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Synthesis of Organophosphorus Derivatives of 2,6-Di-tert-butyl-4-methylphenol

Andrey A. Prishchenko, Mikhail V. Livantsov, Olga P. Novikova, Ludmila I. Livantsova, and Elena R. Milaeva

Department of Chemistry, M. V. Lomonosov Moscow State University, Moscow 119991, Russia

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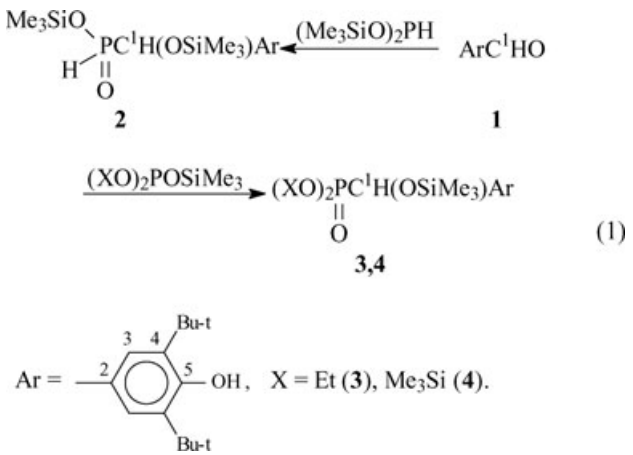
ABSTRACT: *Convenient procedures for the synthesis of 2,6-di-tert-butyl-4-methylphenol (ionol) mono-, di-, and triphosphorus derivatives, starting from the readily accessible 3,5-di-tert-butyl-4-hydroxybenzaldehyde, are proposed, and some properties of the obtained compounds are presented.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:490–494, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20458

INTRODUCTION

Sterically hindered phenols are widely used for preparation of stable phenoxyl radicals and are interesting as biologically active compounds [1]. Phosphorus derivatives of 2,6-di-tert-butyl-4-methylphenol (ionol) are effective antioxidants and promising ligands. However, the methods for synthesis of such compounds are rather complicated and require rigid conditions [2–6]. In this work, we propose convenient procedures for synthesis of a series of ionol phosphorus derivatives with one, two, or three phosphorus-containing groups, starting from the readily accessible 3,5-di-tert-butyl-4-hydroxybenzaldehyde **1** prepared by the procedure described in [7] and trimethylsilyl esters of trivalent phosphorus acids, which are well known as unique organophosphorus synthons [8–10]. In the present study, we found that various trimethylsilyl esters of trivalent phosphorus acids react with aldehyde **1** and its derivatives under mild conditions to form new phosphorus-containing sterically hindered phenols.

RESULTS AND DISCUSSION

So bis(trimethylsiloxy)phosphine and trimethylsilyl phosponites readily add by the carbonyl group of aldehyde **1** in methylene chloride to afford phosphonite **2** or phosphonates **3, 4**, respectively, in high yields (Eq. (1)). Note that under the applied conditions, the sterically hindered hydroxy group of aldehyde **1** is not trimethylsilylated with excess of bis(trimethylsiloxy)phosphine or trimethylsilyl phosphite (cf. [11,12]).



