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Simple, efficient one-pot method for synthesis of novel *N*-attached 1,2,3-triazole containing bisphosphonates

Xiaolan Chen [a,*], Xu Li [a], Jinwei Yuan [b], Lingbo Qu [a,b,*], Shaohui Wang [a], Hanyu Shi [a], Yuchun Tang [a], Likun Duan [a]

[a] College of Chemistry and Molecular Engineering, Zhengzhou University, Key Laboratory of Organic Chemistry and Chemical Biology, Henan Province, Zhengzhou, 450052, PR China
[b] Chemistry and Chemical Engineering School, Henan University of Technology, Henan Province, Zhengzhou 450001, PR China

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ABSTRACT

A practical and efficient one-pot method for synthesis of a novel kind of *N*-attached 1,2,3-triazole-containing bisphosphonates was developed. Michael addition reaction of sodium azide with ethylidene bisphosphonates and 1,3-dipolar click cycloaddition were reasonably integrated into one-pot reaction in the presence of sonication. Vinylidene bisphosphonate, NaN_3, and terminal alkyne were employed as the reactants, $CuSO_4 \cdot 5H_2O$ sodium ascorbate was employed as the catalyst system, and $AcOH/H_2O$ (1:1 v/v) were employed as the solvent system to create an acidic environment to achieve optimal efficiency.

1. Introduction

Nitrogen-containing bisphosphonate (*N*-BPs) drugs are used to treat a variety of bone resorption diseases, such as osteoporosis, Paget's disease, and hypercalcemia due to malignancy.[1] They are thought to act by inhibiting the enzyme farnesyl diphosphate synthase,[2] resulting in inhibition of protein prenylation in osteoclasts. In addition to their use in treating these diseases, bisphosphonates have direct activity against tumor cell growth, as well as the growth of a variety of pathogenic protozoa and some bacteria.[2–4] It is worth mentioning that most of the highly potent third-generation BP drugs contain the nitrogen heterocyclic component in their molecular structures, as those in risedronate and zoledronate (Fig. 1). For the treatment of bone diseases associated with excessive resorption, the cyclic nitrogen bisphosphonates (*N*-BPs) are up to 10,000-fold more active than the first-generation non-nitrogen containing BP.[5–8] Two heterocyclic nitrogen-containing bisphosphonates, risedronate, and zoledronate, are *C*-attached and *N*-attached, respectively, as illustrated in Fig. 1. It is especially worth emphasizing that zoledronic acid, a *N*-attached 1,3-diazole bisphosphonate, is the most potent inhibitor of bone resorption identified to date. Therefore, the purposeful synthesis of new members of *N*-attached cyclic nitrogen containing *N*-BP family should be beneficial for further development of more potent bisphosphonates.

It is noted that despite the 1,2,3-triazole structural moiety itself does not occur in nature, a wide range of compounds containing this functionality have exhibited diverse biologically activities, such as anti-HIV[9] and antimicrobial activities.[10] With respect to introducing 1,2,3-triazole groups into organic molecules, one of the most popular reactions within the click chemistry concept, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC 'click' reaction), discovered by the groups of Sharpless and Meldal[11,12] is a useful approach leading to 1,4-substituted products with high regioselectivity. Our group has recently discovered that the highly regioselective copper(I)-catalyzed 1,3-dipolar cycloaddition reaction can be notably improved in rates and yields in the presence of ultrasound irradiation.[13] Reportedly, simple bisphosphonates could be synthesized by using conjugate addition reactions of nucleophiles, such as amines and Grignard reagents to vinylidene bisphosphonates, followed by treatment with trimethylsilyl bromide (TMSBr) and then methanolysis.[14–19] It is especially worth mentioning here that an important synthetic method, as shown in Scheme 1, finally leading to the *N*-attached bisphosphonates via Michael addition reaction of sodium azide to vinylidene bisphosphonate, followed by reaction with terminal alkynes, has not yet been described. Obviously, it is an extremely attractive idea to create a novel kind of *N*-attached 1,2,3-triazole bisphosphonates

* Corresponding authors. Tel./fax: +86 371 67767051; e-mail address: chenxl@zzu.edu.cn (X. Chen).

