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Microwave-assisted synthesis of (aminomethylene)bisphosphine oxides and (aminomethylene)bisphosphonates by a three-component condensation

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Full Research Paper

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Abstract

A practical method was elaborated for the synthesis of (aminomethylene)bisphosphine oxides comprising the catalyst- and solvent-free microwave-assisted three-component condensation of primary amines, triethyl orthoformate and two equivalents of diphenylphosphine oxide. The method is also suitable for the preparation of (aminomethylene)bisphosphonates using $(MeO)_2P(O)H/(MeO)_3CH$ or $(EtO)_2P(O)H/(EtO)_3CH$ reactant pairs and even secondary amines. Several intermediates referring to the reaction mechanism together with a few by-products could also be identified.

Introduction

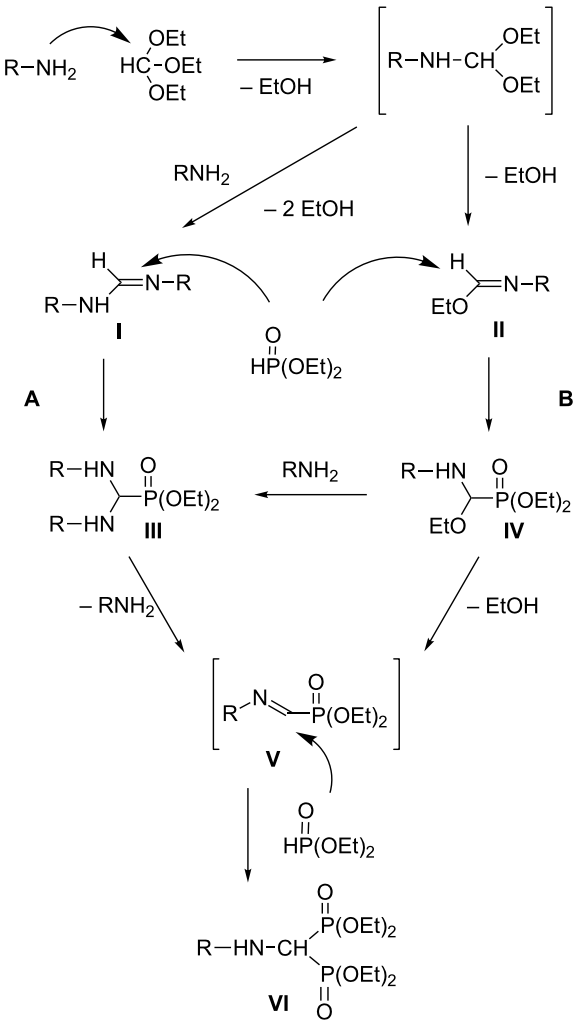
Substituted (hydroxymethylene)bisphosphonic acid derivatives form an important group of drugs used in the treatment of osteoporosis and related bone diseases [1-3]. In the last decades, at least three generations of dronic acid derivatives appeared [4].

(Aminomethylene)bisphosphonic acid derivatives are analogous species, that also have potential bioactivity in bone diseases, besides they display antibacterial, antiparasitic, anticancer and herbicidal activities [5].

(Aminomethylene)bisphosphonates may be prepared in different ways [5]. One of the most convenient and widespread methods is the three-component condensation involving an amine, an orthoformate and a dialkyl phosphite. Usually, primary or secondary amines were reacted with an equivalent,

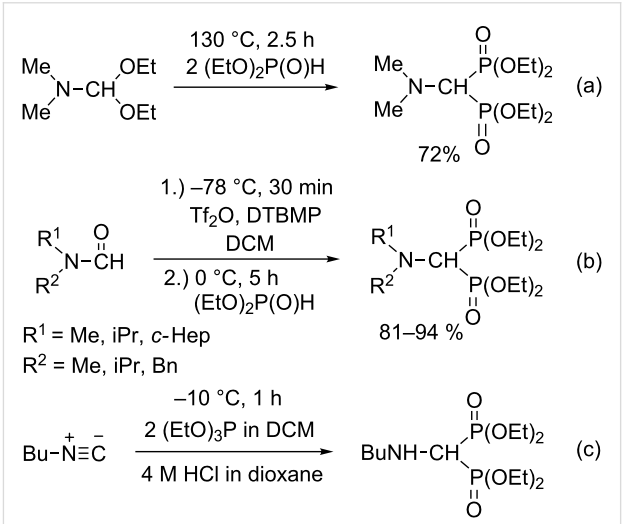
or a small excess of triethyl orthoformate and 2–7 equivalents of diethyl phosphite [6-21]. In most cases, the corresponding acids were the target molecules that were obtained by hydrolysis of the esters [15-21]. The use of crown ethers with an NH unit, or thienopyrimidine amines as starting materials was also reported [22,23]. The catalyst- and solvent-free methods required long reaction times and/or a high temperature [6-14,21-23]. Ionic liquids and a few catalysts were also tried out [24-27], and the synthesis was also described under microwave (MW) irradiation [28-32]. However, most of the MW-assisted syntheses were performed in kitchen ovens [28-30], hence these results cannot be reproduced.

