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Synthesis of Mono- and Bisorganophosphorus Substituted Amides of Unsaturated Carboxylic Acids with PCHNC(O) and Antioxidant Fragments

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ABSTRACT: *The convenient methods for the synthesis of new mono- and bisorganophosphorus substituted amides of unsaturated carboxylic acids with PCHNC(O) and antioxidant fragments, starting from Arbuzov reaction of the highly reactive adducts of corresponding imines and acyl chlorides with trimethylsilyl phosphites are proposed. Some properties of the new synthesized mono- and bisorganophosphorus substituted amides are presented.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 23:27–31, 2012; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20748

INTRODUCTION

Functionalized organophosphorus substituted amides of carboxylic acids are of great interest as effective ligands and promising biological active compounds of different action [1–5]. Also recently, we have proposed the convenient methods for the synthesis of new functionalized mono- and bisorganophosphorus compounds including ionol fragments [6], which were used by us for preparation of stable phenoxyl radicals [7] and were possessed of antioxidative activity [8]. In this work, we propose the unique way for the synthesis of new mono- and bisorganophosphorus substituted amides of unsaturated carboxylic acids with PCHNC(O) and antioxidant fragments (cf. [9,10]), which was based on available imines and the corresponding acyl chlorides [11], and trimethylsilyl phosphites [12].

RESULTS AND DISCUSSION

Note that the substituted *N*-chloromethylamines (amides) are widely used by us for preparing various functionalized aminomethyl organophosphorus compounds [13,14]. In the present study we showed that adducts of imines with unsaturated acyl chloride **A** are convenient aminomethylating synthons for preparing a series of organophosphorus substituted amides **1–5**. Hence, adducts **A**, which are easily formed from anisal(methyl)amine and crotonoyl, cinnamoyl, sorbinoyl, and oleoyl chlorides in methylene chloride (cf. [9]), react with trimethylsilyl phosphites by the Arbuzov reaction scheme to give the corresponding amides **1–5** with high yields (Eq. (1)).

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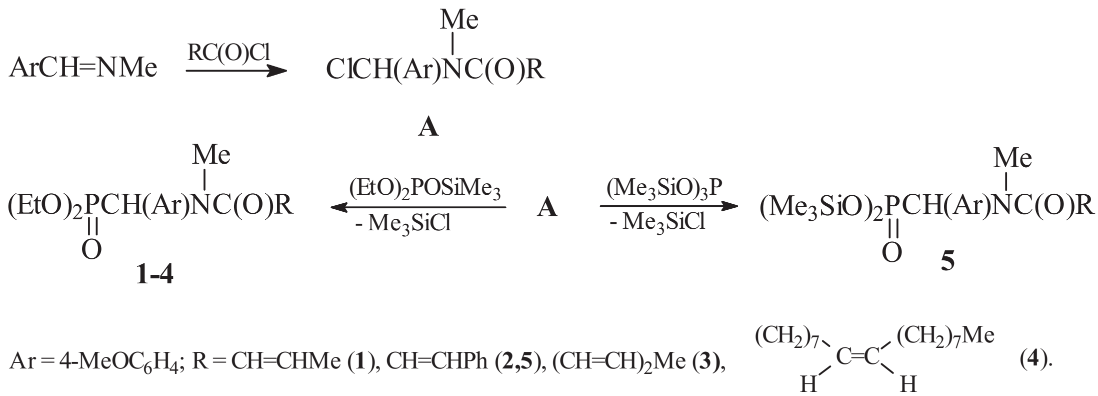
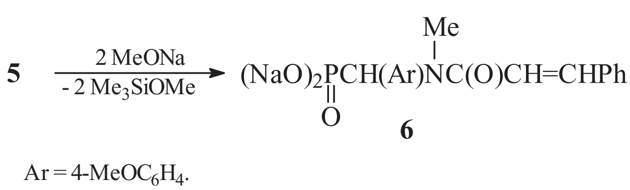


(1)

Treatment of phosphonate **5** with a dilute solution of sodium methylate in methanol gives water-soluble disodium salt **6** as hygroscopic crystals (Eq. (2)), which decomposed on heating above 100–120°C without a definite melting point.