Correspondence to: Andrey A. Prishchenko; e-mail: aprishchenko@yandex.ru

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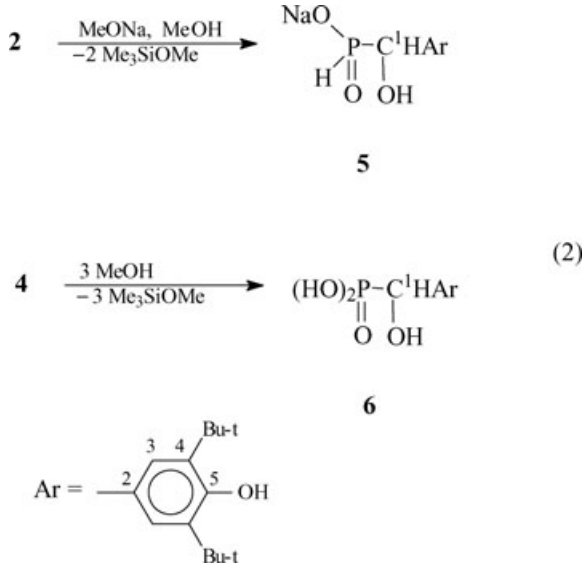
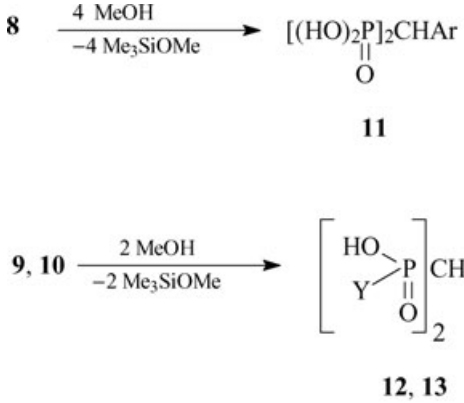
Treatment of phosphonite **2** with dilute sodium methoxide in methanol gave sodium phosphonite **5**, and the reaction of phosphonate **4** with excess methanol gave free phosphonic acid **6** as white hygroscopic crystals (Eq. (2)). Under similar conditions, phosphonate **3** does not react with methanol.



(2)

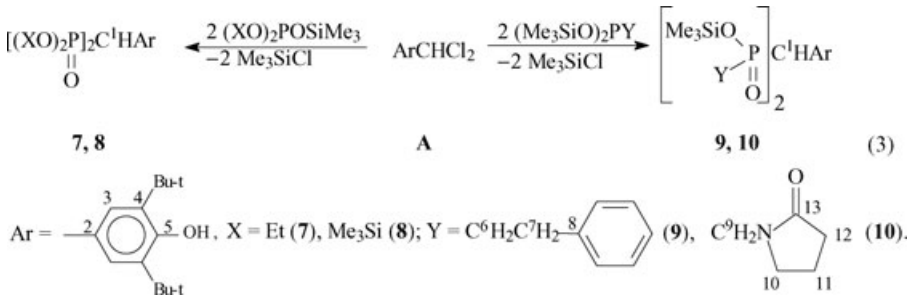
Reactions of trimethylsilyl esters of trivalent phosphorus acids with the easily accessible 2,6-di-tert-butyl-4-(dichloromethyl)phenol **A** prepared from aldehyde **1** by the procedure described in [13] give rise to new methylenediphosphorus compounds, which include sterically hindered phenol fragments. Thus, trimethylsilyl phosphites and functionally substituted trimethylsilyl phosphonites readily react with dichloride A in methylene chloride solution by the Arbuzov reaction scheme to form, respectively, bisphosphonates **7, 8** or bisphosphinates **9, 10** in high yields (Eq. (3)). In these cases, too, the sterically hindered hydroxy group of dichloride A is not trimethylsilylated with excess trimethylsilyl phosphite or trimethylsilyl phosphonites, that is, the sterically hindered phenolic fragment is preserved (cf. [14]).

By the reactions of bisphosphonate **8** and bisphosphinates **9, 10** with excess methanol, we also prepared substituted methylenebisphosphorus acids **11–13** in high yields (Eq. (4)). The products are white hydroscopic crystals. Under mild methanolysis conditions, the phenolic fragments in compounds **8–10** are preserved, whereas the hydrolysis of compound **7** under heating with HCl results in elimination of the tert-butyl groups from the phenolic fragment [15].