The mechanism of the three-component condensation has been investigated by the research group of Krutikov and Kafarski [6,7]. A detailed proposal is shown in Scheme 1 [7]. The first step of the condensation is the reaction of the amine with the orthoformate, in which imine-type intermediates **I** or **II** may be formed. The next step is the nucleophilic addition of diethyl phosphite to the C=N bond of the imines resulting in phosphonates **III** or **IV**, respectively. Then, the elimination of an amine or ethanol and the addition of another unit of diethyl phosphite may lead to (aminomethylene)bisphosphonates (**VI**). If the amine is in predominance over the phosphite in the reaction, the pathway **A** is more likely, but if the phosphite is used in excess, the pathway **B** comes to the fore.



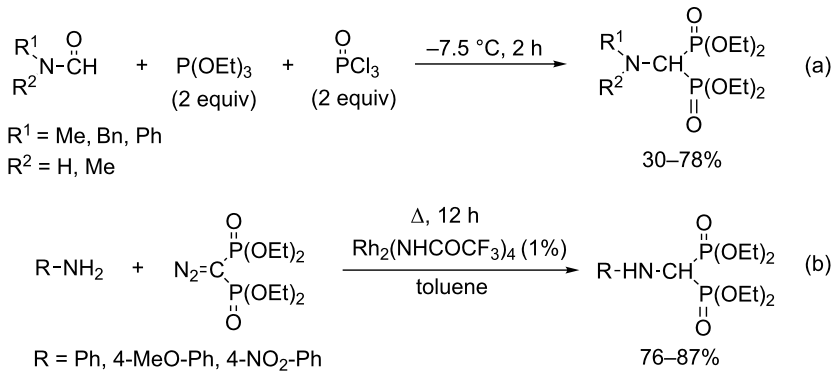
Scheme 1: Proposed routes for the three-component condensation [7].

There are other possibilities to synthesize (aminomethylene)bisphosphonates, such as by the reaction of dimethylformamide diethyl acetal with diethyl phosphite (Scheme 2a) [33], by the condensation of formamides and diethyl phosphite using 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as the base, and trifluoromethanesulfonic anhydride (Tf_2O) as the catalyst (Scheme 2b) [34], or by the reaction of isonitriles with triethyl phosphite (Scheme 2c) [35,36]. (Aminomethylene)bisphosphonates can also be obtained starting from amides, triethyl phosphite and phosphorus oxychloride (Scheme 3a) [37], or in the reaction of amines with diazophosphonate in the presence of a rhodium catalyst (Scheme 3b) [38].



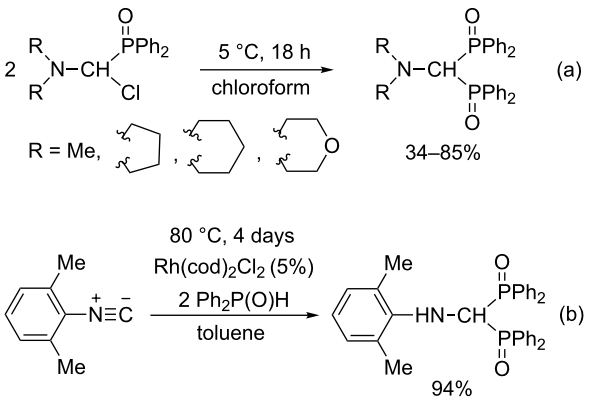
Scheme 2: Synthetic methods for (aminomethylene)bisphosphonates I.

(Aminomethylene)bisphosphine oxides are analogous to (aminomethylene)bisphosphonates, but they are much less studied. Only a few publications were found, which focus on their synthesis [33,39-42], however, a three-component condensation has not been described. They can also be prepared starting from dimethylformamide dimethyl acetal, as in the synthesis of (aminomethylene)bisphosphonates, but in the latter case a secondary phosphine oxide is the P-reagent [33,39]. In addition, (aminomethylene)bisphosphine oxides can be synthe-



Scheme 3: Synthetic methods for (aminomethylene)bisphosphonates II.

sized by the reaction of two molecules of (dialkylamino)(diphenylphosphinoyl)chloromethane (Scheme 4a) [40,41], or by the addition of diphenylphosphine oxide to an isonitrile (Scheme 4b) [36,42].