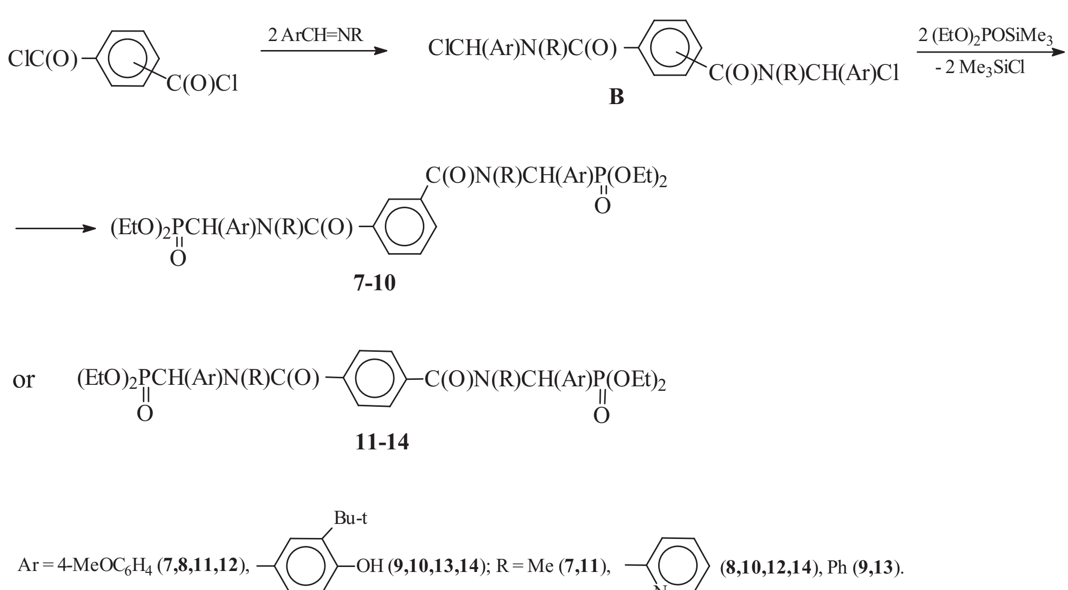


(2)

Similarly, the easily available iso- and terephtaloyl chlorides [11] add readily to different imines in methylene chloride to give intermediates **B**, which react smoothly with diethyl trimethylsilyl phosphite excess under mild conditions, producing bisorganophosphorus substituted bisamides in high yields (Eq. (3)).

The obtained compounds wth chelating properties **1–14** include carbonyl and phosphoryl groups along with the unsaturated fragments, pyridine, and 2,6-di-tert-butylphenol moieties. Therefore, they are of interest as effective polydentate ligands and also as promising antioxidants with the multifunctional mode of action.

The structures of amides **1–14** were confirmed by the ^{1}H, ^{13}C, ^{31}P NMR spectra, which show characteristic signals of the $PC^{1}H(C^{2})N(C^{3})C^{4}(O)$ fragments and signals of substituted unsaturated and aromatic fragments (see Table 1). The ^{1}H and ^{13}C NMR signals of unsaturated and aromatic fragments of these compounds overlap partially or completely. Compounds **1–14** consist of two stereoisomers whose contents were determined by ^{1}H and ^{31}P NMR spectroscopy. The contents of the second isomers of compounds **9,10,12,13** are very low; therefore, here



(3)

TABLE 1 Yields, Product Constants, and NMR Spectral Data for the $PC^1H(C^2)N(C^3)C^4(O)$ Fragments(δ, ppm, J, Hz) of Compounds **1–14**[a]