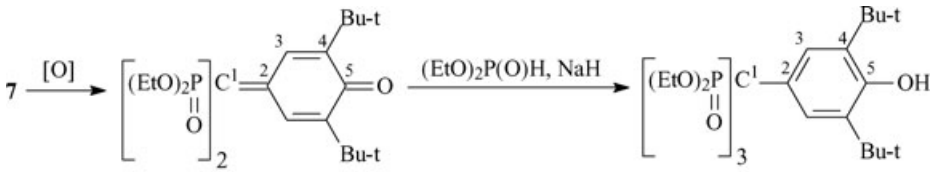


(4)

By the oxidation of diphosphonate **7** by the procedure described in [5], we prepared diphosphorus-substituted methylenequinone **14**, which was further used to synthesize triphosphorus-containing ionol **15**. Thus, 1,6-addition of diethyl phosphite to methylenequinone **14** proceeds readily in the



presence of the sodium hydride as a reaction initiator and yields 85% of compound **15** (cf. [6]).



14 **15** (5)

To conclude, we proposed convenient syntheses of new or hardly accessible ionol derivatives of various structures, which are interesting as effective antioxidants, perspective ligands, and biologically active compounds. The structures of compounds **1–15** were confirmed by the ^{1}H, ^{13}C, and ^{31}P NMR spectra, which show characteristic signals of the $P_nC^1H_m$ fragments and signals of substituted aromatic fragments (see Table 1). As follows from the NMR data, compounds **2** and **10** are mixtures of two stereoisomers in a 7:3 ratio (measured by ^{31}P NMR); in the table, data for the predominating isomer are given first. The methylene proton signals of compounds **9**, **10, 12**, and **13** are partially overlapping. The elemental analyses data of the synthesized compounds, confirmatory of the their compositions, are summarized in Table 2.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ **(1, 2, 4, 7–10, 14, 15),** $(CD_3)_2$ SO **(3, 5, 12, 13)**, or D_2O **(5, 11)** against TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were performed under dry argon in anhydrous solvents. Aldehyde **1**, dichloride **A**, and methylenequinone **14** were prepared according to the procedures described in [7,13,5], respectively.

*O-Trimethylsilyl-3,5-di-tert-butyl-4-hydroxyphenyl(trimethylsiloxy)methylphosphonite (**2**)*

3,5-Di-tert-butyl-4-hydroxybenzaldehyde **1**, 2.3 g, was added with stirring to a solution of 5.3 g of bis(trimethylsiloxy)phosphine in 30 mL of methylene chloride and cooled to 0°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, and the residue was kept at 40°C in a vacuum (0.5 mmHg) for 1 h to obtain 3.8 g of phosphinate **2** as thick oil.

*O,O-Diethyl-3,5-di-tert-butyl-4-hydroxyphenyl-(trimethylsiloxy)methylphosphonate (**3**)*

Aldehyde **1**, 3.1 g, was added with stirring to a solution of 6.2 g of diethyl trimethylsilyl phosphite in 30 mL of methylene chloride and cooled to 10°C. The mixture was stirred for 0.5 h, the solvent was then distilled off, the residue was diluted with 20 mL of hexane, and the mixture was cooled to 0°C. The white crystals that dropped were filtered off and kept in vacuum (0.5 mmHg) for 1 h to obtain 5.4 g of phosphonate **3**.

Phosphonate **4** was prepared similarly.

*Sodium 3,5-Di-tert-butyl-4-hydroxyphenyl-(hydroxy)methylphosphonite (**5**)*

A solution of 3.8 g of phosphonite **2** in 20 mL of methanol was added with stirring to a solution of 0.46 g of sodium methoxide in 10 mL of methanol. The solvent was then distilled off, and the residue was kept in a vacuum (1 mmHg) for 1 h to obtain 2.6 g of salt **5**.

*3,5-Di-tert-butyl-4-hydroxyphenyl(hydroxy)-methylphosphonic Acid (**6**)*

Phosphonate **4,** 3.8 g, was added with stirring to 30 mL of methanol cooled to 10°C. The mixture was heated to boiling, the solvent was distilled off, and the residue was kept in a vacuum (1 mmHg) for 1 h to obtain 2.2 g of acid **6**.