Scheme 4: Synthetic methods for (aminomethylene)bisphosphine oxides.

In this paper, we wish to report the results of our investigations on the synthetic protocol utilizing the three-component condensations of primary or secondary amines, orthoformates and >P(O)H species, such as dialkyl phosphites or diphenylphosphine oxide, and we aimed at the preparation of new derivatives.

Results and Discussion

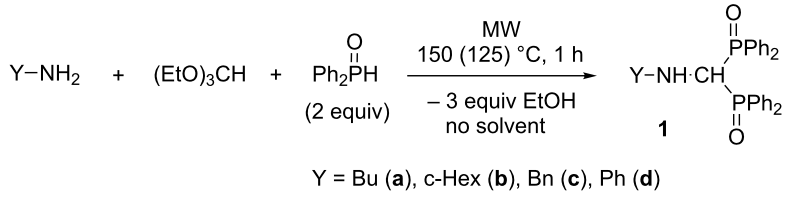
Synthesis of alkylamino- and (phenylaminomethylene)bisphosphine oxides

In the first series of experiments, the condensation of primary amines, such as butyl-, cyclohexyl- and benzylamine or aniline with triethyl orthoformate, and 2 equivalents of diphenylphosphine oxide at 150 °C for 1 h under MW conditions was studied (Scheme 5). To avoid the formation of by-products, benzylamine was reacted at a lower temperature of 125 °C (Table 1, entry 3). The reactions were carried out without any catalyst and solvent. After column chromatography, the new aminomethylenebisphosphine oxides **1a–d** were obtained in yields of 72–82% (Table 1, entries 1–4).

Table 1: Synthesis of alkylamino- and (phenylaminomethylene)bisphosphine oxides **1a–d**.

Entry	Y	*T* (°C)	Yield (%)[a]
1	Bu	150	82 (**1a**)
2	c-Hex	150	79 (**1b**)
3	Bn	125[b]	72 (**1c**)
4	Ph	150	80 (**1d**)

[a]Isolated yield. [b]At 150 °C by-products were formed.



Scheme 5: Synthesis of alkylamino- and (phenylaminomethylene)bisphosphine oxides.

The condensation of simple secondary amines (diethyl-, dibutyl-, *N*-butylmethyl-, *N*-cyclohexylmethyl-, *N*-benzylmethylamine, *N*-methylaniline and morpholine) was also investigated with triethyl orthoformate, and 2 equivalents of diphenylphosphine oxide (Scheme 6, Table 2). The MW-assisted reactions were performed at 150 °C for 1 h under solvent- and catalyst-free conditions, and the (dialkyl-aminomethylene)bisphosphine oxides **2a–g** were obtained in yields of 60–85% after column chromatography (Table 2, entries 1–7). Except for compound **2g**, all (aminomethylene)bisphosphine oxides (**2a–f**) prepared are new compounds. According to the literature method [41], **2g** was synthesized by the reaction of two molecules of (diphenylphosphinoyl)morpholinochloromethane in the presence of chloroform at 5 °C for 18 h in a yield of 41% (Scheme 4a). Using the MW-assisted three-component condensation method, this compound (**2g**) can be synthesized without any catalyst and solvent in a short time (1 h), and in a yield of 85% (Table 2, entry 7).

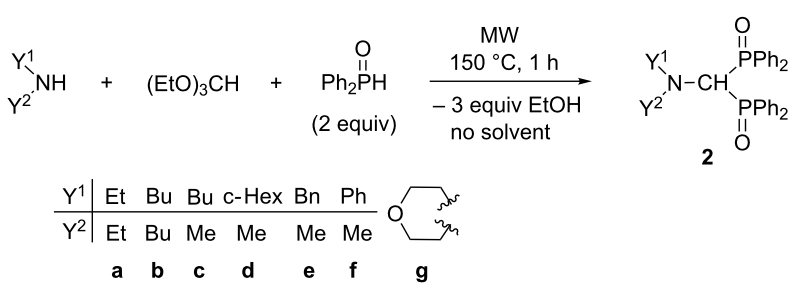
Table 2: Synthesis of (dialkylaminomethylene)bisphosphine oxides **2a–g**.

Entry	Y^1	Y^2	Yield (%)[a]
1	Et	Et	82 (**2a**)
2	Bu	Bu	73 (**2b**)
3	Bu	Me	69 (**2c**)
4	c-Hex	Me	66 (**2d**)
5	Bn	Me	64 (**2e**)
6	Ph	Me	60 (**2f**)
7	$-(CH_2)_2-O-(CH_2)_2-$		85 (**2g**)

[a]Isolated yield.