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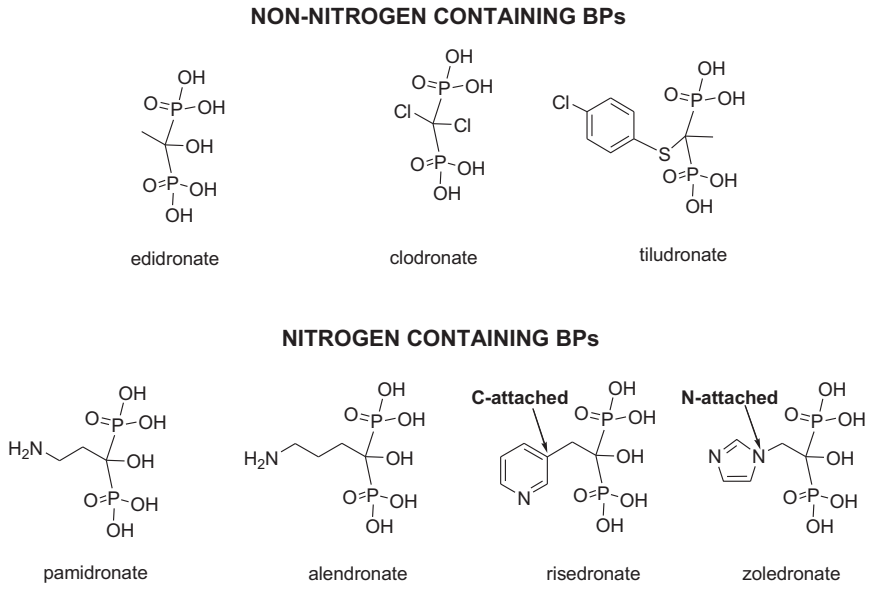
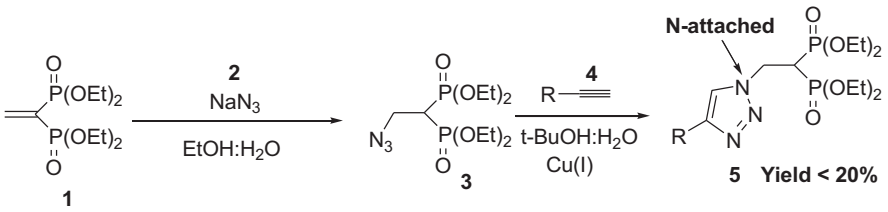


Fig. 1. Structure of bisphosphonics. The acid forms are depicted.



Scheme 1. Synthetic route leading to *N*-attached 1,2,3-triazole-containing bisphosphonates. Reaction condition: **1** (0.1 mmol) reacted with NaN_3 (0.15 mmol) using C_2H_5OH/H_2O (10 mL, v/v, 1/1) as solvent at room temperature around half an hour. The solvents were removed. The residues were diluted with water and extracted with methylene chloride. The residual oil was used directly to react with 4′-methylphenyl acetylene, a terminal alkyne (0.12 mmol), using $CuSO_4 \cdot 5H_2O$ (10% mmol) sodium ascorbate (20% mmol) as its catalyst and *t*-BuOH/H_2O (15 mL, v/v, 1/1) as solvent at room temperature around 9 h in the presence of ultrasound irradiation.

via this method. But it was extremely astonished that, at the very beginning, when the plotted two-step synthetic route, as shown in Scheme 1, was actually carried out in our lab, we obtained the target *N*-attached bisphosphonates in extremely low yield, suggesting that some existing synthetic obstacles, which had seriously prevented from effectively obtaining these especially important novel *N*-attached bisphosphonates, should be known and removed. Herein, we disclose our skillfully designed, so-called a facile and efficient one-pot synthetic method for synthesis of a series of these novel *N*-attached 1,2,3-triazole-containing bisphosphonates, by means of a controlled Michael-type addition followed by ultrasound irradiation promoted-click reaction.