Acids **11–13** were prepared similarly.

*O,O,O,O-Tetraethyl (3,5-di-tert-butyl-4-hydroxyphenyl)methylenebisphosphonate (**7**)*

A solution of 3.7 g of dichloride **A** in 15 mL of methylene chloride was added with stirring to a solution of 6.8 g of diethyl trimethylsilyl phosphite in 20 mL of methylene chloride, cooled to 0°C. The mixture was stirred for 0.5 h, heated to boiling, the solvent was distilled off, the residue was diluted with 20 mL of hexane, and cooled to 0°C. The white crystals that

TABLE 1 Yields, Product Constants and NMR Spectral Data (δ, ppm, J, Hz) of Compounds **1–15**[a]

No	Yield (%)	mp (°C)	δ_H C^1H	$^2J_{PH}$	δ_H C^3H (s)	δ_H OH (s)	δ (C^1)	$^1J_{PC}$	$\delta(C^2)$	$^2J_{PC}$	$\delta(C^3)$	$^3J_{PC}$	$\delta(C^4)$ (s)	$\delta(C^5)$ (s)	δ_P (s)
1	80	189	9.87 s	–	7.75	5.90	191.85 s	–	127.68 s	–	128.75 s	–	136.55	159.70	–
2	85	[b]	4.84 d	8	7.13	5.27	73.59 d	119	123.38 s	–	126.13 s	–	135.83	153.71	24.30
			4.72 d	12	7.12	5.27	74.23 d	118	123.88 s	–	125.81 s	–	135.95	153.89	24.65
3	92	102	4.97 d	12	7.19	6.93	71.74 d	170	124.21 s	–	128.45 s	–	138.94	153.91	20.49
4	85	98	4.81 d	16	7.21	5.16	72.62 d	180	124.17 s	–	128.33 s	–	125.34	153.40	4.93
5	95	159[c]	4.48 d	8.1	7.16	[d]	73.90 d	105	123.96 s	–	129.70 s	–	139.74	152.55	29.42
6	97	198[c]	4.54 d	16	7.17	[d]	71.25 d	159	124.47 s	–	131.08 s	–	138.51	153.75	19.17
7	90	140	3.62 t	24	7.24	5.45	45.19 t	132	120.12 t	6	127.25 t	6	135.87	153.35	19.39
8	89	156	3.40 t	26	7.17	5.16	48.79 t	140	122.89 t	8.5	127.31 t	6	135.70	153.16	0.17
9	91	119	3.29 t	18	7.14	5.20	49.98 t	78.5	120.98 t	7	127.10 t	6	136.34	153.63	37.96
10	94	71	3.94 t	17	7.40	5.30	50.17 t	78	118.60 t	7	126.25 s	–	136.78	153.70	29.91
			3.94 t	17	7.40	5.30	50.97 t	77	119.52 t	5.5	127.72 s	–	135.99	153.63	29.18
11	97	201	3.60 t	26	7.22	[d]	45.85 t	126	123.42 t	7.5	127.04 t	5.5	139.87	152.26	18.35
12	95	202	3.82 t	18	7.36	[d]	49.27 t	75	123.14 t	5.5	127.63 t	6	139.47	153.40	43.20
13	96	122	3.64 t	20	7.27	[d]	49.36 t	74	121.57 t	5.5	127.84 s	–	138.76	153.30	35.01
14	91	74[e]	–	–	8.24	–	127.08 t	161	153.61 s	–	130.38 t	15	151.03	186.33	14.01
15	85	162	–	–	7.89	5.18	57.65 q	116	119.74 q	7	128.81 q	7	134.43	152.79	16.12