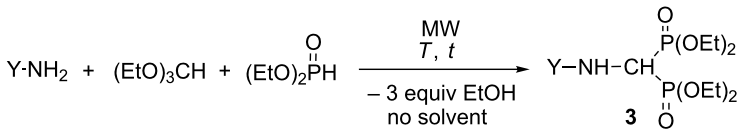
Synthesis of alkylamino- and (phenylaminomethylene)bisphosphonates

In the next stage, our method was extended to the synthesis of alkyl- and (phenylaminomethylene)bisphosphonates by reacting butyl- and cyclohexylamine or aniline, and triethyl orthoformate with diethyl phosphite under MW irradiation in the absence of catalyst and solvent (Table 3). First, the condensation of butylamine, triethyl orthoformate with 2 equivalents of diethyl phosphite was studied at 125 °C. After a 2 h's reaction time, the conversion was 91%, and beside the expected (aminomethylene)bisphosphonate **3a** formed in 81%, the *N*-ethylated by-product **4a** was formed in 19% (Table 3, entry 1). Increasing the temperature to 150 °C, the reaction was completed after 30 min, but the proportion of the main product **3a** was somewhat lower (78%), and another by-product **5a** also appeared in 7% (Table 3, entry 2). The target compound **3a** could be obtained in a yield of 61%. Using 3.5 equivalents of diethyl phosphite at 125 °C for 1 h, the conversion was only 75%, but the expected product **3a** was formed exclusively (Table 3, entry 3). After a longer reaction time of 1.5 h, by-product **4a** also appeared in 22% (Table 3, entry 4). In the reaction with cyclohexylamine, the same tendency was observed (Table 3, entries 5–8), and the corresponding (cyclohexylaminomethylene)bisphosphonate **3b** was obtained in a yield of 68% after column chromatography (Table 3, entry 6). Finally, the three-component condensation of aniline, triethyl orthoformate and diethyl phosphite was studied (Table 3, entries 9–11). Applying 2 equivalents of phosphite, the reaction was not complete, neither at 125 °C, nor at 150 °C (Table 3, entries 9 and 10). Two types of imine intermediates (**6a** and **6b**) could be observed in the reaction mixture beside the expected product **3c**. These intermediates refer to the mechanism of the condensation (see compounds **I** and **V** in Scheme 1, pathway A). Previously, iminephosphonate **6b** was only an assumed intermediate [7], but now we could prove it by ^{31}P NMR and HRMS (Table 4). Increasing the amount of diethyl phosphite to 3 equivalents, the reaction was complete at 125 °C after 1 h, and only **3c** was formed with a yield of 82% (Table 3, entry 11). In the cases discussed, no ethylated or formylated by-products (**4** and **5**, respectively) were formed. (Aminomethylene)bisphosphonates **3b** and **3c** were synthesized earlier in unoptimized experiments to provide compounds **3b** and **3c** in yields of 36% [9] and 53% [8], respectively. The former compound **3b** was characterized only by ^1H NMR [9]. Compound **3c** was also synthesized under MW irradiation in a yield of 75% [31]. It can be seen, that the refined MW-assisted method elaborated by us



Scheme 6: Synthesis of (dialkylaminomethylene)bisphosphine oxides.

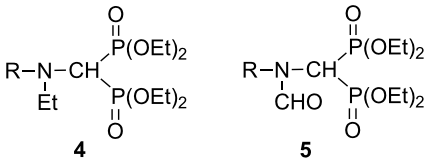
Table 3: The reactions of primary amines with triethyl orthoformate and diethyl phosphite.



Y= Bu (**a**), c-Hex (**b**), Ph (**c**)

Entry	Y	DEP (equiv)	*T* (°C)	*t* (h)	Conversion (%)[a]	Product composition (%)[a]			Yield of **3** (%)[c]
						3	by-products[b]		
							4	**5**	
1	Bu	2	125	2	91	81	19	0	**–**
2	Bu	2	150	0.5	100	78	15	7	61 (**3a**)
3	Bu	3.5	125	1	75	100	0	0	–
4	Bu	3.5	125	1.5	90	78	22	0	–
5	c-Hex	2	125	2	76	83	17	0	–
6	c-Hex	2	150	0.5	100	88	10	2	68 (**3b**)
7	c-Hex	3.5	125	1	63	100	0	0	–
8	c-Hex	3.5	125	1.5	83	86	14	0	–
9	Ph	2	125	2	68	56[d]	0	0	36 (**3c**)
10	Ph	2	150	1	90	70[d]	0	0	52 (**3c**)
11	Ph	3	125	1	100	100	0	0	82 (**3c**)

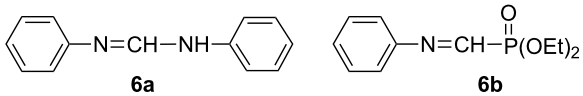
[a]On the basis of GC (entries 1–8) or on the basis of HPLC (entries 9–11). [b]The by-products identified:



4 **5**

R= Bu (**a**), c-Hex (**b**)

[c]Isolated yield. [d]The following intermediates were also formed based on LC–MS:



6a **6b**

Entry	6a [%]	6b
9	29	15
10	18	12

Table 4: Spectral characterization of *N*-ethyl- (**4**) and *N*-formyl- (**5**) (aminomethylene)bisphosphonates and imine-type intermediates **6a** and **6b**.

