in 10 mL of acetone was incubated during 24 h at room temperature. The residue after distilling the volatile components off in vacuum was treated with hexane. Yield 0.70 g (98.0%), mp 204–205°C (heptane–toluene). IR spectrum, ν, cm^{-1}: 3353 br (OH), 1724 (C=O), 1117 (P=O). ^1H NMR spectrum, δ, ppm: 1.43 s (18H, CMe$_3$), 2.11 s (3H, MeCO), 2.90–3.40 m [2H, CH$_2$C(O)], 4.10–4.40 m (1H, CHP), 5.15 br.s (1H, OH), 7.05 d (2H, C$_6$H$_2$, $^4J_{PH}$ = 2.0 Hz), 7.20–

8.20 m (10H, Ph). Found P, %: 6.25, 6.30. $C_{30}H_{37}O_3P$. Calculated P, %: 6.51.

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