No.	*Yield (%)*	*Mp (°C)*	*Ratio (%)*	δ *(H)* C^1H *d*	$^2J_{PH}$	δ (C^1) *d*	$^1J_{PC}$	δ (C^2) *s*	δ (C^3), *s*	δ (C^4) *s*	δ *(C)* $C_{Ar}O$ *s*	δ_P *s*[b]
1	93	oil	65	6.15	22.4	51.72	157.5	123.21[c]	31.90	169.24[c]	159.22	21.01
			35	4.18	19.2	57.58	154.2	132.42	30.46	166.42	159.28	23.23
2	94	91	85	6.37	22.4	52.26	157.6	125.41[c]	32.19	166.43[c]	159.43	21.01
			15	4.32	18.8	54.16	155.6	125.73	31.65	166.57	159.55	23.38
3	95	71	80	6.11	22.4	51.81	157.5	125.36	31.78	166.49[c]	159.20	20.93
			20	4.22	19.2	54.10	155.8	124.70	30.48	166.46	159.27	23.14
4	93	oil	75	6.26	22.4	51.62	158.4	125.55[c]	33.27	172.93	159.36	21.20
			25	4.32	19.4	57.66	156.7	124.95	32.92	173.60	159.17	23.41
5	96	oil	60	6.16	23.6	53.84	168.4	125.71	31.78	166.86[c]	159.33	1.72
			40	4.20	18.5	54.26	171.2	125.65	30.08	166.56	159.21	5.46
6	96	[d]	65	6.24	22.0	55.54	155.0	[e]	31.39	167.17	158.60	15.46
			35	4.47	19.2	56.26	152.4	[e]	31.39	167.42[c]	158.49	13.51
7	89	59	75	6.30	24.0	52.42	157.1	[e]	34.29	170.21	159.60	20.50
			25	4.92	24.0	59.25	155.0	[e]	30.81	166.95	159.60	20.12
8	87	131	60	5.80, 5.82	20.0, 24.0	50.61	155.0	[e]	[e]	172.10	[e]	23.27
			40	5.26, 5.28	20.0, 24.0	58.63	158.0	[e]	[e]	172.70	[e]	20.74
9	86	65	95	4.88	20.1	54.62	151.2	[e]	147.97[c]	165.53	153.62	23.67
			5	–	–	–	–	–	–	–	–	20.86
10	89	94	95	6.39	24.0	57.61	159.0	[e]	160.46	165.76	154.10	21.36
			5	–	–	–	–	–	–	–	–	21.80
11	92	83	80	6.47	20.0	52.52	157.0	[e]	34.42	171.19	[e]	23.56
			20	4.45	20.0	59.33	156.0	[e]	34.78	171.67	[e]	23.84
12	90	91	95	5.92	24.0	50.66	154.2	[e]	157.54[c]	168.50	159.31	23.47
			5	–	–	–	–	–	–	–	–	20.98
13	87	101	98	5.00	20.0	60.21	153.0	[e]	147.79[c]	169.59	153.93	23.74
			2	–	–	–	–	–	–	–	–	23.05
14	88	89	65	6.40	24.0	57.41	161.0	[e]	[e]	165.82	154.09	21.28
			35	6.30	24.0	58.08	160.0	[e]	[e]	165.59	154.09	21.92

[a]All signals of alkyl, alkenyl, aryl, 2-pyridyl, and trimethylsilyl groups are in the standard area. The ^1H NMR spectra of product fragments show expected signals that occasionally look like overlapping multiplets; fragment CH═CHPh of **2**:6.77 d and 7.57 d, $^3J_{HH}$16.
[b]Data of $^{31}P\ \{^1H\}$ spectra.
[c]d (J_{PC}) for compounds, C^2, C^4: **1**, 10.9, 5.0; **2**, 4.0, 3.8;**3**, 3.3;**4**, 4.2;**5**, 5;**6**, 4.2;**9**, 14.0;**12**, 9.0.
[d]This crystalline compound is decomposed by heating.
[e]Overlapping multiplets.