2. Results and discussion

We designed a two-step involving synthetic route as shown in Scheme 1. However we initially failed to obtain the target *N*-attached bisphosphonates effectively. The reason for the failure was investigated and the overall synthetic procedures were re-examined. Initially the step 1 of Scheme 1 was carried out using EtOH/H_2O (v/v, 1/1) as reaction solvent based on the literature.[20] Formation of comp-**3** was traced by ^{31}P NMR spectra techniques as Fig. 2 shown. Although several detectable by-products were produced accompanying with the main reaction, most comp-**1** (δ 13.9 ppm) had chemically reacted to produce comp-**3** (δ 21.7 ppm) within 11 min under the reaction condition. All solvents were subsequently removed by evaporation under reduced pressure. The residues were then diluted with water and extracted with methylene chloride. The organic layer was washed, dried, and evaporated. The residual oil was used directly to react 4′-methylphenyl acetylene in the next step 2 using our previously reported procedure.[13] It is especially worth emphasizing that, after having most comp-**1** chemically reacted to produce comp-**3** within 11 min, the following stepwise procedures did not lead to an efficient synthesis of the final cyclic product **5** (yield<20%), strongly suggesting that there might be something wrong with the following stepwise procedures. Therefore, much more influential factors concerning the reactions were subsequently investigated.

Even though most comp-**1** chemically reacted to produce comp-**3** within 11 min using EtOH/H_2O (v/v, 1/1) as reaction solvent,

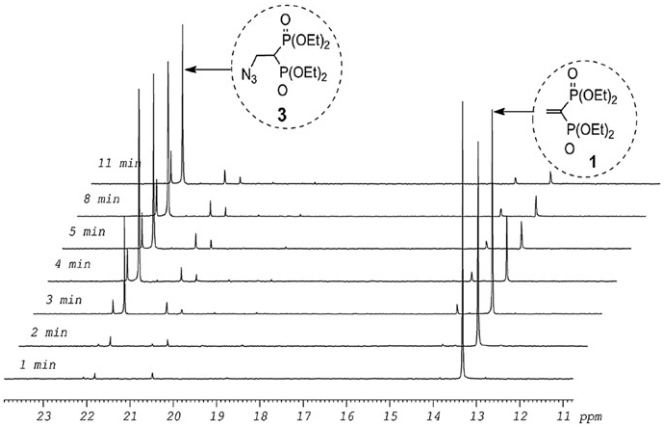


Fig. 2. Stacked plot of the ^{31}P NMR spectra regarding reaction of comp-**1** with NaN_3 in step 1 of Scheme 1. The reaction was carried out using (Comp **1**) vinylidene bisphosphonate 12.5 mg (0.042 mmol) and NaN_3 4.4 mg (0.061 mmol) in the solvent: C_2H_5OH/H_2O (v/v, 1/1) 0.5 mL at room temperature (comp-**1**: δ 13.9 ppm, comp-**3**: δ 21.7 ppm).

several detectable phosphorus-containing by-products were still produced as shown in Fig. 2. There was still a need to develop a better solvent system. The reaction of comp **1** with sodium azide was further investigated in different solvents and ^{31}P NMR traced the processes of these reactions (Fig. 3). It can be seen that none of any comp-**3** was detected within 5 h when acetone was used as the solvent (Fig. 3i), and another polar aprotic solvent DMSO brought about not only a small amount of comp **3** in 50 min, but meanwhile some un-negligible phosphorus-containing by-products at δ 20.1 ppm and δ 14.5 ppm, respectively (Fig. 3ii). The use of acetic acid, a polar protic solvent, greatly enhanced the addition reaction, leading most of comp **1** to comp **3** in 1.5 h, but the process was accompanied by formation of a detectable by-product at δ 20.9 ppm (Fig. 3iii). Correspondingly, the influence of three mixed solvents of acetone, DMSO and acetic acid with water, on Michael addition reaction of sodium azide was subsequently studied, respectively. The reaction in H_2O-acetone resulted in a formation of many unwanted by-products besides producing the targeted product **3** (Fig. 3iv). The reaction in H_2O/DMSO mixed solvent made little improvement in transformation of compound **1** to **3** in comparison with that in DMSO (Fig. 3ii and v). The best solvent among those investigated was H_2O/AcOH solution, by which a complete and clean transformation was made within 15 min (Fig. 3vi).

