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Synthesis of Novel Aminomethylenebisphosphonates and Bisphosphonic Acids, Containing Adamantyl Fragment

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ABSTRACT: *Novel aminomethylenebisphosphonates containing an adamantyl fragment were synthesized by a solvent-free, microwave-assisted, three-component reaction of amines, triethyl orthoformate, and* O,O*-diethyl phosphite. Several bisphophonic acids were prepared from aminomethylenebisphosphonates by the treatment with trimethylsilyl bromide followed by methanolysis.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 22:55–58, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20656

INTRODUCTION

Bisphosphonic acids and bisphosphonates are hydrolytically stable analogues of pyrophosphate in which common P—O—P bonds are replaced by the P—C—P fragments [1]. For over two decades, these compounds have been employed as therapeutic agents for a treatment of bone disorders—hypocalcaemia and osteoporosis [2–6]. Despite this, in the course of investigation bisphosphonates have been found to exhibit antibacterial [7,8], anticancer [9], antiviral [10], herbicide [11], pesticide [12], and many other activities [13,14]. A subclass of bisphosphonates, derivatives of aminomethylenebisphosphonic acids, is practically used as medicine in the osteoporosis treatment [15,16], some of them are biologically tested as estradiol complexes for drug delivery purposes [17]. At the same time, it is well known that different adamantane-containing compounds were shown to have anti-influenza [18,19] and anti-HIV activity [20,21] and activity against epilepsy [22]. To our knowledge, only several examples of aminomethylenebisphosphonates containing adamantyl fragment have yet been described in the literature [10,23].

RESULTS AND DISCUSSION

The simplest and most convenient procedure for the preparation of aminomethylenebisphosphonates and bisphosphonic acids based on the three-component reaction between a primary or a secondary amine, triethyl orthoformate, and *O*, *O*-diethyl phosphite, followed by acidic hydrolysis [24–27].

In the present study, the three-component reaction between aminoadamantanes **1a–d**, triethyl orthoformate, and *O*, *O*-diethyl phosphite was used to obtain novel aminomethylenebisphosphonates

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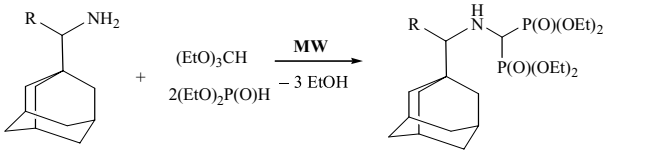
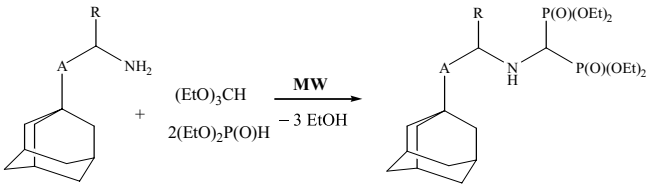
and aminomethylenebisphosphonic acids, containing a biologically active adamantyl fragment. The reaction was carried out under microwave irradiation (400 W, 150°C) under solvent-free conditions without added catalyst during 25–45 min (Eq. (1)). Aminomethylenebisphosphonates **2a–d** were isolated in good yields (62–90%) by column chromatography on silica gel. It should be emphasized that a common process carried out under heating conditions (150°C, 4–5 h) resulted in the reduced product yields due to thermal instability of the imine-type intermediate forming in the process [28].



1 **2**

R= H (**2a**), Ph (**2b**)

(1)



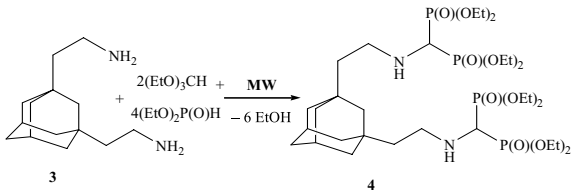
1 **2**

A= OCH_2 (**2c**), CH_2 (**2d**)

R= H (**2c**), Me (**2d**)

Aminomethylenebisphosphonates **2a–d** were adequately characterized by means of ^1H, ^{13}C, and ^{31}P NMR spectroscopy and elemental analysis. In the ^1H NMR spectra, chemical shifts of C*H*P fragments were in 3.09–3.33 ppm area and were shown to be triplets with $^2J_{PH}$ = 21–25 Hz. These data are in accordance with the data reported for the usual aminomethylenebisphosphonates [28,29] (Table 1). In ^{13}C NMR spectra, carbon atoms connected with two P-atoms are triplets with $^1J_{PC}$ = 142–146 Hz in the 51.17–58.26 ppm area (Table 1). ^{31}P NMR spectra of bisphosphonates **2b** and **2d** were found to show two phosphorus signals of the AB type with P—P chemical coupling constant equal to 41.0–42.1 Hz (Table 1). Apparently, the presence of the bulky methylenebisphosphonate fragment slows rotation around a C—N bond, this leads to nonequivalence of the two phosphorus atoms (each atom is in different chemical environment) and the formation of two conformers in solution.