Compounds	δ_P in $CDCl_3$	δ_P [lit.]	$[M + H]^+_{found}$	$[M + H]^+_{requires}$
4a	19.98	–	388.2020	388.2012
4b	20.63	–	414.2162	414.2169
5a	16.08 and 16.16 (*E* and *Z* isomers)	15.69 and 15.98[a] (*E* and *Z* isomers) [43]	388.1659	388.1649
5b	16.00 and 16.06 (*E* and *Z* isomers)	–	414.1797	414.1805
6a	–	–	197.1075	197.1073
6b	17.67	–	242.0936	242.0941

[a]In CCl_4.

may give the (aminomethylene)bisphosphonates **3b** and **3c** in yields of 68% and 82%, respectively.

Next, the condensation of aniline with trimethyl orthoformate and dimethyl phosphite was also performed (Scheme 7). In this case, the reaction was complete after a 1 h heating at 110 °C using 3.5 equivalents of dimethyl phosphite. After column chromatography, the corresponding product **7a** was isolated in a yield of 63%. At higher temperatures, decomposition was observed.

In the next stage, the MW-assisted reaction of secondary amines was studied with triethyl orthoformate and diethyl phosphite (Scheme 8). The condensations were carried out applying 3.5 equivalents of diethyl phosphite at 125 °C for 1 h in the absence of a catalyst and a solvent. In case of *N*-methylaniline, 4.5 equivalents of the P-reagent was necessary to attain complete conversion (Table 5, entry 6). The corresponding (dialkylaminomethylene)bisphosphonates (**8a–g**) were obtained in yields of 65–86% after purification by chromatography (Table 5, entries 1–7).

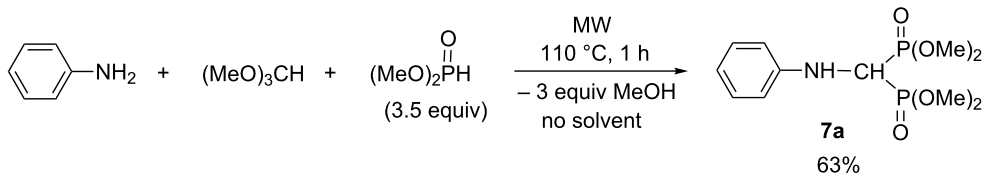
Finally, the three-component condensation of aniline, triethyl orthoformate and dimethyl or dibutyl phosphite was studied (Table 6, Figure 1). Using dimethyl phosphite, the reactions were performed at 110 °C for 1 h, but in case of dibutyl phosphite, the conditions applied were the same as those in the condensations with diethyl phosphite (125–150 °C, 1 h). Using 2 equivalents of dialkyl phosphite, more or less transesterified

Table 5: Synthesis of (dialkylaminomethylene)bisphosphonates **8a–g**.

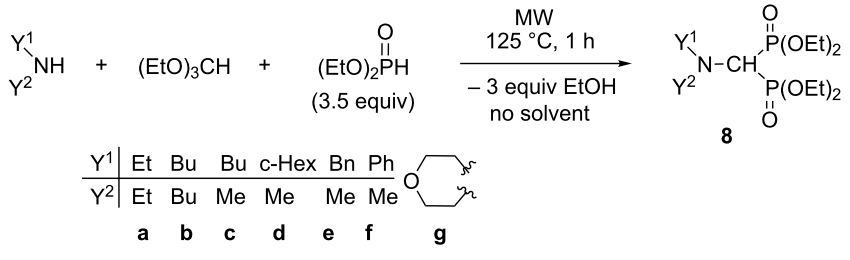
Entry	Y^1	Y^2	Yield (%)[a]
1	Et	Et	86 (**8a**)
2	Bu	Bu	68 (**8b**)
3	Bu	Me	79 (**8c**)
4	c-Hex	Me	72 (**8d**)
5	Bn	Me	70 (**8e**)[b]
6[c]	Ph	Me	65 (**8f**)
7	$-(CH_2)_2-O-(CH_2)_2-$		81 (**8g**)[d]

[a]Isolated yield. [b]It was synthesized in a yield of 61% [10]. [c]4.5 equivalents of diethyl phosphonate was used.[d]It was synthesized in a yield of 46% [4].