Again, the H_2O/AcOH reaction solvent was removed by evaporation under reduced pressure, and the residues were subsequently diluted with water and extracted with methylene chloride. Fig. 4 shows two ^{31}P NMR spectra, one taken directly with the H_2O/acetic acid reaction solution (Fig. 4a), and the other with methylene chloride extraction solution (Fig. 4b). More than one-third original amount of comp-**3** astonishingly decomposed back into comp-**1** after extraction with methylene chloride. That is to say the low yield of the final cyclic product **5** was mostly due to the unwanted decomposition of comp-**3** in this extraction process. The main factors that influence the stability of comp-**3** were therefore investigated.

It was shown above that the best solvent system for reaction of comp-**1** with NaN_3 was H_2O/AcOH, in which a complete and clean transformation was made within 15 min (Fig. 3vi). The effect of temperature on the stability of comp-**3** was investigated by directly

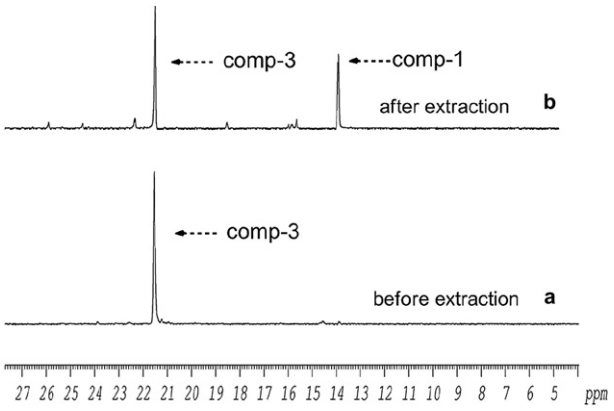


Fig. 4. a: ^{31}P NMR spectrum of the H_2O/AcOH reaction solvent; b: ^{31}P NMR spectrum of the CH_2Cl_2 extraction solution. The reaction was carried out using (Comp **1**) vinylidene bisphosphonate (0.1 mmol) and NaN_3 (0.15 mmol) in the solvent: CH_3COOH/H_2O (v/v, 1/1) 10 mL at room temperature. Comp-**1** (δ 13.9 ppm) and **3** (δ 21.7 ppm).

using this H_2O/AcOH reaction solution. Fig. 5 shows ^{31}P NMR spectra taken with H_2O/AcOH reaction solution at different temperature (25 °C, 30 °C, 40 °C, 50 °C, 60 °C, respectively). Considering that the following stepwise procedures would all be performed at temperatures below 50 °C, 60 °C was chosen as the highest temperature reached for this study. It can be seen that only small amount of comp-**3** begun to decompose after temperature reached 40 °C and then the rate of decomposition increase only slightly afterward with the temperature, exhibiting a higher thermal stability of comp-**3** in the temperature range 25–60 °C.

The effect of pH on the stability of comp-**3** was subsequently investigated. Fig. 3 clearly shows that the transformation efficiencies heavily depend on solvent systems chosen. Increased transformation efficiency resulting from using acetic acid and H_2O/acetic acid as the reaction solvents, seems to indirectly indicate the importance of acidic reaction condition. It's necessary to find out whether or not the stability of comp-**3** relies heavily on the pH of the solution. The H_2O/acetic acid reaction solution was then