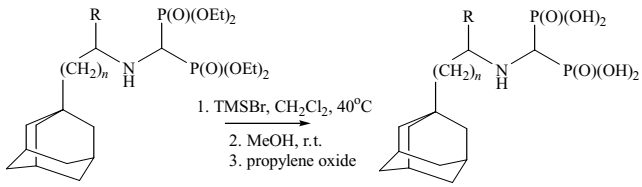
In reaction with amine **3**, containing 2 equiv amino groups, a double excess of the triethyl orthoformate and *O*, *O*-diethyl phosphite was used to give bisphosphonate **4** in high yield (Eq. (2)). The structure and composition of compound **4** were confirmed by the ^1H and ^{13}C NMR spectra and elemental analysis data (Tables 1 and 2). When the reaction was performed with equimolar amounts of amine **3**, triethyl orthoformate, and *O*, *O*-diethyl phosphite, only the formation of compound **4** was noted. No phosphorylation at a single amino group was found.



3 **4**

(2)

To obtain aminomethylenebisphosphonic acids **5a,b,d**, the well-known procedure for alkoxy groups removal from phosphorus esters was used [30,31]. The method is based on the interaction between aminomethylenebisphopsonates **2a,b,d** and trimethylsilyl bromide followed by the treatment with methanol and propylene oxide at room temperature (Eq. (3)). The yields of corresponding acids **5a,b,d** were found to be 85–95%. In the ^{31}P NMR spectra, compounds' **5a,b,d** exhibit chemical shifts in the 10.8–13.2 ppm region (Table 1).



2 **5**

n= 0 (**2a**), 0 (**2b**), 1 (**2d**)

R= H (**2a**), Ph (**2b**), Me (**2d**)

In summary, we synthesized the new class of aminomethylenebisphosphonates containing adamantyl fragment in a three-component reaction under microwave irradiation and in solvent-free conditions. The corresponding aminomethylenebisphosphonic acids were obtained by the established protecting group removal method.

EXPERIMENTAL

All reactions were carried out under microwave irradiation at 400 W using a domestic oven (Daewoo, KOR-4125G). ^1H, ^{13}C, and ^{31}P NMR spectra were recorded at room temperature on a Bruker

TABLE 1 Reaction Time, Yields, and NMR Spectral Data for the $PC^1H(NC^2)P$ Fragments (δ, ppm; J, Hz) of Compounds **2, 4**, and **5**[a]

Compound	*Reaction Time (min)*	*Yield (%)*	*$\delta(H)$ C^1H t*	*$^2J_{PH}$*	*$\delta(C^1)$t*	*$^1J_{PC}$*	*$\delta(C^2)$ s*	*δ_P*
2a	35	73	3.15	21.7	55.47	143.9	52.70	19.4
2b	45	62	3.09	21.9	58.26	154.2	54.13	20.04[b]
2c	25	90	3.33	21.5	54.43	146.6	50.52	19.7
2d	28	88	3.30	22.2	51.17	146.1	52.49	20.0[b]
4	30	67	3.18	21.6	53.22	147.1	51.55	18.9
5a	3 h	85	2.99	18.4	–	–	–	10.8
5b	3 h	92	2.94	18.9	–	–	–	10.9
5d	3 h	95	3.08	19.1	–	–	–	13.2