(aminomethylene)bisphosphonates (**9–11** and **3c**) were also formed beside the expected (phenylaminomethylene)bisphosphonates **7a** or **7b** (Table 6,entries 1 and 6, 7). The transesterified by-products (**9-11** and **3c**) were indentified by GC–MS (Figure 2) or LC–MS, and were proved by HRMS (Table 7). The composition of the reaction mixture for the experiment marked by Table 6, entry 6 was analyzed by ^{31}P NMR (see Figure 3). It was observed that increasing the quantity of dialkyl phosphite, the proportion of the by-products was decreased, and the condensations became more selective for the desired product (**7a** or **7b**) (Table 6, Figure 1). In the reaction with dimethyl phosphite, the best result was achieved using 20 equivalents of the P-reagent, but in case of dibutyl phosphite, a 15-fold excess was sufficient (Table 6, entries 5 and 10).

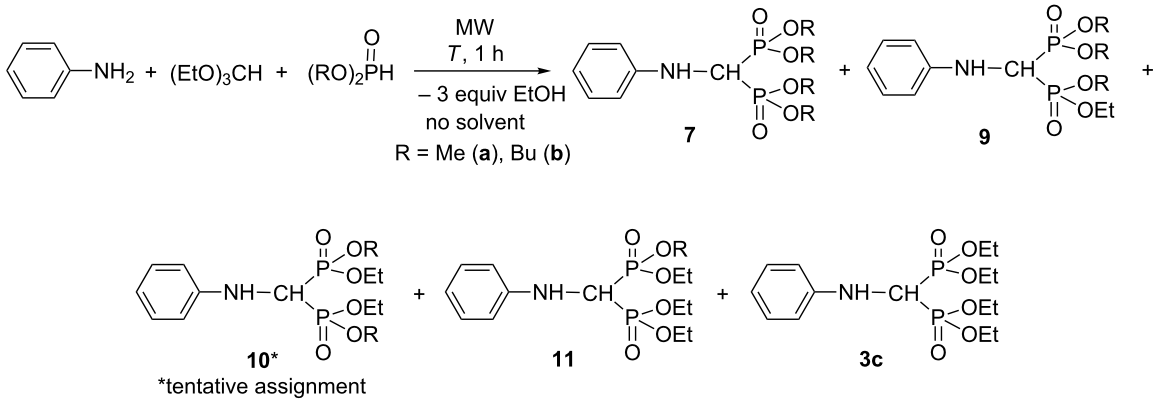


Scheme 7: Synthesis of tetramethyl (phenylaminomethylene)bisphosphonate.



Scheme 8: Synthesis of (dialkylaminomethylene)bisphosphonates.

Table 6: Condensation of aniline, triethyl orthoformate and dimethyl or dibutyl phosphite.



Entry	R	Dialkyl phosphite (equiv)	*T* (°C)	Product composition (%)[a]				
				7	**9**	**10**	**11**	**3c**
1	Me	2	110	14	36	36	11	3
2	Me	6	110	54	37	9	0	0
3	Me	10	110	77	18	5	0	0
4	Me	15	110	87	13	0	0	0
5	Me	20[b]	110	**91**	9	0	0	0
6	Bu	2	150	19	23	29	26	3
7	Bu	2	125	54	33	10	3	0
8	Bu	6	125	82	16	2	0	0
9	Bu	10	125	93	7	0	0	0
10	Bu	15[b]	125	**95**	5	0	0	0

[a]On the basis of GC (entries 1–5) or on the basis of HPLC (entries 6–9). [b]The product composition has not changed using a larger excess of dialkyl phosphite.