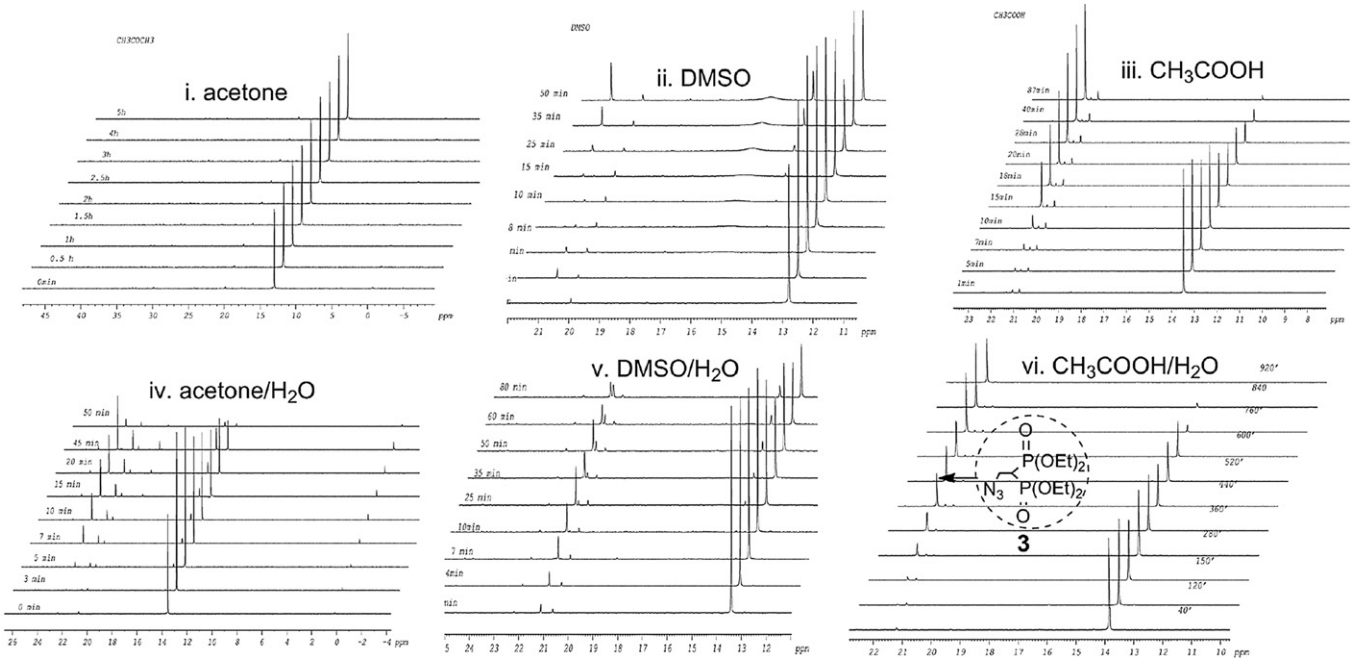


Fig. 3. Stacked plots of the ^{31}P NMR spectra via the synthetic route shown in Scheme 1 in different solvent. The reaction was carried out using (Comp **1**) vinylidene bisphosphonate (0.04 mol), NaN_3 (0.061 mmol) in different solvent (0.5 mL) at room temperature (i. acetone, 5 h; ii. DMSO, 1 h; iii. CH_3COOH, 1.5 h; iv. acetone/H_2O (v/v, 1/1), 1 h; v. DMSO/H_2O (v/v, 1/1), 1.5 h; vi. CH_3COOH/H_2O (v/v, 1/1), 15 min).

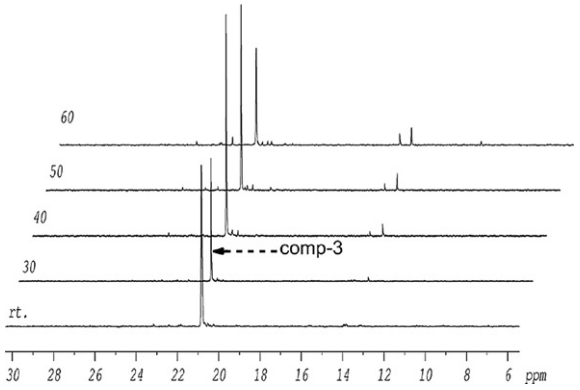


Fig. 5. ^{31}P NMR spectra taken with H_2O/AcOH reaction solution at different temperatures (25 °C, 30 °C, 40 °C, 50 °C, 60 °C).