[a]All signals of alkyl, adamantyl, and ethoxy groups are in the standard areas. In the ^{1}H NMR spectra, the CH_3 fragment for compounds: **2a**, 1.31 t, $^3J_{HH}$ 4.8; **2b**, 1.27 t, $^3J_{HH}$ 6.1; **2c**, 1.29 t, $^3J_{HH}$ 7.1; **2d**, 1.31 t, $^3J_{HH}$ 4.8; **4**, 1.20 t, $^3J_{HH}$ 6.0; the $POCH_2$ fragment for compounds: **2a**, 4.18 m; **2b**, 4.13 m; **2c**, 3.44 m; **2d**, 4.17 m; **4**, 4.07 m; the NCH_2 fragment for compounds: **2a**, 2.45 s; **2c**, 2.91 t, $^3J_{HH}$ 5.1; the NCH(Ph) fragment for compound: **2b**, 2.81 s; the NCHC fragment for compound **2d**, 2.34 m; the NCH_2C fragment for compound **4**, 2.73 t, $^3J_{HH}$ 5.5; the $COCH_2$ fragment for compound **2c**, 3.44 t, $^3J_{HH}$ 5.1; the CCH_2C fragment for compound **4**, 1.25 t, $^3J_{HH}$ 5.5. In the ^{13}C NMR spectra, the adamantyl fragment for compounds: **2a**, 28.33, 33.67, 37.12, 40.44; **2b**, 28.06, 36.35, 38.54, 40.15; **2c**, 30.41, 36.42, 41.50, 71.88; **2d**, 28.62, 32.23, 37.00, 42.85; **4**, 28.94, 32.47, 36.50, 42.10; the CH_3 fragment for compounds: **2a**, 16.42; **2b**, 16.50; **2c**, 16.43; **2d**, 16.30; **4**, 16.35; fragment $POCH_2$ for compounds: **2a**, 62.70; **2b**, 73.53; **2c**, 62.81; **2d**, 62.80; **4**, 61.75**;** the NCH_2 fragment for compound **2a**, 62.70; the NCH(Ph) fragment for compound: **2b**, 65.22; the $COCH_2$ fragment for compound **2c,** 76.81; the CCH_2C fragment for compound **4,** 44.52; the NCHC fragment for compound **2d,** 52.49.
[b]AB system $^2J_{PP}$ for compounds: **2b**, 42.1; **2d**, 41.4.

DPX-400 spectrometer (400.13, 100.61, and 161.98 MHz, respectively) in $CDCl_3$ or D_2O against TMS (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). Analytical thin layer chromatography (TLC) was carried out with "Silufol" silica gel plates (supported on aluminum); The revelation was done by chemical staining (iodine vapor). Column chromatography was performed using silica gel 60 (230–400 mesh, Merk). All reagents, except commercial products of satisfactory quality were purified with literature procedures prior to use.

O,O,O,O-Tetraethyl Adamantylmethylaminomethylenebisphosphonate (**2a**). A mixture of 1.65 g of adamantylmethylamine **1a**, 2.23 g of triethyl orthoformate, and 5.52 g of *O*, *O*-diethyl phosphite in a 20-mL flask was exposed to microwave irradiation for 35 min. The aminomethylenebisphosphonate **2a** was purified by chromatography on silica gel ($CHCl_3$–MeOH 50:1) to give 3.29 g of the product.

The compounds **2b–d** were prepared similarly.

Octaethyl [Adamantane-1,3-diylbis(ethane-2,1-diylimino)]bis (methylenebisphosphonate) (**4**). A mixture of 1.23 g of adamantane-1,3-diylbis(ethane-2,1-dyilamine) **3**, 4.46 g of triethyl orthoformate, and 11.04 g of *O*, *O*-diethyl phosphite in a 50-mL flask was exposed to microwave irradiation for 30 min. The aminomethylenebisphosphonate **4** was purified by chromatography on silica gel ($CHCl_3$–MeOH 50:1) to give 5.31 g of the product.

N-Methylaminomethylenedisphosphonic Acid (**5a**). To a stirred solution of 2.25 g of *O*,*O*, *O*,*O*-tetraethyl adamantylmethylaminomethylenebisphosphonate **2a** in 20 mL of methylene chloride, a solution of 3.8 g of trimethylsilyl bromide in 5 mL of methylene chloride was added dropwise

TABLE 2 Elemental Analyses Data of Synthesized Compounds

Compound	*Empirical Formula*	*Formula Weight*	*Calcd. (%)*		*Found (%)*	
			C	*H*	*C*	*H*
2a	$C_{20}H_{39}NO_6P_2$	451.47	53.21	8.71	53.16	8.72
2b	$C_{26}H_{43}NO_6P_2$	527.57	59.19	8.22	59.10	8.16
2c	$C_{21}H_{41}NO_7P_2$	481.50	52.38	8.58	52.31	8.57
2d	$C_{22}H_{43}NO_6P_2$	479.52	55.10	9.04	55.09	9.13
4	$C_{32}H_{66}N_2O_{12}P_4$	794.76	48.36	8.37	48.31	8.35
5a	$C_{14}H_{29}NO_6P_2$	369.33	45.43	7.91	45.39	7.88
5b	$C_{20}H_{33}NO_6P_2$	445.42	53.93	7.47	53.88	7.45
5d	$C_{16}H_33NO_6P_2$	397.39	48.36	8.37	48.33	8.34

at 0°C. Then the reaction mixture was heated up to 40°C for 3 h. The solvent was removed at 20°C, and 10 mL of propylene oxide was added. Acid **5a** precipitated as white crystals to give 1.44 g of product.

The compounds **5b,d** were prepared similarly.

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