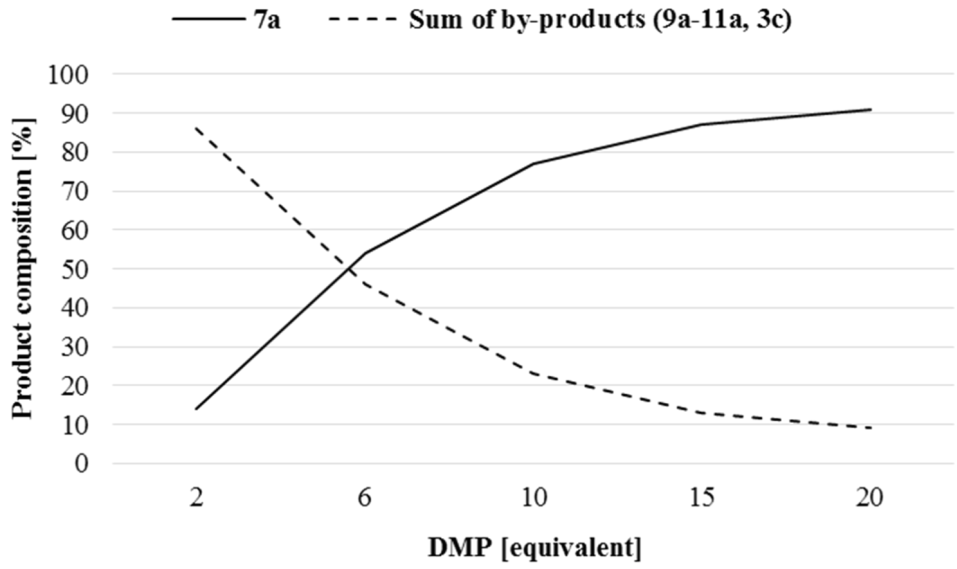


Figure 1: Effect of the quantity of dimethyl phosphite (DMP) on the product composition (from Table 6, entries 1–5.)

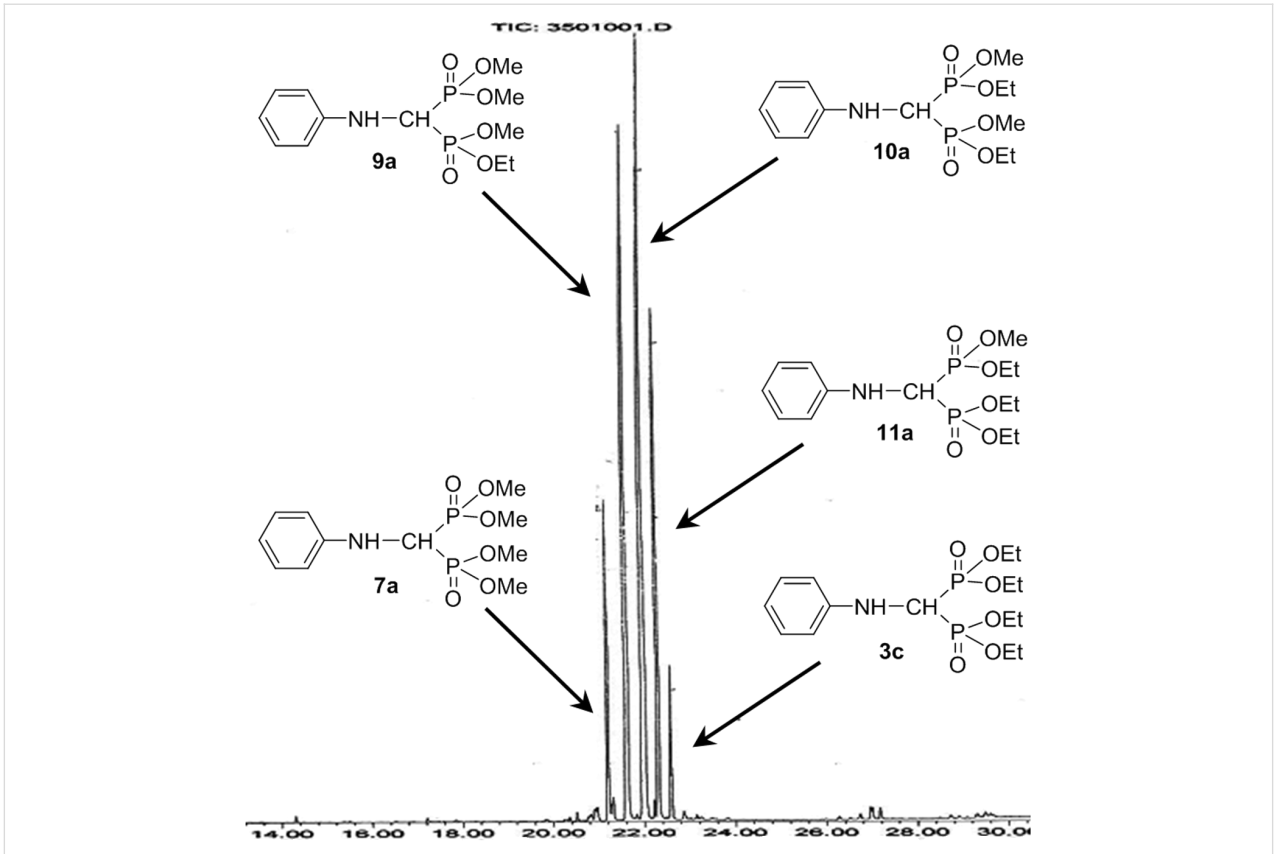


Figure 2: GC–MS chromatogram for the condensation of aniline, triethyl orthoformate and 2 equivalents of dimethyl phosphite (from the exp. marked by Table 6, entry 1).