adjusted to different pH with different amount saturated NaOAc solution. ^{31}P NMR spectra of the reaction solution at different pH are shown in Fig. 6i. It can be seen that the Michael addition reaction of sodium azide to α,β-unsaturated bisphosphonates involves an equilibrium process, which depends heavily upon solvent acidity (Fig. 6ii). Comp-**3** began to decompose when the pH reached 4.69. More than half the original amount of comp-**3** decomposed back into comp-**1** when the pH reached 5.60. The study of the effect of pH on the stability of comp-**3** thereby well disclose the reason why, as illustrated in Fig. 4(a), one-third original amount of comp-**3** decomposed back into comp-**1** after extraction by non-acidic methylene chloride solvent.

Here we propose a novel one-pot synthesis of these novel *N*-attached 1,2,3-triazole containing bisphosphonates, as described in Scheme 2. Tetraethylvinylidene bisphosphonate (**1**), sodium azide (**2**), and 4′-methylphenyl acetylene terminal alkyne (**4**) were added to AcOH/H_2O (1:1 v/v) solvents. Following our previously reported procedure,[13] $CuSO_4 \cdot 5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) were added to as the catalyst system of the 1,3-dipolar cycloaddition of azides with terminal alkynes. The resulting mixture was subjected to sonication at room temperature for 9 h. In the one-pot synthesis, a low pH reaction environment was created by employing AcOH/H_2O (1:1 v/v) as the reaction solvent. The equilibrium position of Michael addition reaction (Fig. 6) lay far to the right. Once unstable comp-**3** was synthesized in this acidic solvent, it reacted with the terminal alkyne to form a stable end product **5**. An efficient synthesis of comp-**5** was thereby achieved expectedly. It is well known that an overall yield is always slightly lower than that attained in a single step. Two reactions, one Michael addition reaction of sodium azide and the other 1,3-dipolar cycloaddition were

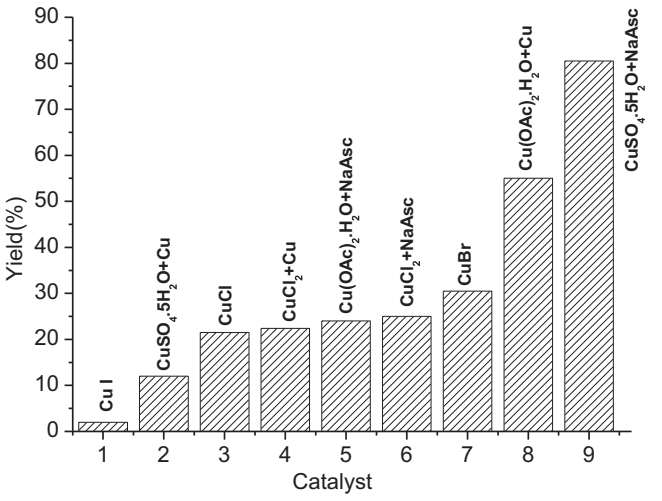
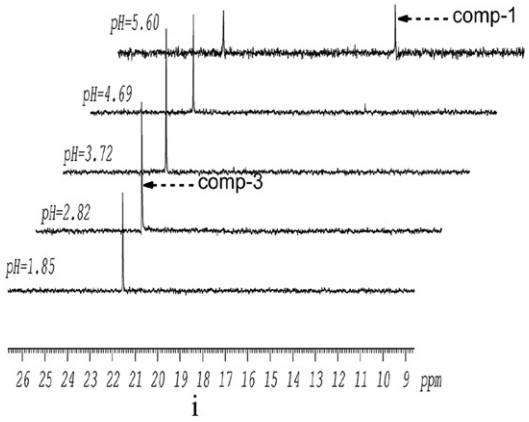


Fig. 7. The yields of one-pot reaction using vinylidene bisphosphonate, sodium azide, and 1-ethynyl-4-methylbenzene as reactants, CH_3COOH/H_2O (1:1, v/v) as the reaction solvent. The reaction was catalyzed by different catalyst systems under sonication for 9 h at room temperature, respectively.