TABLE 2 Elemental Analyses Data of Compounds **1–14**

No.	Empirical Formula	Formula Weight	Calcd. (%) C	Calcd. (%) H	Found (%) C	Found (%) H
1	$C_{17}H_{26}NO_5P$	355.38	57.46	7.38	57.32	7.30
2	$C_{22}H_{28}NO_5P$	417.44	63.30	6.76	63.12	6.64
3	$C_{19}H_{28}NO_5P$	381.41	59.83	7.40	59.69	7.26
4	$C_{31}H_{54}NO_5P$	551.75	67.48	9.86	67.37	9.78
5	$C_{24}H_{36}NO_5PSi_2$	505.69	57.00	7.17	56.89	7.11
6	$C_{18}H_{18}NNa_2O_5P$	405.30	53.34	4.48	53.23	4.41
7	$C_{34}H_{46}N_2O_{10}P_2$	704.68	57.95	6.58	57.78	6.49
8	$C_{42}H_{48}N_4O_{10}P_2$	830.81	60.72	5.82	60.59	5.73
9	$C_{58}H_{78}N_2O_{10}P_2$	1025.21	67.95	7.67	67.81	7.54
10	$C_{56}H_{76}N_4O_{10}P_2$	1027.19	65.48	7.46	65.43	7.39
11	$C_{34}H_{46}N_2O_{10}P_2$	704.68	57.95	6.58	57.69	6.52
12	$C_{42}H_{48}N_4O_{10}P_2$	830.81	60.72	5.82	60.64	5.74
13	$C_{58}H_{78}N_2O_{10}P_2$	1025.21	67.95	7.67	67.76	7.58
14	$C_{56}H_{76}N_4O_{10}P_2$	1027.19	65.48	7.46	65.30	7.42

we give for them ^{31}P NMR parameters only. The elemental analysis data of synthesized compounds are summarized in Table 2.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**1–5,7,11**), CD_3OD (**6**) or $(CD_3)_2SO$ (**8–10,12–14**) against TMS (^1H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were performed under dry argon in anhydrous solvents. Starting imines, unsaturated acid chlorides, and trimethylsilyl phosphites were prepared according to the procedures in [11,12], respectively.

O,O–Diethyl [4-anisyl(N-methyl-N-crotonoylamino)methyl]phosphonate (1). A solution of 5.2 g of crotonoyl chloride in 10 mL of methylene chloride was added dropwise with stirring at 0°C to a solution of 9 g of anisal(methyl)amine in 20 mL of methylene chloride. After 1 h, a solution of 14 g of diethyl trimethylsilyl phosphite in 15 mL of methylene chloride was added. The solvent was distilled off, 25 mL of hexane was added to the residue, and the mixture was cooled to –10°C. The precipitated thick oil was removed from solvent and kept in a vacuum (0.5 mm Hg) for 1 h. Phosphonate **1**, 16.5 g, was obtained.

Amides 2–5 Were Prepared Similarly

Disodium 4-anisyl(N-methyl-N-cinnamoyl)methylphosphonate (**6**). A solution of 6 g of phosphonate **5** in 10 mL of diethyl ether was added with stirring and cooling at 10°C to a solution of 1.3 g of sodium methylate in 30 mL of methanol. The resulting mixture was heated to the boil, the solvent was removed in a vacuum, and the residue was kept in a vacuum (1 mm Hg) for 1 h to obtain 4.6 g of the salt **6**, as yellow hygroscopic crystals.

1,3-Bis{N-methyl-N-[4-anisyl(diethoxyphosphoryl)methyl]aminocarbonyl}benzene (7). A solution of 4.06 g of isophtaloyl chloride in 10 mL of methylene chloride was dropwise added to a solution of 6 g of anisal(methyl)amine in 15 mL of methylene chloride at 0°C under stirring. After 1 h, this mixture was added to a solution of 8.5 g diethyl trimethylsilyl phosphite in 10 mL of methylene chloride. The mixture was stirred for 2 h at 20°C. The solvent was removed, and to the residue was added 3 mL of hexane. This mixture was cooled to –10°C. The solvent was decanted, and the precipitated crystals were kept in a vacuum of 0.5 mm Hg for 1 h, yielding 12.5 g of phosphonate **7**. Bisphosphonates **8–14** were obtained analogously.

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