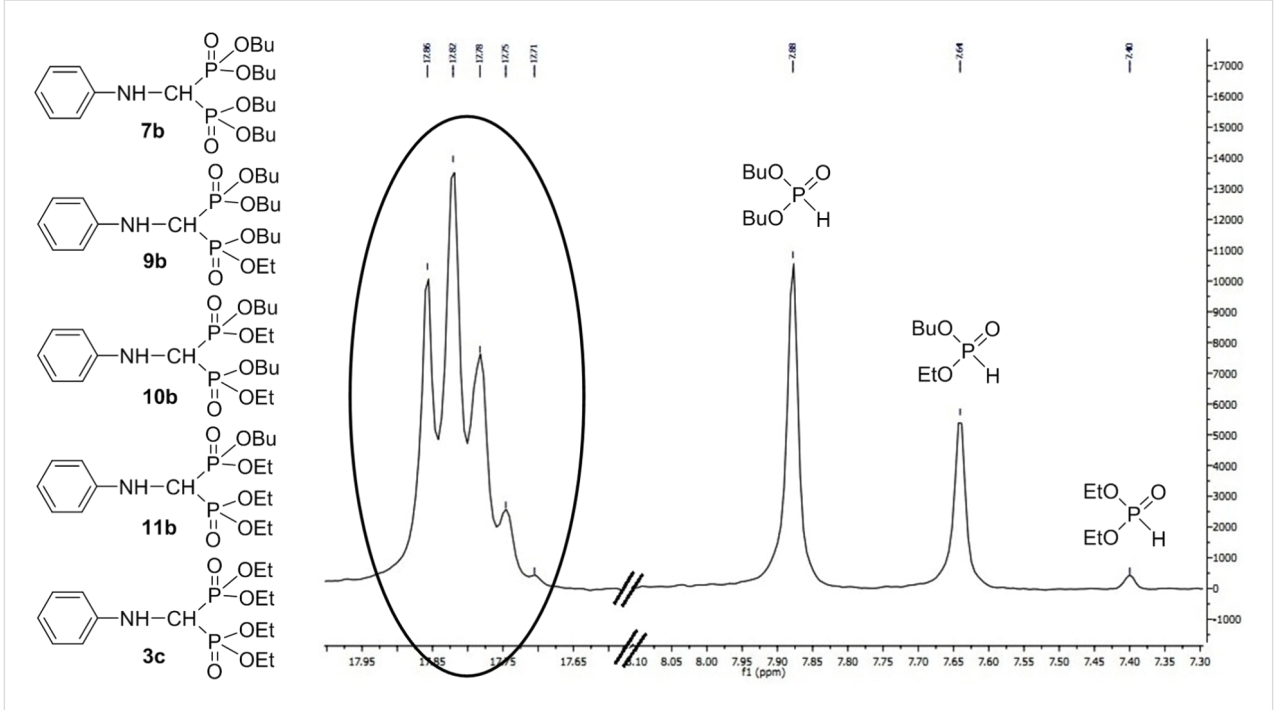


Figure 3: ^{31}P NMR spectrum for the condensation of aniline, triethyl orthoformate and 2 equivalents of dibutyl phosphite (from the exp. marked by Table 6, entry 6).

Table 7: Mass spectral characterization of (aminomethylene)bisphosphonates.

	R = Me (b)		R = Bu (c)	
	$[M + H]^+_{found}$	$[M + H]^+_{requires}$	$[M + H]^+_{found}$	$[M + H]^+_{requires}$
7	324.0760	324.0760	492.2648	492.2638
9	338.0921	338.0917	464.2329	464.2325
10	352.1072	352.1073	436.2011	436.2012
11	366.1231	366.1230	408.1711	408.1699
3c	380.1382	380.1386	380.1382	380.1386

Conclusion

In summary, we have developed a facile, solvent- and catalyst-free MW-assisted method for the synthesis of (aminomethylene)bisphosphine oxides (AMBPOs) and (aminomethylene)bisphosphonates by the condensation of a primary or secondary amine, an orthoformate, and diphenylphosphine oxide or a dialkyl phosphite. This method is a novel approach for the preparation of AMBPOs and an optimized process for the synthesis of (aminomethylene)bisphosphonates. Twenty-two derivatives were isolated and characterized, except two, all of them are new compounds. Furthermore, a few intermediates supporting the mechanism of the condensation, and several by-products were also identified.

Supporting Information

Experimental procedures, characterization data, details of the NMR structural determination of all products and copies of ^{31}P, ^{1}H, and ^{13}C NMR spectra for all compounds synthesized are presented in Supporting Information File 1.

Supporting Information File 1

Experimental, NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-146-S1.pdf]

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