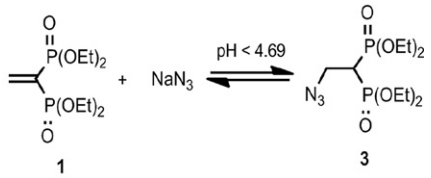
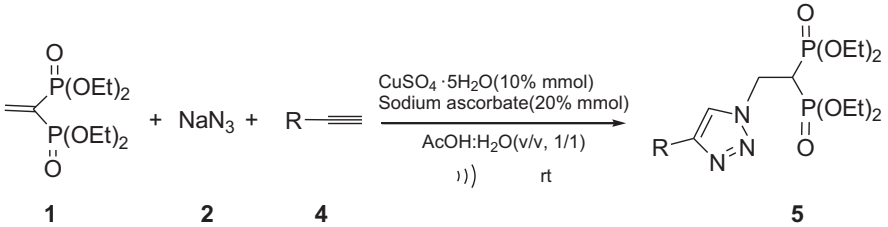
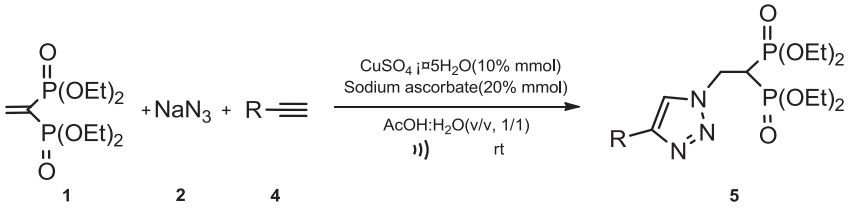


Fig. 6. i. ^{31}P NMR spectra of comp-**3** (δ 21.7 ppm) at different pH (1.85, 2.82, 3.72, 4.69, 5.60, respectively); ii. A pH-dependent equilibrium of Michael addition reaction of sodium azide to α,β-unsaturated bisphosphonates. The different pH solutions were made from 0.5 mL CH_3COOH/H_2O (v/v, 1/1) reaction solution with different amount saturated NaOAc solution.

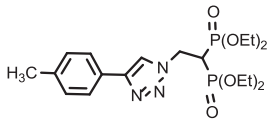
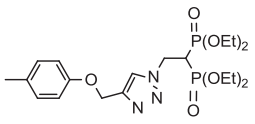
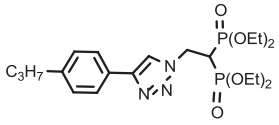
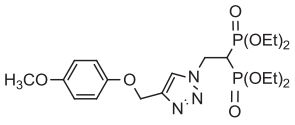
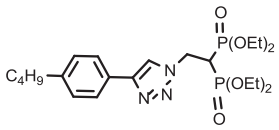
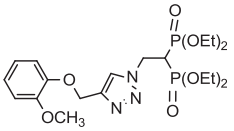
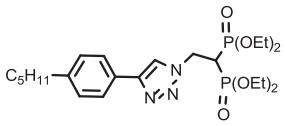
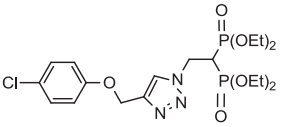
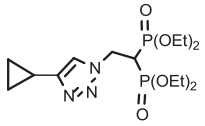
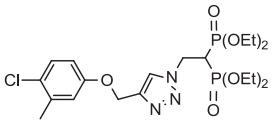
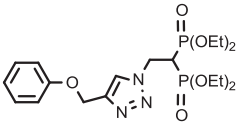
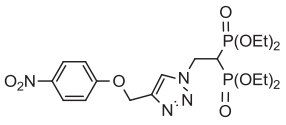
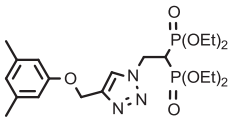
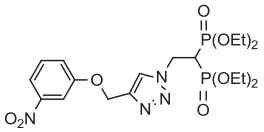