[a]All signals of the trimethylsilyl, tert-butyl, and ethoxy groups are in the standard area. PH fragment. ^{1}H NMR spectrum, δ, ppm (J, Hz): **2**: 6.91 d ($^1J_{PH}$ 552) and 6.83 d ($^1J_{PH}$ 552); **5**: 6.67 d ($^1J_{PH}$ 510.3). ^{13}C NMR spectrum, δ, ppm (J, Hz). **9**: 33.17 d (C^6, $^1J_{PC}$ 96), 28.66 d (C^7, $^2J_{PC}$ 4), 141.29 d (C^8, $^3J_{PC}$16); **10**, first isomer: 43.61d (C^9, $^1J_{PC}$ 108), 48.47s (C^{10}), 17.79s (C^{11}), 30.00s (C^{12}), 174.66 d (C^{13}, $^3J_{PC}$ 3); **10**, second isomer: 43.50 d (C^9, $^1J_{PC}$ 106), 48.40s (C^{10}), 17.72 s (C^{11}), 30.00 s (C^{12}), 174.46 s (C^{13}); **12**: 31.59d (C^6, $^1J_{PC}$ 94), 27.96 d (C^7, $^2J_{PC}$ 3), 142.26 d (C^8, $^3J_{PC}$ 17); **13**: 42.75 d (C^9, $^1J_{PC}$ 106), 48.08 s (C^{10}), 17.94 s (C^{11}), 30.15 s (C^{12}), 174.31 s (C^{13}).
[b]Oily substance.
[c]With decomposition.
[d]Broad signal.
[e]Orange crystals.

TABLE 2 Elemental Analyses Data of Compounds **2–15**

No	Empirical Formula	Formula Weight	Calcd (%)		Found (%)	
			C	H	C	H
2	$C_{21}H_{41}O_4PSi_2$	444.69	56.72	9.29	56.59	9.16
3	$C_{22}H_{41}O_5PSi$	444.62	59.43	9.29	59.09	9.22
4	$C_{24}H_{49}O_5PSi_3$	532.88	54.09	9.27	53.94	9.20
5	$C_{15}H_{24}NaO_4P$	322.32	55.90	7.50	55.65	7.46
6	$C_{15}H_{25}O_5P$	316.34	56.95	7.97	56.78	7.89
7	$C_{23}H_{42}O_7P_2$	492.53	56.09	8.59	55.92	8.49
8	$C_{27}H_{58}O_7P_2Si_4$	669.05	48.47	8.74	48.26	8.68
9	$C_{37}H_{58}O_5P_2Si_2$	700.99	63.40	8.34	63.28	8.23
10	$C_{31}H_{56}N_2O_7P_2Si_2$	686.91	54.21	8.22	54.03	8.16
11	$C_{15}H_{26}O_7P_2$	380.33	47.37	6.89	47.19	6.97
12	$C_{31}H_{42}O_5P_2$	556.62	66.89	7.60	66.68	7.69
13	$C_{25}H_{40}N_2O_7P_2$	542.56	55.35	7.43	55.26	7.52
14	$C_{23}H_{40}O_7P_2$	490.52	56.32	8.22	56.15	8.13
15	$C_{27}H_{51}O_{10}P_3$	628.61	51.59	8.18	51.47	8.09

dropped were filtered off and were kept in a vacuum (0.5 mmHg) for 1 h to obtain 5.7 g of compound **7** (cf. [4]).

Compounds **8–10** were prepared similarly.

*3,5-Di-tert-butyl-4-hydroxyphenyltris(diethoxyphosphinoyl)methane (**15**)*

Diethyl phosphite, 7.5 g, was added with stirring to a mixture of 3.3 g of methylenequinone **14** and 0.01 g of sodium hydride. When the mixture decolorized, 30 mL of hexane and 3 mL of water were added. The mixture was stirred for 0.5 h, the organic layer was separated, heated to boiling, and cooled to 10°C. The white crystals that dropped were filtered off and were kept in a vacuum (0.5 mmHg) for 1 h to obtain 3.6 g of compound **15** (cf. [6]).

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