Scheme 2. One-pot synthesis of novel *N*-attached 1,2,3-triazole-containing bisphophonates **5**. Yield: 80.5%. Catalyzed by $CuSO_4 \cdot 5H_2O$ (10% mmol), sodium ascorbate (20% mmol), vinylidene bisphosphonate (**1**) (0.1 mmol), NaN_3 (**2**) (0.15 mmol), and (4′-methylphenyl acetylene)terminal alkyne (**4**) (0.12 mmol) reacted in AcOH/H_2O (1:1 v/v) 10 mL at room temperature around 9 h in the presence of ultrasound irradiation to form **5**. The residues were subsequently diluted with water and then extracted with methylene chloride. The crude product was purified by column chromatography eluted with ethyl acetate.

Table 1
One-pot preparation of *N*-attached 1,2,3-triazoles bisphosphonate



1 2 4 5

Compd	Product	Isolated yield (%)	Compd	Product	Isolated yield (%)
a		80.5	**h**		76.4
b		84.7	**i**		78.6
c		82.6	**j**		73.4
d		82.3	**k**		71.1
e		70.1	**l**		72.6
f		75.2	**m**		79.2
g		79.3	**n**		77.4

Reaction condition: $CuSO_4 \cdot 5H_2O$ (10% mol) sodium ascorbate (20% mmol), vinylidene bisphosphonate (1) (10 mmol), NaN_3 (2)(15 mmol) and terminal alkyne (4) (12 mmol) reacted in $AcOH/H_2O$ (1:1 v/v) 30 mL at room temperature around 9 h in the pressure of ultrasound irradiation.

involved in the one-pot reaction. If one-step is a 90% yield, the overall final product yield is 81%. It is to say that the 81% overall yield, in this case, is a relatively high overall yield considering a two-step involving reaction. Consequently, as illustrated in Scheme 2, a relatively high overall yield (80.5%) of final product **5** was subsequently achieved via this specially designed one-pot synthesis.

More catalyst systems were then explored using the above one-pot synthesis as illustrated in Fig. 7. It can be concluded that the $CuSO_4 \cdot 5H_2O$/sodium ascorbate was still the best catalyst system among the nine catalyst systems tested. The scope of the reactants was then enlarged to cover more different terminal alkynes as shown in Table 1. The optimized one-pot method practically and efficiently brought about a successful synthesis of a series of novel *N*-attached 1,2,3-triazole-containing bisphosphonates as expected. As could be seen from Table 1, in all cases, *N*-attached 1,2,3-triazole-containing bisphosphonates **5a**–**n** were obtained in good to excellent yields. Furthermore the yields of the corresponding target products are not influenced obviously by various substituted groups attached to the benzene ring, no matter electron withdrawing groups such as $-NO_2$, $-X$, or electron donating groups such as $-OCH_3$. This observation is also consistent with earlier research in terms of the influence of functional groups upon click chemistry synthesis.[21]

3. Conclusions

In conclusion, a practical and efficient one-pot method for synthesis of a novel kind of *N*-attached 1,2,3-triazole-containing bisphosphonates was developed. Two reactions, one Michael addition reaction of sodium azide with vinylidene bisphosphonate and the other 1,3-dipolar click cycloaddition, in this case, were skillfully integrated into one-pot reaction in the presence of

sonication. Vinylidene bisphosphonate, NaN_3, and terminal alkyne were employed as the reactants, $CuSO_4 \cdot 5H_2O$ sodium ascorbate was employed as the catalyst system, and $AcOH/H_2O$ (1:1 v/v) were employed as the solvent system to create an acidic environment to achieve optimal efficiency. The approaches described here obviously have significant advantages in terms of experimental simplicity, mild reaction condition and easy work-up, and would surely represent a convenient tool for the synthesis of a variety of this novel type of *N*-attached 1,2,3-triazole-containing bisphosphonates.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.078.

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